ASTRAZENECA LP et al v.BREATH LIMITED et al Doc. 1163

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

ASTRAZENECA LP and ASTRAZENECA AB, Plaintiffs, v. BREATH LIMITED, Defendant.	Consolidated Civil Action No. 08-1512 (RMB/AMD) **REDACTED OPINION (PUBLIC)**
ASTRAZENECA LP and ASTRAZENECA AB, Plaintiffs, v. APOTEX, INC. and APOTEX CORP., Defendants.	
ASTRAZENECA LP and ASTRAZENECA AB, Plaintiffs, v. SANDOZ, INC., Defendant.	
ASTRAZENECA LP and ASTRAZENECA AB, Plaintiffs, v. WATSON LABORATORIES, INC., Defendant.	

Dockets.Justia.com

Appearances

John E. Flaherty, Esquire
Ravin R. Patel, Esquire
McCarter & English LLP
Four Gateway Center
100 Mulberry Street
Newark, New Jersey 07102

Jay I. Alexander, Esquire
Stephen P. Anthony, Esquire
Christopher Sipes, Esquire
Keith A. Teel, Esquire
Covington & Burling LLP
1201 Pennsylvania Avenue, NW
Washington, DC 20004

Danielle L. Goldstein, Esquire
Covington & Burling LLP
One Front Street
San Francisco, Ca. 94111

Attorneys for Plaintiffs AstraZeneca LP and AstraZeneca AB

Eleonore Ofosu-Antwi, Esquire
Liza M. Walsh, Esquire
Connell Foley, LLP
85 Livingston Avenue
Roseland, New Jersey 07068

William A. Rakoczy, Esquire
Amy D. Brody, Esquire
Heinz J. Salmen, Esquire
Natasha White, Esquire
Rakoczy Molino Mazzochi
Siwik LLP
6 West Hubbard Street, Suite 500
Chicago, Illinois 60654

Attorneys for Defendant/Counterclaim Plaintiffs Breath Limited and Watson Laboratories, Inc.

Eric I. Abraham, Esquire
Christina L. Saveriano, Esquire
Hill Wallack, LLP
202 Carnegie Center
Princeton, New Jersey 08543

Richard J. Basile, Esquire
David W. Aldrich, Esquire
St. Onge Steward Johnson & Reens, LLC
989 Bedford Street
Stamford, Connecticut 06905-5619

Attorneys for Defendants/Counterclaim Plaintiffs Apotex, Inc. and Apotex Corp.

Sheila R. Wiggins, Esquire
Duane Morris, LLP
One Riverfront Plaza
1037 Raymond Blvd., Suite 1800
Newark, New Jersey 07102

Eric D. Frank, Esquire
Duane Morris LLP
1940 Route 70 East, Suite 200
Cherry Hill, New Jersey 08003

Gretchen P. Miller, Esquire
Steptoe & Johnson
1330 Connecticut Avenue, NW
Washington, DC 20036

Taras A. Gracey, Esquire
Thomas A. Rammer, II, Esquire
Steptoe & Johnson
115 S. LaSalle Street
Suite 3100
Chicago, Illinois 60603

Attorneys for Defendant/Counterclaim Plaintiff Sandoz, Inc.

Table of Contents

BUMB, United States District Judge:

I. INTRODUCTION

This matter comes before the Court upon remand from the Federal Circuit for further proceedings consistent with the Circuit's new claim construction related to U.S. Patent No. 7,524,834 (the "'834 Patent"). The '834 Patent is entitled "STERILE POWDERS AND METHODS FOR PRODUCING THE SAME," and is addressed in relevant part to sterile budesonide compositions. Plaintiffs AstraZeneca LP and AstraZeneca AB (collectively, "AstraZeneca") bring this consolidated action for patent infringement against the defendants, Breath Limited, Watson Laboratories, Inc. (collectively, "Breath/Watson"), Sandoz, Inc. ("Sandoz"), Apotex Corp., and Apotex, Inc. (collectively, "Apotex," and together with Breath/Watson and Sandoz, "Defendants"), based upon their filings of Abbreviated New Drug Applications ("ANDAs"). See ANDA Nos. 78-404, 202558 (Breath/Watson), 78-202 (Apotex), 20-1966 (Sandoz).

AstraZeneca originally alleged infringement of U.S. Patent Nos. 6,899,099 and 6,598,603. See AstraZeneca LP v. Apotex, Inc., 623 F. Supp. 2d 579 (D.N.J. 2009), aff'd, 633 F.3d 1042 (Fed. Cir. 2010). The Court found no likelihood of success on the merits of claims for infringement of U.S. Patent No. 6,899,099, and claims 29 and 30 of the '603 Patent because the patented claims were likely invalid as a matter of law as they

did not functionally alter a known product so as to create a new patentable product. Id. The Federal Circuit agreed.[1] 633 F.3d at 1065. As to the other asserted claims of the '603 Patent, the Court found – and was affirmed on appeal – that those claims were invalid as obvious under the prior art. AstraZeneca, 542 F. App'x at 978-81. The Court further found the claims invalid as anticipated by prior art. 2013 WL 1385224, at *28-32. As such, only the '834 Patent remains at issue in this protracted litigation.

The '834 Patent is also invalid as obvious. Given the Federal Circuit's broad claim construction, the Court finds that Defendants have clearly and convincingly demonstrated that the '834 Patent is invalid as obvious because a POSA, whom the parties agree was motivated to prepare a sterile budesonide composition, would have had a reasonable expectation of successfully doing so using the well-known techniques of sterile filtration/aseptic recrystallization, moist heat sterilization, ethylene oxide sterilization, or irradiation.[2] Accordingly, the Court enters judgment against Plaintiffs and in favor of

[1] The Court subsequently dismissed these claims without prejudice. See AstraZeneca LP v. Breath Ltd., No. 08-1512, 2013 WL 1385224, at *1 n.2 (D.N.J. April 3, 2013), overruled on other grounds, 542 F. App'x 971 (Fed. Cir. 2013).

[2] The Court rejects Defendants' invalidity arguments based upon anticipation, as well as lack of enablement and written description, for the reasons below.

Defendants. This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Rule 52(a).

II. BACKGROUND

A. The Asserted Claims of the '834 Patent

Claims 1 and 50 of the '834 Patent, the independent claims at issue, teach a powder and suspension, respectively, comprising a "micronized powder composition." Specifically, claim 1 recites:

> A pharmaceutically acceptable, micronized powder composition at least 98.5% by weight of which is pure budesonide or an ester, acetal or salt thereof, wherein the composition meets the criteria of sterility according to the US Pharmacopoeia [sic] 23/NF18, 1995, pages 1686-1690 and 1963-1975.

'834 Patent col.11 ll.48-52 (emphasis added). Claim 50 recites:

> A pharmaceutically acceptable suspension consisting of a micronized powder composition at least 98.5% by weight of which is pure budesonide or an ester, acetal or salt thereof, suspended in an aqueous solution, wherein the suspension meets the criteria of sterility according to the US Pharmacopoeia [sic] 23/NF18, 1995, pages 1686-1690 and 1963-1975.

'834 Patent col.13 ll.54-60 (emphasis added). The dependent claims – claims 2 and 51 – include the additional limitation that 98.5% of the "micronized powder composition" is pure budesonide. '834 Patent col.11 ll.53-54 & col.13 ll.61-63.

B. Markman Hearing

After the Markman hearing, this Court construed "micronized powder composition" as a product-by-process claim, to mean "heat-sterilized finely divided dry particles." See

AstraZeneca, 2013 WL 1385224, at *43. The trial thus focused on AstraZeneca's heat sterilization process, for which AstraZeneca has another patent that is not at issue in this case.[3] See U.S. Patent No. 6,392,036.

C. Federal Circuit Decision

On appeal, the Federal Circuit reversed this Court's claim construction, construing the disputed term "micronized powder composition" to mean "finely divided dry particles" ***without requiring any particular process for sterilizing the particles***. AstraZeneca, 542 F. App'x at 976-78. In light of the broadened claim construction, much of the remand proceedings centered on what was known in the art regarding the five conventional sterilization techniques. Defendants contend that now that AstraZeneca successfully obtained a broader claim construction not limited to a particular process, the so-construed patent is vulnerable to invalidity challenges based upon a significantly greater selection of prior art. See Sandoz Br., Docket No. 908, at 1, 8 ("AstraZeneca paid a steep price for its victory in the Federal Circuit.").

D. Remand Proceedings

On remand, the parties argued that additional claim terms required construction. As to these terms, the Court concluded

[3] As such, the evidence and testimony adduced in the first trial must be viewed through this prism.

that "pharmaceutically acceptable" means what the parties have always agreed – "acceptable for administration as a pharmaceutical." Docket No. 980 at 22 (citing Joint Claim Construction Chart, Docket No. 93; AstraZeneca's Preliminary Claim Constructions to Breath for the '834 Patent, Declaration of Heinz J. Salmen, Docket No. 975, Ex. 1 at 2 ("'Pharmaceutically acceptable' requires no construction and should be accorded its plain meaning.")). The Court also concluded that, in accordance with the Federal Circuit's decision, "meets the criteria of sterility according to the US Pharmacopoeia [sic] 23/NF18, 1995, pages 1686-1690 and 1963-1975" means "sterile." See Sept. 24, 2014 Tr. 32:12-24 (citing 542 F. App'x at 973, 977).

In addition, Plaintiffs moved for a preliminary injunction on remand. In the interest of judicial efficiency and expediency, the Court consolidated the preliminary injunction hearing with the trial on the merits pursuant to Federal Rule of Civil Procedure 65(a)(2). Docket No. 980 at 43. Subsequently, the Court conducted a 13-day bench trial from October 6 through October 29, and November 17 through November 18, 2014. Upon the conclusion of the trial, the parties submitted voluminous post-trial briefing materials after which the Court held closing arguments.

E. Defendants' Sterilization Processes

In manufacturing their products, both Sandoz and Apotex use moist heat sterilization. Sandoz combines unsterile budesonide with water for injection and Polysorbate 80, a wetting agent, into a drug slurry. Sandoz then moist heat sterilizes the drug slurry at 115° C for 30 minutes. Sandoz then sonicates the drug slurry to address particle size or agglomeration issues.

Apotex's micronized budesonide starting material is a dry and nonsterile powder. Apotex prepares a concentrated budesonide slurry by mixing water for injection, polysorbate 80 (surfactant) and micronized budesonide in an appropriate vessel. The slurry is moist heat sterilized in an autoclave at 121.1° C for not less than 12 minutes.

Breath/Watson uses a filter sterilization process. The unsterile budesonide powder is dissolved in an organic solvent and then filtered through a sterilizing filter. The sterile budesonide solution is combined with water, which causes the budesonide to precipitate and crystallize into particles. See Docket No. 717 at 126-27. The particles are dried, micronized, and aseptically combined with inactive ingredients to form the final products. See Defs.' Joint Resp. to Pls.' Proposed Findings of Fact and Conclusions of Law ("DRFOF 2013"), Docket No. 673, ¶ 160.

III. LEGAL ANALYSIS

A. Asserted Claims on Remand

As the case now stands on remand, the following claim analysis applies to the independent claims:

> 1. "A pharmaceutically acceptable, [finely divided dry particles] at least 98.5% by weight . . . wherein the composition [is sterile] . . . ."
>
> 50. "A pharmaceutically acceptable suspension consisting of [finely divided dry particles] at least 98.5% by weight . . . suspended in an aqueous solution, wherein the suspension [is sterile] . . . ."

'834 Patent col.11 ll.48-52; col.13 ll.54-60. Again, the dependent claims – claims 2 and 51 – include the additional limitation that 98.5% of the "micronized powder composition" is pure budesonide. '834 Patent col.11 ll.53-54 & col.13 ll.61-63.

B. Infringement

AstraZeneca contends Defendants' submissions of their ANDAs for generic versions of Pulmicort Respules® budesonide inhalation suspension were acts of infringement of the '834 Patent. To establish infringement, AstraZeneca bears the burden of proving by a preponderance of the evidence that each element of a claim is found in the accused product. See Allen Eng'g Corp. v. Bartell Indus., Inc., 299 F.3d 1336, 1345 (Fed. Cir. 2002).

Defendants have not contested that each of the accused products meets each of the elements of the asserted claims:

(1) pharmaceutically acceptable, PFOF ¶¶ 103, 111, 118; (2) consisting of a micronized powder composition, PFOF ¶¶ 99, 104, 112, 119; (3) at least 98.5% of which is pure budesonide or an ester, acetal or salt thereof, PFOF ¶¶ 100, 105, 113, 120; and (4) suspended in an aqueous solution, PFOF ¶¶ 106, 114, 121. Prior to this Court's construction of the term "meets the criteria of sterility" as "sterile," Defendants had contested infringement because AstraZeneca had not submitted test results establishing that the accused products meet the criteria of sterility set forth in the 1995 USP. However, as each of the Defendants conceded that its accused products were "sterile," this argument is rejected. See Sept. 14, 2014 Tr. 31:02-10, 34:05-07, 34:15-20.

Accordingly, the Court finds that AstraZeneca has demonstrated infringement by a preponderance of the evidence.

C. Invalidity Defenses

As a defense to infringement, Defendants assert the following grounds for invalidity: obviousness, anticipation, lack of written description, and lack of enablement.

In addressing these arguments, the Court adopts the definition of a person of ordinary skill in the art ("POSA") that was set forth in the prior trial and agreed to by the parties:

> A person of ordinary skill in the art . . . would have

> had a medical degree with three years of experience in treating patients, particularly children with asthma, or either a doctorate or degree in pharmaceutics, chemical engineering, or a related field and three to five years of practical experience in one or more aspects of the pertinent arts, or a master's degree in pharmaceutics, chemical engineering, or a related field, and five to seven years of practical experience in one or more aspects of the pertinent arts.

2013 WL 1385224, at *10 (quoting 2012 Trial Tr. 3935:24-3936:13 (Chipps)).

1. Reduction to Practice of the Invention

The parties agree that the "critical date" of the '834 patent is November 11, 1997, one year prior to the earliest U.S. filing date to which the '834 patent can claim priority. Velander v. Garner, 348 F.3d 1359, 1363 (Fed. Cir. 2003). In an attempt to circumvent several prior art references (i.e., Leuschner and Harris), AstraZeneca has put forth evidence that it reduced its invention to practice by at least March 1997, and certainly by July 1997.[4] Heretofore, the Court has not decided this issue and thus it remains ripe for consideration.

[4] AstraZeneca also submitted a Rule 131 Declaration to the PTO to support an invention date prior to October 9, 1997, the date of the Harris publication described in detail infra. See DTX 0004 at 017761; see also 37 C.F .R. § 1.131 (Under Rule 131, "[w]hen any claim of an application . . . is rejected, the applicant or patent owner . . . may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based."). Notably, "[t]he PTO examines an applicant's affidavit for compliance with [Rule 131], but the PTO does not otherwise investigate the applicant's assertions about his invention date." Spectralytics, Inc. v.

"To antedate (or establish priority) of an invention, a party must show either an earlier reduction to practice, or an earlier conception followed by a diligent reduction to practice." See Purdue Pharma L.P. v. Boehringer Ingelheim GmbH, 237 F.3d 1359, 1365 (Fed. Cir. 2001) (citation omitted). "In order to establish an actual reduction to practice, the inventor must prove that: (1) he constructed an embodiment or performed a process that met all the limitations of the interference count; and (2) he determined that the invention would work for its intended purpose. . . . The inventor must also 'contemporaneously appreciate that the embodiment worked and that it met all the limitations of the interference count." Henkel Corp. v. Procter & Gamble Co., 560 F.3d 1286, 1289 (Fed. Cir. 2009) (citation omitted); see also Purdue Pharma, 237 F.3d at 1365-66. The patentee bears the burden of producing evidence supporting an earlier invention date but the burden of proof remains on the defendant "to establish by clear and convincing evidence that the patentee's invention date does not precede the date of the ostensible prior art reference." Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc., 585 F. Supp. 2d 568, 575-76 (D. Del. 2008) (citing Spectralytics,

---

Cordis Corp., 576 F. Supp. 2d 1030, 1043 (D. Minn. 2008) (citing Manual of Patent Examining Procedure § 715), aff'd, 485 F. App'x 437 (Fed. Cir. 2012).

576 F. Supp. 2d at 1045).[5] AstraZeneca points to laboratory reports, dated March 1997, demonstrating inter alia that heating the substance for 60 minutes at 110° C would result in more than a 7 log reduction in Bacillus subtilis spores. See PTX 1034 at 1335867; PTX 1527. Redacted versions of these laboratory reports were submitted with AstraZeneca's Rule 131 Declaration. PTX 5A. Dr. George Zhanel, an expert for AstraZeneca, and Dr. Cheryl Larrivee-Elkins, one of the named inventors on the '834

[5] Defendants have moved to strike what they characterize as new arguments, theories, and evidence concerning AstraZeneca's reduction to practice of the invention, submitted in the remand proceeding, as violative of this Court's September 24, 2014 Order. See Docket No. 1134. At that time, the Court ordered that AstraZeneca would not be permitted to submit additional evidence on reduction in practice. Sept. 24, 2014 Tr. 53:16-55:5. The Court further noted that, in the original trial, it had offered AstraZeneca the opportunity to brief the issue of whether Dr. Elkins should be permitted to testify as to "alternative" invention dates, but AstraZeneca chose not to do so Id. As AstraZeneca pointed out in its post-trial submission, Docket No. 1155, however, Defendants agreed during the September hearing that that they had "no problem with [AstraZeneca] citing to all of [the evidence from the 2012 proceeding] in the posttrial fact findings," which Defendants also intended to do. Id. at 46:21-47:5.

Although the Court has found it difficult to pin down AstraZeneca on the date by which it purports to have reduced its invention to practice, see DRFOF 2013 ¶¶ 230-31 (March 26, 1997, or June 24, 1997); Pls.' Rep. to Defs.' Joint Proposed Findings of Fact ("PRFOF"), Docket No. 1128, ¶ 4 (March or July 1997); Docket No. 1155 (March or summer 1997), the evidence AstraZeneca relies upon was largely introduced in the prior trial with the exception of testimony from Dr. Zhanel that it would be routine to create a sterile suspension using sterile powder – a fact that Defendants do not dispute. See Defs.' Joint Proposed Findings of Fact ("DFOF"), Docket No. 1109, ¶ 25. As such, the Court does not find that AstraZeneca's findings of fact are violative of its Order and thus denies Defendants' motion.

Patent, testified that a six or seven log reduction was the "standard" used to define the goal of a sterilizing process because it indicates a 1/1 million sterility assurance level. See 2012 Trial Tr. 615:2-11; id. at 4213:9-16. Dr. Zhanel further testified that a POSA would understand from the laboratory data that this experiment would result in a sterile product as it demonstrates rapid spore reduction. Id. at 4276:9-4277:16. Although Defendants' expert, Dr. Scott Sutton, testified that this data only demonstrates spore reduction and not a sterilized product, he acknowledged that he was the "wrong person to ask" how the spore reduction translated into sterility. Id. at 2463:14-18, 2465:20-23. However, while the conclusion expressed in the documents was that heating for 60 minutes at 110°C "will give" more than a 7 log reduction, PTX 1034 clearly demonstrates that the samples were not actually heated at that time and temperature. PTX 1034 at 1335866-67; cf. Purdue Pharma, 237 F.3d at 1365 ("To prove actual reduction to practice, 'an inventor must establish that he actually prepared the composition . . . ." (citing Estee Lauder Inc. v. L'Oreal, S.A., 129 F.3d 588, 592 (Fed. Cir. 1997))). Similarly, PTX 1527 provides no information regarding sterility of the heat-treated samples, and the testing conducted was not intended to even address sterility. See PTX 1527 at 1339829.

In fact, Dr. Elkins testified that the March data indicated "we were honing in on something that would be acceptable to the [FDA]," but that they had to "confirm this is real." 2012 Trial Tr. 615:19-616:1. However, their first attempts at doing so proved "unsuccessful and concerning." See id. at 617:1-4. Even as of April 23, 1997, Dr. Elkins informed others that the "microbiological validation of the cycle is not going well" and that they had been unable to replicate the earlier results. See PTX 1533 at 1350873.

The evidence suggested that by May 1997 AstraZeneca felt confident that it could produce a sterile product through dry heat sterilization in combination with aseptic processing, and had begun preparing data to update the FDA on its findings. See PTX 523 at 1336448-49; 2012 Trial Tr. 620:3-622:5 (Elkins). Soon thereafter, AstraZeneca contends that batch records show it prepared a batch of Pulmicort Respules® on May 10, 1997 that was sterile, pure, micronized, and pharmaceutically acceptable. See PTX 401 at 0321477; AstraZeneca's Proposed Findings of Fact ("PFOF"), Docket No. 1111, ¶ 83. Defendants argue that AstraZeneca presented no testimonial evidence corroborating this internal documentation, which in any event shows no analysis of the suspension was performed until the end of June.[6] See Defs.'

[6] Defendants also point to the fact that the documentation was not certified by a supervisor until October 21, 1997. See

Joint Responses to AstraZeneca's Proposed Findings of Fact ("DRFOF"), Docket No. 1127, ¶ 83. Defendants' reliance on Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1171-72 (Fed. Cir. 2006), is misplaced. There the Federal Circuit simply held that an inventor's claim to an earlier reduction in practice date must be sufficiently corroborated, not that every piece of evidence must be corroborated, as Defendants suggest here. However, the Court is inclined to agree with Defendants that, while the batch records show a budesonide suspension was manufactured on May 10, 1997, the test results demonstrating the claim limitations of sterility were not recorded until June 24, 1997, at the earliest.[7] PTX 401 at 0321473, 0321477. The analysis of the impurities and degradation products did not occur until July 9, 1997. Id. Thus, the evidence suggests that, until those tests were performed, AstraZeneca was unaware of whether it possessed a budesonide suspension that met all of the limitations of the asserted claims.

PTX 401 at 0321477. The Court does not find this to be particularly relevant as the dates of the individual analyses are provided in the batch records.

[7] AstraZeneca argued that the method code 0403.037 indicated that a USP sterility test had been performed, but there was no evidence submitted in support of that argument. However, in light of the Court's claim construction, the fact that the batch records reflect that the product must be sterile and record "SATISFACTORY" results is sufficient evidence of sterility. See PTX 401 at 321473.

Defendants also argue that, even if sufficient to demonstrate reduction in practice of the suspension, the evidence presented fails to demonstrate reduction in practice of the powder composition prior to the '834 Patent's critical date. Although the Court acknowledges the limited evidence directly confirming AstraZeneca's possession of the powder, the Court finds that Defendants have failed to demonstrate by clear and convincing evidence that AstraZeneca had not reduced its invention to practice (powder and suspension) prior to the challenged prior art references.[8]

As such, the Court finds that AstraZeneca has submitted sufficient evidence demonstrating that it reduced its invention to practice at least by July 9, 1997. See, e.g., Streck, Inc. v. Research & Diagnostic Systems, Inc., 659 F.3d 1186, 1193 (Fed. Cir. 2011) ("When testing is needed to establish that an invention worked for its intended purpose, the inventor must have recognized that the tests were successful." (citing Estee Lauder, 129 F.3d at 594-95)), cert. den'd by 132 S. Ct. 2442.

2. Obviousness

Although patents are presumed valid, an accused infringer can rebut this presumption with clear and convincing evidence of invalidity. Sciele Pharma Inc. v. Lupin Ltd., 684 F.3d 1253,

[8] This timeline could explain AstraZeneca's willingness to stipulate that the Steckel reference is prior art. See infra note 16.

1260 (Fed. Cir. 2012) (citing 35 U.S.C. § 282; Microsoft Corp. v. i4i Ltd. P'ship, -- U.S. --, 131 S. Ct. 2238, 2245 (2011)). To be clear, the burden of establishing invalidity by clear and convincing evidence remains on the party asserting invalidity. In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1078 (Fed. Cir. 2012). A patent is invalid as obvious if the differences between the claimed invention and prior art are such that the invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made. Sciele Pharma, 684 F.3d at 1259 (quoting 35 U.S.C. § 103(a)). Whether a patent claim is obvious is a question of law based on four underlying facts: 1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the prior art and the claims at issue; and (4) such secondary considerations as commercial success, long-felt but unsolved need, and the failure of others. Id. (quoting Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)); see also KSR Int'l. Co. v. Teleflex, Inc., 550 U.S. 398, 406 (2007).

Generally, this inquiry considers whether a person skilled in the art would have had (1) a reason to combine the teachings of the prior art references to achieve the claimed invention, and (2) a reasonable expectation of success in doing so. In re Cyclobenzaprine, 676 F.3d at 1068-69 (internal citations

omitted). "[O]bviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." In re O'Farrell, 853 F.2d 894, 903-04 (Fed. Cir. 1988); see also Bayer Schering Pharma AG v. Barr Labs., Inc., 575 F.3d 1341, 1350 (Fed. Cir. 2009); Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007).[9]

In KSR, the Supreme Court cautioned that this inquiry must be "expansive and flexible" and must account for the fact that a person of ordinary skill in the art is also "a person of ordinary creativity, not an automaton." Id. at 415, 421. There need not be "precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." Id. at 418.

Importantly, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." Id. at 417. Relevant to this analysis is whether there was a reason or motivation to combine

[9] To the extent AstraZeneca's experts suggest that there must be a guarantee of success, see, e.g., Trial Tr. 2314:5-2315:13, 1595:2-1596:23, 2264:1-9, this is erroneous. The key question is whether there was a reasonable expectation of success.

the known elements in the manner claimed by the patent. Id. at 418. Indeed, "[o]ne of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." Id. at 419-20. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." Id. at 420.

Finally, an invention is "obvious-to-try" and therefore invalid under 35 U.S.C. § 103 if it results from a skilled artisan merely pursuing "known options" from "a finite number of identified, predictable solutions." In re Cyclobenzaprine, 676 F.3d at 1070 (quoting KSR, 550 U.S. at 421) (internal quotations omitted).

Defendants contend that the asserted claims are obvious in light of prior art setting forth five conventional sterilization techniques, each of which Defendants assert could have been used by a POSA with a reasonable expectation of successfully obtaining the claimed products. The Court will address the prior art concerning each technique in turn. First, however, it will address whether a POSA in 1997 would have been motivated to prepare the sterilized budesonide compositions that are the subject of the asserted claims.

a. Motivation

By 1997, AstraZeneca was marketing and selling a pharmaceutically acceptable, aqueous suspension consisting of highly pure, micronized budesonide powder in Europe under the name PULMICORT®. See PULMICORT RESPULES adver., 49 Thorax: J. of British Thoracic Soc'y (April 1994), DTX 1026. It is undisputed that European Pulmicort discloses a pharmaceutically acceptable, aqueous suspension consisting of a highly pure, micronized budesonide powder composition and thus encompasses all of the elements of asserted claims 50 and 51, ***except for sterility***. See Trial Tr. 421:11-13 (Plaintiffs stipulating that European Pulmicort meets all claim limitations of claims 50 and 51 except sterility); DFOF ¶ 31. In addition, by 1997, AstraZeneca was marketing and selling Pulmicort® Turbuhaler®, a dry powder inhaler dispensing budesonide inhalation powder. DTX 694 at 0299768. Pulmicort® Turbuhaler® discloses a pharmaceutically acceptable, micronized powder composition of highly pure budesonide. PRFOF ¶ 62. Thus, the Pulmicort® Turbuhaler® discloses every element of asserted claims 1 and 2, ***except for sterility***. Because these prior arts disclosed all limitations of the asserted claims except for sterility, the

question before the Court is whether it would have been obvious to a POSA to create a ***sterilized*** budesonide composition.[10]

Defendants argue - and AstraZeneca agrees - that, by 1997, a POSA would have been motivated to prepare the sterile budesonide powder and suspension that are the subject of the asserted claims because of FDA and industry expectations, as well as sterility requirements applicable to other pharmaceutical products on the market. See Trial Tr. 795:12-19.

This is true even though the FDA proposed rule at the time dealt only with solutions. Specifically, around the time of the '834 Patent, in September 1997, the FDA had issued a proposed rule (the "Proposed Rule") requiring "that all [aqueous-based] inhalation solutions for nebulization be manufactured as sterile." DTX 872 at 018500.[11] AstraZeneca hones in on the fact that the Proposed Rule explicitly refers only to "solutions" - and not suspensions, which are the focus of the '834 Patent. However, several experts testified that POSAs understood the Proposed Rule to apply to all aqueous-based inhalation products,

[10] Defendants also contend that the International Patient Package Leaflet ("IPPL") meets all of the claim limitations, but AstraZeneca disputes this on grounds that it fails to disclose the purity of the budesonide. See Astra Draco, IPPL, PULMICORT® Suspension for Nebulisation (Aug. 18, 1994), DTX 751; PRFOF ¶ 31.

[11] The parties stipulated that the 1997 Proposed Rule, although published on September 23, 1997, is prior art. See Docket No. 701 at ¶ 177; see also infra note 16.

whether solutions or suspensions. See Trial Tr. 194:13-195:9 (Moldenhauer); 2012 Trial Tr. 2935:22-2937:25 (Miller). Moreover, Defendants introduced the testimony of Dr. Kenneth H. Muhvich, who assisted with drafting the Proposed Rule beginning in 1994. Trial Tr. 1044:1-8; 2012 Trial Tr. 2742:12-2743:14. According to Dr. Muhvich, the FDA began drafting the Proposed Rule in Spring 1994 in response to a recent case of contaminated inhalation solution products involving Copley Pharmaceuticals. 2012 Trial Tr. 2743:7-14. Dr. Muhvich testified, however, that while he used the term "solutions" in the Proposed Rule, he intended for the term to broadly cover "all aqueous-based products for nebulization, including suspensions." Trial Tr. 1044:5-15. The reason for this is that the health risks from contaminated aqueous-based inhalation products are virtually the same, regardless of whether they are solutions or suspensions. See id. at 1045:18-23, 1046:10-17.

In the FDA's Final Rule, published on May 26, 2000, the FDA required "all . . . aqueous-based drug products for oral inhalation be manufactured sterile" (the "Final Rule"). DTX 915 at 024785. Thus, the Final Rule clearly covered solutions and suspensions. During the original trial, the Court questioned Dr. Muhvich about a statement in the Final Rule in which the FDA noted "[o]ne comment [to the Proposed Rules] suggested that the rule cover inhalation suspension products, stating that they

contain more nutrients that contaminating microorganisms can metabolize than do inhalation solutions, and suggested that the title of the rule be modified to reflect this change." DTX 915 at 024786. Dr. Muhvich agreed that whoever was the commentator was not well-versed, was not paying attention, or was generally confused about whether or not the rule covered suspensions. See 2012 Trial Tr. 2772:15-24. Subsequently, during this trial, AstraZeneca submitted adequate evidence that the comment referenced in the Final Rules and discussed during Dr. Muhvich's testimony was, in fact, a letter signed by Dr. Muhvich. Accordingly, AstraZeneca contends that, in light of this discovery, Dr. Muhvich's prior testimony regarding the broad scope of the Proposed Rule has been "call[ed] into serious question" and AstraZeneca urges the Court to accord less weight to that testimony when it considers industry skepticism, see infra. The Court declines to do so.

AstraZeneca admittedly possessed the comment letter as of July 2014, but made the calculated decision not to question Dr. Muhvich about it during Dr. Muhvich's deposition in September 2014, shortly before the remand trial. When questioned as to why, AstraZeneca's counsel stated they "didn't trust the answers we would get."[12] See Trial Tr. 2845:2-4, 2851:5-10. Instead,

[12] Nor did AstraZeneca provide the comment to Defendants until after the start of the remand trial. See id. at 2845:11-

AstraZeneca asks this Court to conclude, based upon a single line of inquiry from Dr. Muhvich's 2012 testimony, that he is not a credible witness. AstraZeneca's failure to seek an explanation from Dr. Muhvich when it had an opportunity to do so precludes this Court from making such conclusion. It is clear to this Court that in 2012 when the Court questioned him, Dr. Muhvich forgot that he had authored the comment. Indeed, when questioned, he did not have before him the comment letter purportedly reflecting his signature.

In any event, the comment letter is not necessarily inconsistent with Dr. Muhvich's testimony. Dr. Muhvich has steadfastly maintained that when he drafted the FDA Proposed Rule he intended for it to cover all aqueous-based products, both solutions and suspensions, because of the contamination risks associated with such products. See 2012 Trial Tr. 2749:23-2750:9. The comment does not contradict this testimony, but instead could be viewed as an attempt merely to make this intention absolutely clear to the industry. This interpretation is borne out by the statement in the Final Rule that the agency "agrees that further clarification of products covered by the

14; Docket No. 1076. There is no evidence that Defendants were aware of the fact that Muhvich was the author of the comment prior to that time.

rule is warranted." DTX 915 at 024786 (emphasis added).[13] See further discussion infra.

Regardless, both parties' experts agree that a POSA would understand at the time of the invention that the trend in the industry was moving toward the requirement that all aqueous-based inhalation products be manufactured as sterile. See, e.g., Trial Tr. 2492:20-2495:6 (Akers);[14] id. at 432:3-10 (Myrdal); 2012 Trial Tr. 2443:21-2444:5 (Sutton); id. at 2935:4-2936:16, 2937:8-25 (Miller). This understanding is consistent with Dr. Muhvich's testimony that the FDA was publicly advising the industry by Fall 1994 that it expected all aqueous-based inhalation products, suspensions or solutions, to be sterile. 2012 Trial Tr. 2750:21-2752:13. In fact, Dr. Poochikian of the FDA instructed AstraZeneca during a pre-NDA meeting held on

[13] See also 2012 Trial Tr. 2773:13-23 ("Q. So you would agree with me that at least some amount of the public did not understand the scope of this rule, correct? A. No, I disagree with that contention. What you need to understand, clearly, is -- is that people are putting in big investment to making any drug product, and they want to make sure, absolutely sure, that if they're going to put millions of dollars into investing in a low-dosing machine or other machine that's going to make the inhalation product you're talking about, that -- that the scope of the rule is -- that they understand clearly what -- the scope of that rule and what the requirements are.").

[14] Id. at 2495:9-15 (Akers) ("I think a person of ordinary skill in the art would have read the FDA's proposed rule literally, but I think they would have understood that there was a perceived need in the industry, a perceived need for industry to supply inhalent products that where aqueous-based as sterile products. . . . Whether they were solutions or suspensions.").

November 20, 1996 that "the Division expects sterile products for both solutions and suspension for inhalation . . . ." DTX 760 at 1335702. AstraZeneca's witness, Dr. Zhanel, does not contradict this testimony. See Trial Tr. 1752:11-23 ("Q. And you heard from Ms. Moldenhauer, Doctor Miller and Mr. Zaccheo that people of ordinary skill in the art in 1997 were being told by FDA, you're going to make a suspension, you better make it sterile, you were here for that, right? A. I heard them use those words. Q. And you have no basis to disagree with that testimony, do you? A. That's what they said. My understanding is that the FDA was telling AstraZeneca, try to make this sterile. Q. Just like they were telling everybody else of ordinary skill in the art, right, about suspensions? A. I don't know what FDA was telling everybody about – I don't know what the FDA was telling everybody.").

Moreover, the testimony at trial demonstrates that there were sterile parenteral and ophthalmic products already on the market. The FDA required these products to be sterile because the manner in which they are administered, like inhaled products, permits them to "bypass the body's natural defense mechanisms" and thus contaminated versions of these products carry increased risks. See, e.g., Trial Tr. 339:4-16 (Zaccheo). As Kenneth Avis explained in "Sterile Products," a chapter

contained within The Theory of Practice and Industrial Pharmacy (Lachman et al. eds., 3d ed. 1986),

> [P]arenteral products are unique among dosage forms of drugs because they are injected through the skin or mucous membranes into internal body compartments. Thus, because they have circumvented the highly efficient first line of body defense, the skin and mucous membranes, they must be free from microbial contamination and from toxic components as well as possess an exceptionally high level of purity. All components and processes involved in the preparation of these products must be selected and designed to eliminate, as much as possible, contamination of all types, whether of physical, chemical, or microbiologic origin.
>
> Preparations for the eye, though not introduced into internal body cavities are placed in contact with tissues that are very sensitive to contamination. Therefore, similar standards are required for ophthalmic preparations.

DTX 960 at 025799. Mr. Mike Zaccheo, Defendants' expert, credibly testified that because a POSA would appreciate that suspensions and solutions inhaled directly into the lungs similarly bypass the body's defenses, a POSA would understand the benefits of making these products sterile. Trial Tr. 341:12-342:2. Thus, the Court concludes that the Proposed Rule, as well as the FDA's contemporaneous communications to AstraZeneca and other industry participants, provided POSAs with a strong motivation to prepare a sterilized budesonide composition.

b. Prior Art Sterilization Techniques

Under the current claim construction, the asserted claims are not limited to any particular sterilization method and, thus, as long as it was obvious to make the claimed product using any sterilization process, the claims are invalid as obvious. The parties agree that at the time of the '834 Patent, there were five well-known, conventional sterilization techniques for sterilizing steroids such as budesonide: (1) sterile filtration followed by aseptic crystallization; (2) moist heat; (3) dry heat; (4) ethylene oxide ("EO"); and (5) irradiation. PRFOF ¶ 8. In other words, faced with the motivation to prepare a sterilized suspension or solution, a POSA had five "tools" in her "toolbox." Trial Tr. 3407:2-4. As set forth below, each of these sterilization methods had well-known disadvantages. Yet, a POSA had within her toolbox several methods to address them.

The Court now turns to each of these known sterilization techniques. In doing so, the Court recognizes that before it can make a determination that the asserted claims are invalid as obvious, the Court must consider all of the evidence, including evidence of secondary considerations. See, e.g., In re Cyclobenzaprine, 676 F.3d at 1078. Thus, while the Court has chosen to include its discussion of the secondary considerations after its discussion of each sterilization process for

organizational purposes only, the Court has in fact considered the secondary considerations along with its consideration of the prior art as to each process.

i. **Sterile filtration/crystallization**

Defendants first argue that a POSA would have had a reasonable expectation of success in creating the claimed sterilized budesonide compositions using conventional sterile filtration/crystallization in combination with standard aseptic processing. Defendants contend that the asserted claims are invalid as obvious over any one of (a) the IPPL, European Pulmicort®, or Pulmicort® Turbuhaler® and (b) the 1994 FDA Inspection Guide, Lachman, Ansel, or Remington 1995 (and optionally Steckel or Harris).

a) 1994 FDA Inspection Guide

In July 1994, the FDA issued guidelines for use by its inspectors when examining manufacturers of bulk drug substances. DTX 1000. Entitled "Guides to Inspections of Sterile Drug Substance Manufacturers", the guide set forth:

> In the preparation for a sterile bulk drug substance inspection, a flow chart with the major processing steps should be obtained. Generally, the manufacture of a sterile bulk substance usually includes the following steps:
>
> 1. Conversion of the non-sterile drug substance to the sterile form by dissolving in a solvent, sterilization of the solution by filtration and collection in a sterilized reactor (crystallizer).

2. Aseptic precipitation or crystallization of the sterile drug substance in the sterile reactor.

3. Aseptic isolation of the sterile substance by centrifugation or filtration.

4. Aseptic drying, milling and blending of the sterile substance.

5. Aseptic sampling and packaging the drug substance.

These operations should be performed in closed systems, with minimal operator handling. Any aseptic operations performed by an operators[] [sic] other than in a closed system should be identified and carefully reviewed.

DTX 1000 at 029003. As written, the FDA Inspection Guide described the "usual" steps for sterile filtration/crystallization: (1) dissolving a nonsterile substance in an appropriate solvent to create a solution and filter-sterilizing the solution; (2) aseptic precipitation or crystallization; (3) aseptic isolation of the sterile substance by centrifugation or filtration; (4) aseptic drying, milling and blending; and (5) aseptic sampling and packing. DFOF ¶ 11. Moreover, the FDA Guide explicitly recognized that sterile filtration in combination with aseptic processing was routinely used to produce sterile products by 1997.

Defendants introduced evidence that a POSA would have had a reasonable expectation of successfully preparing the claimed sterilized budesonide compositions in the asserted claims by following each of the "usual" steps set forth in the 1994 FDA

Inspection Guide (and other prior arts discussed herein). Defendants presented considerable and convincing testimony that, by 1997, a POSA who wanted to make sterile budesonide would know to start with highly pure, pharmaceutically acceptable budesonide. DFOF ¶ 19. In fact, highly pure budesonide of pharmaceutical grade – and therefore acceptable for administration as a pharmaceutical - was commercially available by 1997. DFOF ¶ 20.

As to Step 1 of the FDA Inspection Guide, both parties' experts agreed that a POSA would know that budesonide was "readily soluble in a variety of organic solvents" under conditions that were well-known to a POSA by 1997. Trial Tr. 1678:3-11 (Zhanel); id. at 371:12-22 (Zaccheo); see also PRFOF ¶ 16. For example, U.S. Patent No. 5,556,964, entitled "Process for the Manufacture of Budesonide," was issued September 17, 1996 to Robert G. Hofstraat et al. ("Hofstraat"), and describes a process in which crude budesonide is dissolved in methanol at about 60°C and then filtered through a closed filter. DTX 892 at col.2 ll.28-30. The experts also agreed that a POSA would know to pass the nonsterile budesonide solution through a 0.2 micron sterilizing filter, which would exclude all microorganisms, dead or alive, as well as any matter larger than the 0.2 pore size. See, e.g., Trial Tr. 334:13-335:3 (Zaccheo); id. at 1680:5-16, 1673:22-1674:15 (Zhanel); see also PRFOF ¶ 17.

Indeed, as Dr. Zhanel testified, a POSA in 1997 would have known that solutions could be readily filter-sterilized. Trial Tr. 1673:14-21.

Regarding Step 2 of the FDA Inspection Guide process, Hofstraat further discloses that a POSA could recrystallize the budesonide out of the solution and obtain pure budesonide with an isomer ratio of 1:1. DTX 892 at col.2 ll.45-51; see also Trial Tr. 1679:19-1680:16 (Zhanel). Hofstraat explained this could be done by adding an antisolvent, water, for injection through the same sterilization filter. See DTX 892 at col.2 ll.45-51; Trial Tr. 373:6-12 (Zaccheo). These reactions could take place as part of a closed system in a sterile reactor, which provides aseptic conditions, as suggested by the FDA Guide.[15] DTX 1000 at 029003; see also Trial Tr. 375:4-10 (Zaccheo) (testifying that a POSA would know to carry out steps under aseptic conditions). In addition, a June 13, 1997 article, entitled "Micronizing of steroids for pulmonary delivery by supercritical carbon dioxide," written by H. Steckel[16] et al. ("Steckel"), and published in the International

[15] Other prior art references also recognize the need and availability of a closed system for aseptic processing, particularly in the context of crystallization. DTX 986 at 028821; DTX 865 at 018418 (referring to crystallization in a "sterilized pressure vessel").

[16] The parties stipulated that Steckel is prior art under 35 U.S.C. § 102(b). Docket No. 701 at ¶ 179; see also Docket No. 1068-1 at 1 (incorporating by reference earlier stipulations of

Journal of Pharmaceutics, taught that budesonide could be dissolved in an organic solvent and crystallized into finely-divided dry particles without affecting the purity and morphology of the budesonide. DTX 871 at 018486, 018496; PRFOF ¶ 68.

AstraZeneca disputes that Steckel discloses pharmaceutically acceptable, micronized budesonide with purity greater than 99%. See PRFOF ¶ 40. This is unfounded. Indeed, Dr. Zhanel, AstraZeneca's witness, conceded his understanding of Steckel to be "using pharmaceutical grade budesonide of over 99 percent purity."

> Q. So what Steckel found or what Steckel informed the skilled person is that when he took his steroids of Budesonide, dissolved them in organic solvent like methanol, treated them with supercritical carbon dioxide and micronized them and then recrystallized them back out, he found no decomposition in purity, correct?
>
> And I'm referring to the conclusions on page 11 of 14 of DTX 871.
>
> A. Correct.

Trial Tr. 1667:2-10. Other AstraZeneca witnesses agreed with Dr. Zhanel. See Trial Tr. 2319:10-23 (Akers) ("Q. And the budesonide they were working with was pharmaceutical grade 99

---

fact). That stipulation is binding. Roberts v. Biancamano, No. 09-6212, 2013 WL 775708, at *4 (D.N.J. Feb. 27, 2013) ("Factual assertions in pretrial orders are generally considered judicial admissions, conclusively binding on the party who made them." (citation omitted)).

percent pure, correct? A. Correct."); 2012 Trial Tr. 3792:6-15 (Williams) ("Q. Now look at Page BREATH(Bud) 18492 [of DTX 871], the right column, under materials. What does this portion of Steckel say with respect to the purity of the corticosteroids? A. So here, this is Steckel describing what they used, and it says the steroids listed in Table 2 were used for the experiments. All of them were of pharmaceutical grade with a content of active ingredient greater than 99 percent. So that [] would be understood by a skilled person to mean that the materials that Steckel started with, that they ordered and got in, had a 99 percent or greater purity."). Moreover, Dr. Robert O. Williams, III, agreed that Steckel teaches methods for micronization, or reducing particle size, of steroids. See Trial Tr. 2819:23-2820:10 (Williams) ("Q. Can we refer to this as the Steckel reference? A. I'll understand that. Q. The methods for reducing particle size by supercritical carbon dioxide that are described in Steckel, are those consistent with the methods that you're familiar with? A. I'm familiar with this method. Q. Okay. Any reason to believe that the authors of Steckel were unable to achieve the particle size, the micronized particle size that they claimed to achieve in this publication? A. No, I accept what -- I know Bern Muller who's

the senior – he's the professor in Germany. I accept these results."); see also 2012 Trial Tr. 3791:16-19 (Williams).[17]

The evidence also demonstrated that Step 3 of the FDA Inspection Guide, aseptic isolation of the sterile substance, and Step 4, aseptic drying, milling,[18] and blending, were "routine" processes used by POSAs at the time of the '834 Patent. See, e.g., Trial Tr. 378:2-9 (Zaccheo); DFOF ¶¶ 170-71. Even AstraZeneca's expert, Dr. James Akers, acknowledged that a POSA would know how to dry, mill, and blend budesonide to form a finely-divided, dry budesonide powder. See Trial Tr. 2262:17-21. And, other prior art references explained how this could be done aseptically. See DFOF ¶ 171. For example, Dr. Michael J. Akers[19] et al. disclosed in a 1997 publication that the dried sterile drug substance is aseptically discharged into suitable bulk containers or to the milling unit. DTX 986 at 028822. Dr. Michael Akers further disclosed the necessity of designing the

[17] AstraZeneca further disputes the testimony of Mr. Zaccheo and Dr. Myrdal that Steckel discloses the appropriate budesonide solvent conditions for a sterile filtration process. See PRFOF ¶ 41. Yet, AstraZeneca's own witness, Dr. Williams, testified that a POSA "would know how to design the studies to look at -- in finding a -- if that was possible for Budesonide and dichloromethane, a compatible filter to pass the solution through." See Trial Tr. 2823:6-9.

[18] A POSA would understand milling as "the mechanical reduction in particle size" used to achieve the desired particle range. Trial Tr. 379:19-24 (Zaccheo).

[19] Dr. Michael Akers, author of several prior art references cited by the parties, is not related to Dr. James Akers, AstraZeneca's expert.

overall sterilization process to account for aseptic filling to minimize product exposure and thus contamination risks. See id.; see also DTX 988 at col.22 ll.38-39 (describing sterile micronization of sterile drug crystals); Trial Tr. 380:15-18.

As for sterile suspensions, the parties agree that as of 1997, "it was a matter of routine for a POSA to create a sterile, pharmaceutically acceptable, suspension of micronized budesonide when starting with sterile, micronized budesonide powder." PFOF ¶ 84; see also DFOF ¶ 25.[20]

Based upon the above evidence, Mr. Zaccheo credibly opined that, by following the typical sterilization steps laid out in the 1994 FDA Inspection Guide, a POSA would have a reasonable expectation of successfully preparing a sterile budesonide composition (powder and suspension). Trial Tr. 381:3-6.

b) Lachman: The Theory and Practice of Industrial Pharmacy (1986)

Mr. Zaccheo also opined that it would have been obvious to a POSA in 1997 how to prepare the sterile compositions in the asserted claims (both powder and suspension) based upon the

[20] In another article by Dr. Michael Akers, he explains the two basic methods for preparing parenteral suspensions: "(1) sterile powder and vehicle are combined aseptically, or (2) sterile solutions are combined and the crystals are formed in situ." DTX 862 at 018395; see also DTX 2093 at 030999 (Ansel also disclosed the preparation of sterile suspensions by combining a fine powder drug substance with an insoluble liquid, while recognizing that pre-sterilization of the individual components and aseptic filling may be necessary); DTX 2351 at 028998; DTX 962 at 025870.

teachings of Lachman. Published in 1986, Lachman taught that sterile filtration was the "method of choice" for heat-labile, or heat sensitive, substances and is often "an ideal technique." Specifically, Lachman stated:

> Filtration is frequently the method of choice for sterilization of solutions that are chemically or physically unstable under heating conditions. In many applications, ***sterile filtration*** is an ideal technique. Sterile filtration of liquids and gases is commonly used in the pharmaceutical industry. Final product solutions or vehicles for suspensions are sterile-filtered prior to an aseptic filling process. Sterile filtration of bulk drug solution prior to an aseptic crystallization process eliminates the possibility of organisms being occluded within crystals.

DTX 960 at 025756.

Lachman went on to explain that aseptic processing was routine after sterile filtration.

In 1997, there were two methods of manufacturing sterile products: terminal sterilization or aseptic processing from sterilized components. Trial Tr. 336:20-337:5 (Zaccheo). Terminal sterilization refers to a process by which a pharmaceutical product is prepared under clean conditions and sealed in its final container, which is then subjected to a sterilization process. Trial Tr. 335:4-14 (Zaccheo); DTX 2105 at 5000006. It is "terminal" because there are no further steps that need to be undertaken. Trial Tr. 335:4-14 (Zaccheo). Aseptic processing, on the other hand, "involves the filling or

assembly of presterilized drug products under aseptic conditions into presterilized containers." DTX 2105 at 500005. Aseptic conditions refers to "the absence of living organisms." Trial Tr. 336:5 (Zaccheo). Because sterile filtration can only be conducted on solutions, it cannot be a terminal sterilization process for a suspension; in other words, there are subsequent steps that must be conducted under aseptic conditions to achieve a sterile suspension. Id. at 335:4-14 (Zaccheo). As Lachman explained:

> **Aseptic Processing.** Sterilization of a solution by filtration provides an extremely clean solution, removing dirt particles as well as microorganisms in the micron size range. After sterilization, however, the filtrate must be transferred from the receiver and subdivided into the individual final containers. The objective of this process, known as ***aseptic processing***, is to exclude every microorganism from all steps of the process subsequent to filtration. Accomplishing this requires a rigidly controlled aseptic environment and technique. The difficulty of maintaining such an aseptic condition is the greatest problem associated with sterilization by filtration; however, for solutions that are adversely affected by heat, this may be the only way in which sterilization can be accomplished.
>
> ***Aseptic processing is technically not a sterilization process, but is mentioned here because of its close involvement with sterilization by filtration. It is used for products that cannot be terminally sterilized, that is, sterilized after they have been sealed in the final container.***

DTX 960 at 025793-94 (emphasis added); see also Trial Tr. 350:1-4 (Zaccheo).

Motivated to produce a sterilized budesonide product – powder, solution or suspension - a POSA also understood from Lachman (and other "Bibles in sterility")[21] that routine optimization of a sterilization process would be necessary depending upon the specific characteristics of the substance or product to be sterilized. Lachman (and others) taught "to arrive at a safe process for any particular material it becomes a compromise between the ideal process and the practical process" and that within each process there would be a range of operating parameters that can be used . . . ." Trial Tr. 345:19-25 (Zaccheo). As Mr. Zaccheo testified, the process of determining what constitutes "an optimized process" is just "simple routine process optimization with the characteristics of the product in view." Id. at 346:2-3.

Mr. Zaccheo credibly testified that, while Lachman recognized the difficulty of maintaining a completely aseptic environment, a POSA would not have been discouraged from using sterile filtration as a sterilization technique for budesonide. This is so, Mr. Zaccheo explained, because POSAs were aware of the availability at that time of facilities and equipment that could be used to create an aseptic environment. See id. at

[21] Dr. Zhanel testified that these treatises are the bibles in sterility: "So our Bibles in sterility are the Remingtons, the Lachmans, the Ansels. I was educated from all of them." Trial Tr. 1293:25-1294:1.

350:16-351:5. Indeed, the 1994 FDA Guide discussed above illustrates Mr. Zaccheo's point. The Guide described such facilities and equipment and advised its inspectors how to identify problem areas during an inspection to eliminate risks associated with contamination. See, e.g., DTX 1000 at 029004-06. For example, the FDA Guide advised that if any processes occurred outside of a "closed system" then they must be identified and carefully reviewed. Id. at 029003. Therefore, as Mr. Zaccheo testified, POSAs would have realized that closed systems for use in aseptic processing were available at least as of the time when the FDA was advocating their use in sterilization processes in 1994. See Trial Tr. 377:11-15.

Moreover, Lachman recognized that the use of aseptic processing in conjunction with other sterilization techniques may be the only viable means of producing certain pharmaceutical products. DTX 960 at 025794. If it was well-known that certain pharmaceutical products could only be sterilized in this fashion, then the equipment and facilities necessary to accomplish it must have been available at that time. See also Trial Tr. 375:16-25 (Zaccheo).

c) Ansel: Pharmaceutical Dosage Forms and Drug Delivery Systems (1995)

Defendants also rely upon Ansel, a 1995 publication that reinforced the advantages of sterile filtration for heat-

sensitive compounds like budesonide. See Trial Tr. 353:20-354:14. Ansel stated:

> Sterilization by filtration, which depends upon the physical removal of microorganisms by absorption on the filter medium or by a sieving mechanism, is used for the sterilization of heat-sensitive solutions. . . .
>
> Commercially available filters are produced with a variety of pore-size specifications. . . .
>
> The major advantages of bacterial filtration include its speed in the filtration of small quantities of solution, its ability to sterilize effectively thermobile materials, the relatively inexpensive equipment required, and the complete removal of living and dead microorganisms as well as other particulate matter from the solution. One serious disadvantage to the use of bacterial filters is the possibility of a flaw in the construction of the filter and thus some uncertainty of sterility, a circumstance not true of methods involving dry- or moist-heat sterilization in which the procedures are just about guaranteed to give effective sterilization. Also, filtration of large volumes of liquids would require more time, particularly if the liquid were viscous, than would, say, steam sterilization. In essence, the bacterial filters are useful when heat cannot be used and also for small volumes of liquids.

DTX 2093 at 030995-96.

Ansel also discussed the use of aseptic processing in combination with sterile filtration and other sterilization methods:

> In the preparation of parenteral solutions, the required ingredients are dissolved according to good pharmaceutical practice either in water for injections, in one of the alternate solvents, or in a combination of solvents. The solutions are then usually filtered until sparkling clear through a membrane-type filter. After filtration, the solution

> is transferred as rapidly as possible and with the least possible exposure into the final containers. The product is then sterilized, preferably by autoclaving, and samples of the finished product are tested for sterility and pyrogens. In instances in which sterilization by autoclaving is impractical due to the nature of the ingredients, the individual components of the preparation that are heat or moisture labile may be sterilized by other appropriate means and added aseptically to the sterilized solvent or to a sterile solution of all of the other components sterilizable by autoclaving.

DTX 2093 at 030999. Armed with the knowledge that budesonide is a heat-sensitive compound, a POSA would have been persuaded to try sterile filtration followed by aseptic processing as suggested by Ansel (and Lachman).

Ansel also confirms that it would have been a matter of routine for a POSA to create a sterile suspension from a sterile micronized budesonide powder. Ansel specifically disclosed the preparation of sterile suspensions for parenteral use and the necessity of utilizing aseptic processing techniques in these preparations. According to Ansel,

> Suspensions of drugs intended for parenteral use may be prepared by reducing the drug to a very fine powder with a ball mill, micronizer, colloid mill, or other appropriate equipment and then suspending the material in a liquid in which it is insoluble. It is frequently necessary to sterilize separately the individual components of a suspension before combining them, as frequently the integrity of a suspension is destroyed by autoclaving.

DTX 2093 at 030999.

d) Remington: The Science and Pharmacy (1995)

The Science and Pharmacy was published by Remington in 1995 ("Remington") and, as with Lachman and Ansel, addressed the five conventional sterilization techniques. DTX 2351 at 028980. Like Lachman, Remington also taught that sterile filtration is "one of the oldest methods" and also "the method of choice for solutions that are unstable to other types of sterilizing processes." Id. at 028994 ("Over the past 30 years, membrane filters have become the method of choice for the sterilization of heat-labile sterile products."). Significantly, Remington discusses the use of sterile filtration to remove bacteria from steroids in organic vehicles followed by aseptic crystallization. Id. Remington recognizes that "aseptic processing is a technique frequently used in the compounding of prescriptions or commercial products that will not withstand sterilization but in which all of the ingredients are sterile." Id. at 028998. He further suggests the use of laminar-airflow devices or barrier technology to ensure aseptic conditions. Id.

e) Harris: U.S. Patent No. 6,187,765 (1997)

Although U.S. Patent No. 6,187,765, entitled "Mometasone Furoate Suspensions for Nebulization," provisional app. dated Oct. 9, 1997, issued to David Harris et al. ("Harris"), is not deemed prior art under this Court's holding that AstraZeneca reduced its invention to practice prior to Harris' publication

date, Defendants contend that Harris may still be considered by the Court as contemporaneous art that confirms a POSA's reasonable expectation of success. The Court agrees with Defendants that, while Harris is not deemed prior art, it is still relevant to the Court's analysis of a POSA's understanding at the time of the invention. See, e.g., Netscape Comm'ns Corp. v. ValueClick, Inc., 707 F. Supp. 2d 640, 655 (E.D. Va. 2010) ("Although the Levergood patents and the Kristol, Holtman, and Behlendorf proposals are excluded from the content of the prior art, these references may yet be relevant to a different factual predicate under Graham, namely the characteristics and understanding of an individual of ordinary skill in the art at the time of invention. In this regard, the Federal Circuit has long held that 'evidence adduced in support of the § 102 defenses . . . can be probative on the issue of the level of skill in the pertinent art [under § 103] even if it be considered inadequate to establish the existence of a § 102 defense."); see also Ecolochem, Inc. v. Southern Cal. Edison Co., 227 F.3d 1361, 1379 (Fed. Cir. 2000) ("The fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art.").

Example 1 of Harris is directed to a method of preparing a "[s]terile mometasone furoate monohydrate" (a

glucocorticosteroid like budesonide) using a sterile filtration process. DTX 971 at col.6 11.26-62. Example 2 teaches how to create a sterile suspension using the sterile mometasone of Example 1. Id. at col.6 1.65 to col.7 1.40. Harris thus discloses a nebulized aqueous suspension of a micronized corticosteroid for use in treating disorders of the lower airway (i.e., pharmaceutically acceptable). Id. at col.1 11.10-30, 37-42.

In its June 4, 2014 Opinion, the Court held that the '834 Patent appeared vulnerable to a validity challenge in light of the teachings of Harris. Docket No. 980 at 35-39. In a nutshell, the Court viewed Harris to be a step-by-step procedure on how to prepare a pharmaceutically acceptable, sterile corticosteroid suspension, similar to the process contained in the FDA's 1994 Inspection Guide but with more detailed steps. Indeed, a chart prepared by Defendants demonstrates the similarities among the 1994 FDA Inspection Guide, Harris, and a prior art publication by AstraZeneca's expert, Dr. Akers:

1994 FDA Inspection Guide ("usually")	Harris (1997) Example 1	Akers & Agalloco[22] (1993) ("typically")
Step 1: Conversion of the nonsterile drug substance to the sterile form by dissolving in a solvent, sterilization of the solution by filtration and collection in a sterilized reactor (crystallizer).	(1) Dissolve mometasone furoate in acetone (organic solvent), mix to form a clear solution; (2) Pump solution through a sterilizing filter into sterile precipitation vessel;	**Step 1**: Sterile filtration
Step 2: Aseptic precipitation or crystallization of the sterile drug substance in the sterile reactor.	(3)-(4) add sterile purified water; maintain temperature (45-50° C); stir (5)-(6) maintain stirring and temperature, precipitate will begin to form; add sterile purified water (6)-(8) stir, cool to ambient temperature	**Step 2:** Crystallization (carried out under sterile conditions)
Step 3: Aseptic isolation of the sterile substance by centrifugation or filtration	(9) filter the precipitate and wash with sterile purified water;	**Step 3:** Filtration (carried out under sterile conditions)
Step 4: Aseptic drying, milling and blending of the sterile substance.	(10) dry in vacuum oven (30-35° C), 12-24 hours Final product is dried mometasone furoate monohydrate; milling/micronization (Example 2)	**Step 4:** Washing, drying, milling and blending (carried out under sterile conditions)

See Watson Closing Slide 42. Harris thus confirms that a POSA would have had a reasonable expectation of successfully creating the claimed sterile budesonide compositions using sterile

[22] James Akers & James Agalloco, Validation of Sterilization Processes and Sterile Products, in 3 PHARMACEUTICAL DOSAGE FORMS: PARENTERAL MEDICATIONS, at 231 (Leon Lachman et al., eds., 1993).

filtration/aseptic crystallization in combination with aseptic processing.

AstraZeneca argues, however, that if Harris is not deemed prior art,[23] then "the message from Harris must be it is considered inventive," Trial Tr. 3496:12-13 (counsel), and "stands for . . . the belief in the industry that achieving a sterile corticosteroid suspension . . . is novel and non-obviousness . . . ." Id. at 3501:15-18. The record contains no evidence to support AstraZeneca's argument, however, as nowhere in the patent does Harris assert that sterile filtration followed by aseptic crystallization is a novel and nonobvious process.

Nor does Harris claim a sterile product. Although Harris discloses the preparation of a sterile product, made by following the steps of the FDA's 1994 Inspection Guide, Harris does not claim a sterile product but a "nebulizer suspension" without mention of sterility.[24] Thus, the "message" to be

[23] Ironically, AstraZeneca argues that if it is prior art, a POSA would not have expected success using Harris because it contained no process simulation data that allowed a POSA to credit Harris' claim to sterility. Pls.' Resp. Br. 17-19. Counsel argued, "The Harris patent is like this isolated ship that has no data in it, it just sits there . . . ." Trial Tr. 3501:3-5. Yet, if it is not prior art, then AstraZeneca argues it is novel.

[24] The record was not developed as to the invented product. At most, Mr. Zaccheo testified that it was a nebulizer suspension consisting of mometasone furoate monohydrate which

deduced from Harris can only be that it was obvious that a sterile corticosteroid product could be produced from a well-known sterile filtration/aseptic crystallization process. AstraZeneca's contention that Harris confirms that achieving such a sterile corticosteroid suspension in 1997 was novel is belied by the simple fact that Harris does not claim a sterile product.

The above evidence clearly and convincingly demonstrated that in 1997 sterile filtration was considered the "method of choice" for sterilizing heat-labile or heat sensitive pharmaceutical products such as budesonide, see DFOF ¶ 14, and it had been in use for more than 30 years at the time of the '834 Patent. For this reason, a POSA would have been motivated to use this method to sterilize budesonide. See Trial Tr. 333:12-17 (Zaccheo).

Moreover, the Court is persuaded by Mr. Zaccheo's testimony that a POSA in 1997 would have been able to routinely optimize the usual steps set forth in the 1994 FDA Inspection Guide to create a sterile form of the pharmaceutically acceptable, highly pure, micronized budesonide compositions available as European Pulmicort® or Pulmicort® Turbuhaler® with a reasonable

---

"could have been a brilliant invention from a product point of view." Trial Tr. 404:6-11.

expectation of success. This is so because a POSA knew the appropriate solvent conditions for budesonide and routinely employed sterile filtration, crystallization, and micronization techniques as set forth in the 1994 Guide. Once a sterile powder had been obtained, it would have been a routine process to create the suspension. PFOF ¶ 84; see also DFOF ¶ 25.

Although preparation of a sterile micronized budesonide composition requires a POSA to conduct several steps subsequent to the sterile filtration of the budesonide solution (e.g., micronization/milling, combination with solvent to create suspension), the evidence conclusively demonstrates that a POSA would understand that those steps should and could be conducted in an aseptic environment. See, e.g., Trial Tr. 2563:1-8 (Zaccheo) ("Q. Would a person of ordinary skill in the art be able to conduct the crystallization step described in Hofstraat under aseptic conditions in 1997? A. Yes, they would. Especially as part of a closed system. THE COURT: I'm sorry, especially -- THE WITNESS: As part of a closed system. Q. Without undue experimentation? A. Yes."); id. at 2561:22-25 (Zaccheo) ("Q. Mr. Zaccheo, would this type of closed system crystallization technology be available to a person of ordinary skill in the art in 1997? A. Yes, it would."). Indeed, as of 1997, aseptic processing techniques were widely-used in the preparation of pharmaceutical products, as even AstraZeneca

recognized in 1997, though it has now retreated from such concession. See PTX 523 ("[O]ur efforts were directed to the possibility of sterilizing all components of the drug product prior to final mixing of the suspension and proceeding with the manufacturing method under aseptic conditions."). Although some of the prior art (such as Lachman) acknowledged contamination risks associated with aseptic processing, the Court is persuaded by the testimony that a POSA in 1997 could routinely optimize the usual processing steps and all of the relevant materials, equipment, and procedures necessary to do so were known and available in 1997.

AstraZeneca's response to Defendants' evidence actually serves to confirm this Court's obviousness finding. Importantly, AstraZeneca does not dispute that sterile filtration was a known sterilization process. Nor does it dispute that a POSA had a reasonable expectation of successfully performing a sterile filtration of a budesonide solution. Trial Tr. 2284:16-20 (Akers) ("Q. And I think we agreed the sterilization step, you have no problem with that, the skilled person could reasonably expect success in performing a sterile filtration of the budesonide solution, correct? A. They could reasonably expect success . . . ."). And their own witness, Dr. Akers, agreed that the steps in the 1994 FDA Inspection Guide were typical in 1997. See PTX 2110 at 54 ("The preparation of

sterile solids typically includes a sterile filtration, followed by crystallization, filtration, washing, drying, milling, and blending, all of which are carried out under sterile conditions."); see also chart supra. As he testified:

> Q. Now, you called these steps typical in PTX-2110 because skilled persons were in fact performing them in the field, correct?
>
> A. There's no dispute from me that people were making sterile drug substances aseptically and that they needed to be validated at the time that Mr. Agalloco and I wrote this chapter, that's the purpose of writing it.
>
> Q. And skilled persons were in fact performing filtration and aseptic crystallization steps, correct?
>
> A. Yes. And some of them no doubt were skilled.

Trial Tr. 2299:12-21.

Rather, AstraZeneca attempts to salvage the '834 Patent by claiming that the use of sterile filtration in combination with aseptic processing involved technical capabilities and equipment that were not available to a POSA in 1997. Specifically, it avers, the necessary sophisticated equipment, such as isolators, was not available. See Trial Tr. 2242:4-16 (Akers). AstraZeneca also argues, the "very significant" likelihood of contamination eliminated any reasonable expectation of success with the process.[25] In support, AstraZeneca cites to the FDA's

[25] In addition, AstraZeneca supplements its argument with the fact that sterile filtration in combination with aseptic processing is at the bottom of certain decision trees. See Trial Tr. 397:4-21 (Zaccheo); Trial Tr. 2211:3-2215:25 (Akers).

1991 proposed rule entitled "Use of Aseptic Processing and Terminal Sterilization in the Preparation of Sterile Pharmaceuticals for Human and Veterinary Use" (the "1991 Proposed Rule"). DTX 2105 ("there is a substantial likelihood that at least some drug products will be microbiologically contaminated"). In essence, AstraZeneca argues that a POSA had no reasonable expectation of successfully preparing a sterilized micronized budesonide product using known and routine processes (i.e., sterile filtration and aseptic processing) because this particular drug substance (i.e., budesonide) required a POSA to employ several known and routine processes after the sterile filtration step and a POSA would understand that when these processes were conducted aseptically it could yield a contaminated drug product 1 out of every 1000 times the POSA followed the routine and well-known steps.

The FDA's 1991 Proposed Rule, which was never implemented and dealt with terminal sterilization, is of limited value. Although there is a risk of contamination, Dr. Akers acknowledged that aseptic processing could be done:

Thus, it contends that this evidences demonstrates that a POSA would be further dissuaded from using sterile filtration. This evidence is not persuasive. As Dr. Akers testified, this decision tree merely provides a "framework for an organization that is developing sterile processes for a new drug to follow with respect to selecting the appropriate technology for the manufacture of that product." Trial Tr. 2215:19-22 (Akers).

> Q. Just a couple questions about this. Now, does the patent-at-issue here, the '834 patent, speak only to, using the words here, large scale manufacturing?
>
> A. No.
>
> Q. So it could be -- it could be producing the materials in a laboratory?
>
> A. It could be.
>
> Q. But why do you find this of relevance to the opinions you are offering about sterile filtration and recrystallization and aseptic processing?
>
> A. Well, I think that whether you were doing this at the laboratory scale or a larger scale, these are complex manufacturing steps that would have required some form of human intervention, and human intervention and aseptic processing is directly associated with risk.

Trial Tr. 2218:12-2219:1. But, Dr. Akers went on to explain that a POSA could create a sterile product in a closed system as long as there was no equipment malfunction:

> Q. Assuming no minor equipment malfunctions, and that the skilled person performs the steps properly, in a closed system, the result of an aseptic crystallization, drying, milling, will be a sterile product, correct?
>
> A. I'm going to stipulate that a closed system means that there's no opportunity or requirement for human intervention.

Trial Tr. 2316:8-13; see also id. at 2315:14-21 (Akers) ("Q. So the skilled person, following the proper procedure in 1997, using a closed system, could adequately perform an aseptic crystallization, aseptic isolation, aseptic milling, correct? A. Even then, there would be -- there would be risk, because

any time we do aseptic processing, it only requires a minor mistake, a minor miscue, a minor equipment malfunction, in order to lose the integrity required to retain asepsis.").

Dr. James Akers further explained the challenges presented by aseptic processing set forth in a 1987 article by Dr. Michael Akers entitled, "Formulation Design and Development of Parenteral suspensions." DTX 862. There, Dr. Michael Akers notes that

> Recrystallization and size reduction techniques are common in large-scale manufacturing, but if these must be done under aseptic conditions, a significant challenge must be confronted. Sterilization of drug and vehicle may not be unusually difficult, but aseptically combining, dispersing, and mixing drug and vehicle again cause great potential difficulties on a large scale.

DTX 862 at 018397. Yet, the following testimony of Dr. Akers, which this Court found to be credible and neutral, demonstrates that the real issue at the time of the '834 Patent of which AstraZeneca complains was not whether there was a technological impossibility, but whether an inventor was willing to invest in the necessary infrastructure to manufacture the claimed product on a large-scale basis. See Trial Tr. 2244:1-9 (Akers) ("[The process] requires a very substantial physical plant to accomplish."). As the cross-examination testimony of Dr. Akers demonstrates:

> Q. I'd like to start out by seeing where we can agree and maybe narrow the focus a little bit on the state-

of-the-art. As an initial matter, you agree that the skilled person in 1997 would know about the availability of non-sterile European budesonide nebulizing suspension that was pharmaceutically acceptable and contained highly pure budesonide, correct?

A. Yes.

Q. Now, the skilled person in 1997 also would have known of the availability of highly pure, 99 percent pure pharmaceutical grade budesonide . . . ?

A. Yes.

Q. Now, the skilled person in 1997 that wants to make a sterile budesonide product is going to want to start with the highest purity budesonide possible, correct?

A. You certainly want to start with sufficiently pure budesonide, yes.

. . .

Q. Now, the skilled person in 1997 would be trained in and familiar with conventional sterilization techniques for sterile products, including sterile filtration, correct?

A. They would.

Q. And the skilled person in 1997 would know that a conventional sterile filtration employs a 0.22 micron pore size filter that excludes all microorganisms, dead or alive, as well as any other particulate matter larger than the filter pore size?

A. They would have understood that such a filter had a mean pore size rating of .2 micrometers, which implies that some pores may have been larger, some may have been smaller.

Q. And the skilled person would have understood that a filter of that size, .22 microns, would be a sterilizing filter, correct?

A. It’s commonly called a sterilizing grade filter.

Q. And the skilled person in 1997 would know that in order to sterile filter a dry steroid powder like budesonide, they would first have to put that powder into solution, correct?

A. Correct.

Q. And the skilled person in 1997 would also know how to dissolve budesonide and make a solution using organic solvents like methanol, correct?

A. They would.

Q. And the skilled person in 1997 would know how to then take and sterile filter a budesonide solution with a 0.22 micron pore size sterilizing filter which would result in a sterile filtrate or sterile budesonide solution, correct?

A. They would.

Q. Now, I want to put aside aseptic conditions. So, my next question, just exclude or ignore aseptic conditions. Putting those aside, the skilled person in 1997 would know how to crystallize highly pure budesonide from solution without losing purity, correct?

A. They would.

. . .

Q. Now, again, putting aside aseptic conditions for the moment, the skilled person in 1997 would know how to dry and mill recrystallized budesonide to form a finely dry divided budesonide powder, correct?

A. Correct.

Q. Now, assuming the skilled person already had in hand sterile budesonide that was 98.5 percent pure finely divided dry powder that was pharmaceutically acceptable, the skilled person would know how to aseptically combine that sterile budesonide powder with other pre-sterilized aqueous components to form a sterile budesonide suspension, correct?

A. If we stipulate - - if we stipulate that claim of sterility through the manufacturing process that would be required to get to that endpoint, could achieve sterility, and they did indeed have a sterile product, then I agree with you, that could be combined into a suspension.

Q. And that would be a routine aseptic filling process to the skilled person in 1997, correct?

A. The aspects of it downstream of the mixing of the powder with the vehicle would be considered relatively routine.

Q. Okay. Now, the skilled person in 1997 would have known that most sterile pharmaceutical products were made using some form of aseptic processing, correct?

A. Yes.

Q. And, in fact, the skilled person in 1997 would have known that if you cannot terminally sterilize a pharmaceutical product, you would likely have to use some type of aseptic processing, correct?

A. Correct.

Q. Now, all that said, I want to narrow the issue. You've already told me that it's routine to take the sterile powder and make the suspension. So, your primary opinions are that it would be complex and the skilled person would not reasonably expect success to do the aseptic crystallization, isolating, drying and milling processes, correct?

A. I believe that would be a far more risk intensive activity than terminally sterilizing it, and that one would not have been assured of absolute success.[26]

Q. So, you take no issue with the filtration step, correct?

[26] Absolute success is not required. See, e.g., In re O'Farrell, 853 F.2d at 903-04.

> A. Products for which terminal sterilization is inapplicable, generally because they lack the chemical stability to withstand terminal sterilization, are made by aseptic processing. In my view, the preferred process is to terminally sterilize the bulk drug substance.
>
> Q. But the skilled person would know if you can't do that, you can't terminally sterilize, you would have to use aseptic processing?
>
> A. With the condition that you can't do it, ***you would have to use aseptic processing***.

Trial Tr. 2259:22-2264:20 (emphasis added).

AstraZeneca contends that filter sterilization and aseptic processing required "sophisticated equipment" that was "capable of running complex aseptic processes" was not available in 1997. See Pls.' Br. 30-31. AstraZeneca places undue emphasis on large-scale technical capabilities, however. Under the asserted claims, a POSA – who is not defined as a pharmaceutical manufacturing company - does not have to have a reasonable expectation of successfully preparing the claimed product in a scaled-up process.[27] Defendants presented clear and convincing evidence before this Court that sterile powder or suspension

[27] AstraZeneca's own witness, Dr. Akers, agrees:

> Q. And as Mr. Rakoczy pointed out yesterday, it doesn't matter if a lab scale, bench scale, ramped up or commercial scale, none of that, there's no limitations in claims 1 and 50 that require any kind of commercial scale, right?
>
> A. Right, I understand.

Trial Tr. 2451:1-5.

could have been produced in 1997 in a laboratory.[28] See, e.g., DTX 1000 at 029003-06; Trial Tr. 377:11-15 (Zaccheo) (POSAs "would have understood that not only was aseptic crystallization well known and used by 1997, but they would have realized that closed systems were available to conduct this even as early as 1995 when the FDA was saying that that's where they should be performed."); see also DTX 960 (Lachman) at 025794. Indeed, AstraZeneca's own witness, Dr. Akers, agreed. See, e.g., Trial Tr. 2315:12-14 ("Could it be done? Under ideal conditions? Yes."). Specifically, Dr. Akers stated, "I'm saying [POSAs would] have a reasonable doubt that they could follow that approach [sterile filtration in combination with aseptic processing] and make a product that was consistently sterile." Id. at 2318:12-14. A "reasonable doubt" as to a "consistently sterile" product, does not equate to no "reasonable expectation of success of making a sterile product." See also id. at 2336:4-10 (Akers) ("Q. And once we have that sterile steroid

[28] Plaintiffs rely upon evidence regarding a Crystal Pharma plant in 2004 to argue that until that time the required equipment was unavailable. See, e.g., Trial Tr. 2537:21-2538:3 (McAffer). However, that evidence says nothing as to the availability of any equipment in 1997; at best, it demonstrates only that Crystal Pharma decided to make an investment in its infrastructure that may (or may not) have been necessary to manufacture a sterilized budesonide product through sterile filtration and aseptic processing at a large scale. Accord Trial Tr. 2252:1-9 (Akers). As noted above, the evidence adduced at trial demonstrated the knowledge and equipment for a small scale production was available to a POSA as of 1997. See supra.

powder, I believe you told me earlier that a skilled person could easily take that powder and aseptically fill and combine it with the presterilized aqueous components to form a suspension, correct? A. That's -- that certainly was a very well developed form of the art in 1997."). Another AstraZeneca witness, Dr. Zhanel, concurred. Id. at 1672:2-6. ("Q. While you call it complex, most products in 1997 were made with some form of aseptic processing, correct? A. My understanding is that many products in 1997 were made using some aseptic processing. Yes.").

In short, the record does not support that the equipment was not available at the time. As discussed above, the FDA's own Inspections Guide discussed equipment use. Moreover, Dr. Akers testified that isolators began being installed and verified for use in the mid-1980s. He explained, "the purpose of isolators could be to provide, I would prefer to say rather than to provide sterility, they were to provide a human free aseptic processing environment superior to a man clean room . . . ." Id. at 2428:15-18. Dr. Akers also acknowledged that the use of an isolator to conduct the last steps of the sterilization and aseptic filling process would "mitigate the risks associated" with those steps and that, while isolators were available long before 1997, "it was not a common technology

in sterile bulk drug manufacturing." Id. at 2242:4-16 (emphasis added), 2265:24-2267:8 (citing DTX 2351).

Notably, AstraZeneca concedes that "[a]septic processing of 40 million units of budesonide nebulizing suspension could potentially result in 40,000 contaminated units as opposed to 40 units with terminal sterilization." PFOF ¶ 77. In other words, the use of aseptic processing, even in AstraZeneca's view, would result in a sterilized budesonide product 999 times in 1,000.[29] Dr. Akers candidly admitted that aseptic processing, while difficult, could be done in 1997. See Trial Tr. 2317:13-20 ("THE COURT: I just want to make sure I understand your testimony, Doctor. It sounds like you're saying that if these risks were removed and if there were a closed system and there weren't malfunctions in the equipment or human error, that a [POSA] would be able to aseptically process, assuming all of

[29] Defendants correctly note that the asserted claims do not require a particular sterility assurance level ("SAL"). In any event, as Drs. Akers and Agalloco, AstraZeneca's experts, acknowledged in 1996, "It has been stated frequently that the SAL afforded by aseptic process is 10^{-3}. We also believe that this assumption dramatically understates the process capability of the majority of aseptic processes currently being conducted in the health care industry. We must point out that the 10^{-3} value is also an arbitrary one that is not supported by the technical literature." DTX 962 at 025868. Not only is that amount arbitrary, but Drs. Akers and Agalloco further conclude that "[t]he process capability of aseptic processing cannot be derived as accurately or assuredly as it can for a destructive physical process. ***This does not in any way impugn the suitability of aseptic processes for sterile product manufacturing.***" Id. at 025868 (emphasis added).

those facts. THE WITNESS: Assuming they got it absolutely right, Judge Bumb.").

There is no doubt that a terminal sterilization process, such as the heat sterilization process for which AstraZeneca obtained a separate patent, reduces the chances of contamination through human error of the kind to which Dr. Akers testified. But that does not permit AstraZeneca to patent a product that could have been successfully created through implementation of other well-known and routine sterilization processes. See, e.g., Cubist Pharm., Inc. v. Hospira, Inc., No. 12-367, 2014 WL 6968046, at *15 (D. Del. Dec. 8, 2014) ("[O]bviousness 'cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.'" (quoting Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007))). It is interesting to note that AstraZeneca also pressed similar, and equally-flawed, arguments before the PTO, which largely rejected them as irrelevant to a product claim. The following summary of the file is instructive.

On February 18, 2005, the Patent Examiner rejected the asserted claims (prior to their amendment) as obvious under Jakupovic:

> It would have been obvious to one having ordinary skill in the art at the time the invention was made to sterilize the respirable, dry powders disclosed by

> JAKUPOVIC by either treatment with ethylene oxide or filtration of the product in solution before precipitation as described in the JAKUPOVIC process. The artisan would have been motivated to sterilize the respirable particles, to prevent microbial growth in the packaged material meant for administration to patients, with a reasonable expectation of success. It is noted that the filter size recommended by JAKUPOVIC would not be adequate for sterilization. However, the reference does not disclose filter size as a variable that controls particle size. See page 4, lines 14-19. Therefore it would be obvious to use a smaller filter and conduct the balance of the process under sterile conditions to obtain a sterile product.

DTX 0004 at 017492-93.

AstraZeneca acknowledged before the Examiner that sterile filtration and aseptic processing were well-known in the art. But, according to AstraZeneca, such technique was not "practicable" for "manufacture of powder pharmaceutical in bulk." Id. at 017536.

Applicants point out that, in general,

> sterilization by filtration may not have been considered a practicable technique for a pharmaceutical powder such as presently claimed—particularly years ago, at the priority date of the present application. One significant reason for this is because the filtration step would have to be carried out while the compound was in solution, a number of process steps upstream from packaging the final sterile powder product. This means that every reagent (e.g., the anti-solvent) and every piece of equipment and packaging material used subsequent to the filtration step would have to be sterilized and then maintained aseptically during use. This would be complicated and difficult to ensure. Further evidence that this technique may not be a method of choice is found in Ansel, for example at page 297, col.1:

One serious disadvantage to the use of bacterial filters is the possibility of a flaw in the construction of the filter and thus some uncertainty of sterility, a circumstance not true of methods involving dry- or moist-heat sterilization in which the procedures are just about guaranteed to give effective sterilization.

Ansel also says that "[m]edicinal preparations sterilized by this method are required to undergo severe validation and monitoring since the effectiveness of the filtered product can be greatly influenced by the microbial load in the solution being filtered" (page 296, col.1), and appears to endorse the technique primarily where only small quantities of solution are involved, e.g., in a pharmacy (see page 296, col.2), last sentence ("filtration of small quantities"); and page 296, col.1-2, carryover paragraph). This suggests that filtration would not be the sterilization technique of choice for manufacture of a powder pharmaceutical in bulk, where speed and convenience in handling large quantities of materials and assurance of sterility of the final product are important criteria. Thus, for a number of reasons outlined above, Applicants submit that one of ordinary skill in the art who understands the complications of maintaining sterility throughout multiple processing and packaging steps, and who has read Ansel's comments, would be dissuaded from trying filtration as a means to sterilize a pharmaceutical powder. Neither Rubinfeld nor any of the other cited references does anything to counter Ansel's teaching-away. If sterilization of a pharmaceutical powder were considered desirable, one of ordinary skill would be more likely to try a straightforward, easily verifiable method such as irradiation, despite the possible loss of purity that would entail. **Applicants were the first to discover a practical way to produce a pharmaceutically acceptable, sterile (or sterilized) powder composition at least 98.5% by weight of which is pure budesonide or an ester, acetal or salt thereof.** As such, Applicants are entitled to claim that composition.

DTX 0004 at 017536-37 (emphasis added). Thus, AstraZeneca argued that because it discovered a "**practical way**" to produce a budesonide composition, it should receive patent protection.

Yet, as the Federal Circuit has ruled, the patent is not limited to a process (a practical way), but rather it covers a product. ***The fact that AstraZeneca admitted to the PTO that there existed a (arguably) less practical way to make the product in and of itself, it seems, should end the obviousness analysis.*** Notably, in Orthopedic Equipment Co. v. United States, 702 F.2d 1005 (Fed. Cir. 1983), the Federal Circuit recognized that while a POSA may not combine two prior art apparatuses for "economic feasibility" reasons, that decision is not relevant to nonobviousness. 702 F.2d at 1013 ("In other words, the fact that the two disclosed apparatus would not be combined by businessmen for economic reasons is not the same as saying that it could not be done because skilled persons in the art felt that there was some technological incompatibility that prevented their combination. Only the latter fact is telling on the issue of nonobviousness."). Similarly, while a drug manufacturing company may not have ultimately utilized sterile filtration in combination with aseptic processing to manufacture sterilized budesonide in bulk due to the associated high costs of maintaining an aseptic environment at that scale, that is not to say that a POSA would not be motivated to employ these well-

known sterilization processes in a laboratory with a reasonable expectation of successfully preparing the claimed sterilized budesonide compositions.

In response to AstraZeneca's arguments, the PTO reminded AstraZeneca that the claims at issue were product claims not drawn to any particular process.

> Applicant further discusses at length possible problems with filtration sterilization. The fact that one process may be more cumbersome than another may be persuasive in prosecuting a process claim but the claims are not drawn to a process. **Applicant has merely speculated that the recited product could not be produced by this process.** Again, argument is not evidence.

DTX 0004 at 017587 (emphasis added).

AstraZeneca did not agree with the Examiner but, nonetheless, in an effort to address the concerns raised by the Patent Examiner, and to sidestep the Jakupovic reference, which taught away from micronizing, AstraZeneca amended the claim to specify that the composition was "micronized." See id. at 017619-20.[30] Ultimately, the Patent Examiner determined the

[30] Much like AstraZeneca argues before this Court, AstraZeneca argued before the Examiner that because the filtration process was too cumbersome, a POSA would not have bothered to try and therefore its product was nonobvious.

> Since the question of whether a given product would have been obvious to make is necessarily linked to the question of whether it would have been obvious to carry out the process required to make it, Applicants do not understand the basis for the Examiner's conclusion. If one of ordinary skill would have considered the hypothetical filtration process to be

above arguments were "moot" in light of Harris. Id. at 017745. The Patent Examiner found that it would have been obvious to prepare a sterile suspension comprising micronized budesonide using the method of Harris, pumping a solution of mometasone furoate through a sterilizing filter, precipitating with water, and micronizing to a preferred particle size of less than 2.0µm. Thus, in light of Jakupovic's teaching, which drew "equivalence between mometasone and budesonide," one would expect a similar sterile suspension comprising micronized budesonide. DTX 0004

> too cumbersome, he/she would not have bothered to try it, and the product would never have been made. Furthermore, many of the issues raised by Applicants in the prior response address whether the significant modification of the Jakupovic process proposed by the Examiner would even work for the purpose intended by Jakupovic-i.e., production of particles of crystalline budesonide of a desired size by direct precipitation in anti-solvent, without the need to use micronization to re-size them. The Examiner has provided no evidence or reasoning to contradict Applicants' quite sensible arguments.
>
> Although the above arguments are more than adequate to rebut the Examiner's prima facie case, Applicants have in fact also amended the claims to provide even more distinctions over the art, in an attempt to move this prosecution along more quickly. Independent claim 65 has been amended to specify that the powder composition was "micronized". Micronization is a typical means of reducing particle size. Jakupovic sought a technique that could produce particles of the desired size while avoiding the need for micronization, since, according to Jakupovic (see carryover paragraph of pages 1-2), micronization can alter the crystalline structure and physical properties of powder particles in undesirable ways.

DTX 0004 at 017619-20.

at 017747. However, once AstraZeneca submitted the Rule 1.131 Declaration in support of a reduction in practice predating the Harris reference, the Examiner accepted the asserted claims. There is no further discussion of filter sterilization or these references.[31]

The Court is well aware that it must give great deference to the Examiner's ultimate decision to allow the asserted claims notwithstanding the Jakupovic/Ansel references. However, it is evident that what was not considered by the Examiner is the evidence Defendants have persuasively put forth in this proceeding. In 1997, a POSA would have known how to dry and mill crystallized budesonide to form a finely-divided (micronized) powder. Indeed, AstraZeneca concedes this point. PRFOF ¶ 23. Moreover, a POSA would have known how to routinely conduct aseptic processing to preserve the sterility of the micronized budesonide composition, for the reasons set forth above. See, e.g., Sciele Pharma, 684 F.3d at 1260 (recognizing Court may afford less weight to references that were before the PTO).

Finally, AstraZeneca argues that both parties' "experts agree" that U.S. Patent No. 3,962,430, filed on July 14, 1975 by Joseph L. O'Neill ("O'Neill"), entitled "Sterilization of Solid

[31] Nearly ten years passed between the filing of the U.S. application and the issuance of the '834 Patent. See generally DTX 0004.

Non-Electrolyte Medicinal Agents Employing Sodium Chloride," teaches that aseptic recrystallization is problematic due to the formation of needle-shaped crystals. DTX 848. The Court finds that AstraZeneca has taken the deposition testimony of Ms. Jeanne Moldenhauer, Defendants' expert, out of context as counsel for Sandoz aptly pointed out. See Trial Tr. 2221:19-2222:5, 2439:6-2442:3. In demonstrating the value of his invention, O'Neill addresses problems in the prior art, including the fact that aseptic recrystallization resulted in the formation of needle-shaped crystals unsuitable for parenteral suspensions. DTX 848 at col.3 ll.36-40. This was a recognized potential disadvantage of the prior art, as Defendants' expert, Ms. Moldenhauer, indicated. However, O'Neill then provided his salt saturation method, which as explained below, resulted in no change in crystal form. Ms. Moldenhauer thus concluded that a POSA would be motivated to try the O'Neill process and would have a reasonable expectation of success that the O'Neill process would result in a sterile budesonide product that would satisfy the asserted claims. Dr. Akers, who read Ms. Moldenhauer's deposition testimony, expressed no opinions disagreeing with her conclusion. See Trial Tr. 2441:17-2442:3.

f) Conclusion

Accordingly, for the reasons set forth above along with the Court's findings below regarding secondary considerations, the Court finds that Defendants have demonstrated by clear and convincing evidence that a POSA, admittedly motivated to create the claimed sterilized budesonide compositions, could have done so utilizing sterile filtration in combination with aseptic processing and would have had a reasonable expectation of success.

ii. Moist Heat Sterilization

Defendants next argue that a POSA would have had a reasonable expectation of success in creating the claimed sterilized budesonide compositions using conventional moist heat sterilization. Defendants contend, that the asserted claims are invalid as obvious over (a) O'Neill and (b) either the IPPL or European Pulmicort®.[32]

Conventional steam sterilization, also known as autoclaving or moist heat sterilization, employs steam under pressure and is the "method of choice . . . where the product is capable of

[32] Defendants also proffer Leuschner (DTX 2097) as an additional prior art reference that renders the asserted claims obvious. However, because the Court finds that AstraZeneca has satisfactorily demonstrated a reduction in practice date prior to September 30, 1997, see supra, the Court does not consider this reference as prior art.

withstanding such treatment."[33] DTX 851 at 018242; PRFOF ¶ 73. According to Ansel, moist heat sterilization destroys bacteria by denaturation and coagulation of essential proteins in the microbial cell. DTX 851 at 018242. While the presence of moisture allows the destruction of bacteria at lower temperatures than when moisture is absent, pressure is used to obtain higher temperatures within the autoclave. Autoclaves are routinely operated at 121°C at 15 pounds pressure for 15 minutes. Id. at 018243. Although AstraZeneca argues that moist heat sterilization was a well-known sterilization technique as of 1997 that would be expected to yield a sterile product, it contends that budesonide could not withstand the temperatures typically used in moist heat sterilization cycles. PRFOF ¶ 76. There are several recognized concerns with the use of moist heat sterilization, including the potential degradation or decomposition of the active ingredient, as well as particle size or agglomeration issues. However, Defendants presented evidence that a POSA would have a reasonable expectation of successfully using moist heat sterilization to create the claimed compositions in spite of these concerns.

First, Defendants presented evidence that the use of moist heat to sterilize a pharmaceutical steroid composition was

[33] Moist heat sterilization can be, but is not necessarily, a terminal sterilization process. Trial Tr. 150:24-151:2 (Moldenhauer).

taught by O'Neill. DTX 848. Ms. Moldenhauer convincingly testified that O'Neill taught a POSA that a corticosteroid suspension could be saturated with an excess of sodium chloride, sterilized by moist heat, and aseptically processed to create a pharmaceutically acceptable product without any degradation or decomposition of the steroid. Trial Tr. 156:3-12. Degradation or decomposition of the steroid would impact the purity of the steroid – in this case, budesonide. See Trial Tr. 461:6-8 (Zaccheo). However, O'Neill experienced no decomposition. ("Analytical studies, including infra-red analysis, indicated intact dexamethasone acetate with no decomposition even after autoclaving the steroid-sodium chloride mixture in Step A for 1 hour at 121°C.) DTX 848 at col.4 ll.60-64. Thus, while some prior art references recognized that moist heat "can be considered unsuitable" for sterilizing heat sensitive materials such as steroids, see PTX 513 at 1332160; DTX 2274 at 0400617,[34] a POSA would also know from O'Neill that the application of moist heat to a steroid can result in a pharmaceutically acceptable, sterilized steroid composition that did not degrade or result in a loss of purity. In addition, a POSA would know based upon the teachings of Lachman that the time, temperature,

[34] See also DTX 2093 at 030999 (explaining moist heat sterilization of a suspension may destroy the integrity of a suspension, thus requiring the ingredients of the suspension to be separately sterilized).

and pressure could be routinely altered to create the optimal steam sterilization cycle. See Trial Tr. 148:3-8 (Moldenhauer); DFOF ¶ 77.

Agglomeration and particle size changes were "well understood" and "well known" consequences of moist heat sterilization of suspensions, which could render the sterilized product pharmaceutically unacceptable. See Trial Tr. 747:24-25 (Dalby); DFOF ¶¶ 78, 80; Trial Tr. 150:8-11 (Moldenhauer). As Dr. Richard Dalby, Defendants' expert, explained, molecules that comprise the drug product particles dissolve in a solution and break away from larger particles. During the cooling phase after moist heat sterilization, these free molecules (1) may associate with other molecules to form new particles that could have a different shape, (2) may associate with other particles that did not completely dissolve to form larger particles, or (3) partially undissolved particles could stick to one another (bridging). See Trial Tr. 746:13-747:23. The potential for particle growth after moist heat sterilization was not a concern unique to budesonide. Id. at 756:18-25 (Dalby). O'Neill acknowledged this problem in describing the value of his invention: when dexamethasone acetate suspended in water or sodium chloride solutions "having a concentration below that of saturated solutions" were then autoclaved, the suspensions

resulted in crystal growth of 300 to 400 microns. DTX 848 at col.3 ll.51-61.

The evidence persuasively demonstrated that particle size growth and agglomeration would not have been concerns for a POSA attempting to create the claimed pharmaceutically acceptable, sterilized budesonide compositions, however, because those compositions do not require any particular particle size or pharmaceutical use that would limit the particle size. It is the route of administration that necessitates specific particle size ranges; thus, even large budesonide particles may be pharmaceutically acceptable in a topical application or in a capsule for oral administration. See Trial Tr. 308:3-20 (Moldenhauer); id. at 2826:20-2827:1 (Williams). Although the asserted claims are not limited to a specific particle size or pharmaceutical use, the Federal Circuit's claim construction does require "finely-divided dry particles." Regardless, the evidence demonstrated that a POSA, admittedly motivated to prepare a pharmaceutically acceptable, sterilized budesonide composition, would not have been dissuaded from using steam sterilization due to the known agglomeration and particle growth issues because POSAs were aware of a number of well-known and routine methods that could be employed before or after steam sterilization to address these concerns, as discussed below. Id. at 161:8-11 (Moldenhauer).

a) Sodium Chloride Saturation

First, a POSA could reduce the amount of solvent available to dissolve the drug particles by using a saturated sodium chloride solution prior to sterilization by moist heat, as described by O'Neill. This is set forth in O'Neill. One object of O'Neill's invention was the elimination of particle size changes during sterilization in the preparation of sterile suspensions. DTX 848 at col.2 ll.6-11; Trial Tr. 148:23-149:2, 150:3-7 (Moldenhauer); id. at 745:3-7 (Dalby). O'Neill taught that adding an excess amount of sodium chloride to a solution, such that the solution was saturated, prevented caking and agglomeration during the steam sterilization process. Id. at 152:3-15 (Moldenhauer); see also DTX 848 at col.3 ll.6-11 ("The addition of sodium chloride in a concentration sufficient to form saturated solutions at both room and elevated temperatures, plus a 10% excess, prevents the solution of the drugs at elevated temperatures, thus eliminating changes in crystal size and form upon re-crystallization during subsequent cooling."). O'Neill's invention theorizes that if one makes the water unavailable to dissolve the glucocorticosteroid during the heating phase, then the drug particles cannot reassociate with one another during the cooling phase, thereby preventing particle size issues. He accomplishes this through the addition of large quantities of sodium chloride, which requires water to

dissolve; because the water is dissolving the sodium chloride, it is not available to dissolve the glucocorticosteroid. Trial Tr. 748:9-23 (Dalby).

Example 1 of O'Neill teaches a sterile aqueous suspension suitable for administration as a parenteral pharmaceutical containing the corticosteroid dexamethasone acetate. DFOF ¶ 95. A suspension of finely divided dexamethasone acetate particles is formed in a solution saturated with sodium chloride and containing a wetting agent. This suspension is autoclaved at 121°C for 20-30 minutes. Other ingredients are separately autoclaved and then aseptically combined. Id. O'Neill explains that tests indicated no crystal size growth or change in form, or degradation. See Trial Tr. 156:5-12 (Moldenhauer); DTX 848 at col.4 ll.56-64. Indeed, AstraZeneca's own witness, whose testimony was introduced by Defendants, Dr. Williams, testified that a POSA would expect the O'Neill method in Example 1 to work on budesonide without resulting in agglomeration. Trial Tr. 2759:12-19.

Dr. Dalby similarly testified that a POSA would have reason to believe the O'Neill method would work on budesonide because it is also a glucocorticosteroid, like the dexamethasone used in O'Neill. Id. at 749:523; see also id. at 149:20-21

(Moldenhauer).[35] Dr. Dalby convincingly explained that a POSA would know that both dexamethasone and budesonide are soluble in organic solvents and have low solubility in water; thus, a POSA would recognize their similar solubility properties and conclude that what works for one may work for the other. See id. at 755:7-756:8. This testimony was unrebutted. Dr. Zhanel even agreed that because steroids have similar chemical structures, a POSA would expect similar outcomes. See id. at 1443:12-20; DFOF ¶ 105.[36]

[35] See also Trial Tr. 6112-15 (Miller) ("Well, first let me say that not every sterilization method may work for every single glucocorticosteroid, but because budesonide is in the same class of compounds as the other glucocorticosteroids that I had testified about, a person of ordinary skill in the art would have a reasonable expectation of success in making a sterile suspension that contained budesonide.").

[36] Dr. Zhanel opined upon a POSA's reasonable expectation of success using EO, dry heat, moist heat, and irradiation. See Trial Tr. 1696:25-1697:2. The Court finds that his testimony was based upon a narrow reading and restrictive approach to the prior art. For example, Dr. Zhanel testified

> What I'm saying is that the [POSA] is looking for the package. Show me that you have sterilized the product alone with purity and pharmaceutically acceptability [sic]. If you tell me you autoclaved something, I'll believe you it's sterile, but show me that it's also pure and pharmaceutically acceptable.

Id. at 1314:15-20; see also id. at 1317:20-23 ("And if all I had was this caption, this wouldn't advance my cause because I don't see the fulfillment of the triad, the purity, the acceptability, along with sterility."); id. at 1404:2-11 ("But what Abshire [DTX 163] really is doing here is he's simply stating that sterilization with antibiotics and steroids occurs with ethylene oxide, but it doesn't help the [POSA] because we have no data showing that we have our package that we're looking for, our

In rebuttal to the foregoing, AstraZeneca cites a number of references that post-date the priority date applicable here,

---

package of three: Sterility, purity and pharmaceutical acceptability."); id. at 1407:1-8 ("But the [POSA] trying to solve their problem looks for the evidence and they see no data that they can see that Clark [DTX 160] is teaching showing our package: Sterility, purity and pharmaceutical acceptability."); id. at 1419:18-1420:4 ("Guy [DTX 853] teaches us about a steroid called loteprednol and what Guy does is he doesn't show us data that the product discussed was actually achieved, he does disclose purity. . . . [B]ut we just don't have all the information that we would like; sterility, purity and pharmaceutical acceptability.").

Dr. Zhanel appeared to discount those prior art references that did not explicitly teach the full "triad" or "package" of limitations. Yet, the law is clear that a patent may be obvious in light of a combination of prior art references. See, e.g., Medichem, 437 F.3d at 1165 ("Evidence of a motivation to combine prior art references 'may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved.'"); In re Merck & Co., Inc., 800 F.2d 1091, 1097 (Fed. Cir. 1986); see also KSR, 550 U.S. at 420 (noting "in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle"). But, for the reasons discussed herein, Defendants have clearly and convincingly shown combinability of the prior art, which Dr. Zhanel avoids.

In addition, Dr. Zhanel utilized a definition of a POSA that injected qualifiers. Although he testified on cross-examination that he did not insert "limited time and resources" limitations into his POSA definition, Trial Tr. 1595:22-1596:4, it is clear that he did. See, e.g., id. at 1477:23-25 ("And a [POSA] has limited time and resources. They are interested in bringing a product to market to help patients . . . ."); id. at 1331:18-22 ("A person of ordinary skill is a very focused person. They know that in the drug discovery business, time is money. And their goal is to advance their discoveries as quickly as possible. So they're going to be very focused with their time."); id. at 1587:23-25. Dr. Zhanel appears to have mirrored AstraZeneca's approach, which, in effect, transforms a POSA into a drug manufacturing company, see discussion of large-scale manufacturing supra. For these reasons, Dr. Zhanel's testimony was not persuasive.

arguing that these references "confirm" what was known in the art as of 1997 and show that a POSA would not have had a reasonable expectation of successfully preparing a sterilized budesonide composition that meets the purity requirement of the asserted claims.[37] See, e.g., PRFOF ¶ 77. Specifically, U.S. Patent No. 6,464,958, filed Oct. 28, 1999 ("Bernini"), notes that beclomethasone dipropionate "suspensions subjected to a wet steam process under conditions similar to those reported in [O'Neill] (121°C. for 15 minutes) undergo a remarkable decrease in the content in active ingredient (about 8-9%), with a corresponding significant increase in degradation products (about 10-11%)." PTX 1764 at col.6 ll.24-32. In addition, U.S. Patent No. 6,863,865, filed Sept. 30, 2002 (the "McAffer Patent"), reports that "the application of a standard autoclaving technique to budesonide suspension has also resulted

[37] See also DTX 971 at col.5 ll.45-50 (Harris states that other sterilization processes usually will not include sterilization steps for the micronized drug substance "since it has been found that the drug undergoes degradation under the influence of . . . sterilizing heat conditions"); Portugal Patent, filed May 22, 1979, DTX 2274 at 0400617 (the "Portuguese Patent") (explaining steroids in powder form are not stable above 60°C). These references provide no further discussion of moist heat sterilization as they are focused on the benefits of the sterilization technique that each reference promotes (i.e., Harris on sterile filtration, and the Portuguese Patent on EO). As such, these references provide minimal evidentiary value as to the state of art; moreover, it is not surprising that each reference would highlight the disadvantages of other sterilization processes in order to accentuate the value of their own inventions.

in a significant increase in the levels of impurities present." PTX 507 at col.8 ll.49-51. These two references suggest that moist heat sterilization causes unacceptable degradation of a steroid and of budesonide in particular.

The Court reserved on Defendants' objections at trial to these later references. The Court overrules the objection, but finds that they have no persuasive value as the question is what was known prior to 1997. These references do not shed credible light on that question. The conclusion that AstraZeneca wants the Court to draw from these references is not only unsupported but it is also contradicted by O'Neill and other more contemporaneous art. See infra note 39; cf. Plant Genetic Sys., N.V. v. DeKalb Genetics Corp., 315 F.3d 1335, 1344 (Fed. Cir. 2003). As described above, O'Neill conducted the experiment as set forth in the patent and provided the results of the experiment, i.e., no crystal size growth or change in form, or degradation. The bare statement in Bernini fails to provide any description of which "conditions" of O'Neill's process that Bernini attempted to replicate; the parenthetical reference suggests only the time and temperature conditions of the wet steam process but does not indicate that Bernini attempted to use the salt saturation technique disclosed by O'Neill. As such, the Court accords little weight to this ambiguous critique

of O'Neill dated more than two years after the relevant time period or to Dr. Zhanel's related testimony.[38]

There is no evidence prior to 1997, however, warning a POSA that budesonide will unacceptably degrade under thermal sterilization conditions. To the contrary, O'Neill discloses a pharmaceutically acceptable glucocorticosteroid product sterilized using a conventional moist heat cycle (121°C for 20 minutes). Thus, while a POSA was aware that degradation can be a potential disadvantage with moist heat sterilization of any substance, which Ms. Moldenhauer acknowledged, Trial Tr. 289:4-13, 22-25, O'Neill demonstrates that it was not a deterrent to a POSA seeking to sterilize a steroid substance and, in fact, degradation did not occur when O'Neill did so.[39] Indeed,

---

[38] AstraZeneca points out that the Patent Examiner relied on the McAffer Patent as showing that moist heat did not render the '834 Patent obvious because it caused degradation. Specifically, the Patent Examiner noted that Table 4 disclosed that "the autoclave sterilization of a suspension of budesonide . . . does not meet the purity requirements of the instant claims." DTX 0004 at 017807. There was insufficient evidence regarding Table 4, and thus the Court declines to give this any weight. Moreover, at the time the Examiner considered this table, Claims 50 and 51 (the suspension claims) were not before the Examiner and thus, O'Neill was not specifically discussed in that context. See infra.

[39] Although the Court does not rely upon them for its findings and conclusions, two post-art references confirm that a POSA would have had a reasonable expectation of successfully sterilizing a glucocorticosteroid such as budesonide using moist heat sterilization without degradation. Entitled "Budesonide Alone or in Combination with Ursodeoxycholic Acid in the Therapy of Cholestatic Liver Diseases, U.S. Patent No. 5,858,998, filed Sept. 30, 1997 ("Leuschner"), discloses the use of budesonide in

Defendants introduced the deposition testimony of Dr. Williams, who stated that "based on O'Neill, [POSAs] would expect substituting in Budesonide in example one . . . then undergoing the autoclave process and the mixing, . . . should produce a suspension of finely divided particles that does not agglomerate." Trial Tr. 2766:6-12. Moreover, a POSA would expect sterility:

> Q. . . . So just following what O'Neill says it says, if you swapped in Budesonide for dexamethasone, follow the procedure, you would -- a [POSA] at the time would reasonably expect to have the resulting product be finely divided Budesonide suspension that is sterile and doesn't agglomerate, is that right?
>
> A. I mean O'Neill uses the word sterile.
>
> Q. Right.

---

oral and parenteral preparations for the treatment of human diseases (i.e., pharmaceutically acceptable). Trial Tr. 157:3-16 (Moldenhauer); DTX 2097. In Example 3, Leuschner discloses the preparation of a budesonide solution for parenteral administration according to which the solution is moist heat sterilized. DTX 2097 at col.6 ll.26-38. Notably, Leuschner does not disclose any degradation or loss of purity after moist heat sterilization of budesonide. A later patent, U.S. Patent No. 6,066,292, entitled "Sterilization Process for Pharmaceutical Suspensions," filed on Dec. 19, 1997 ("Purwar"), acknowledges that O'Neill exemplifies the prior art. See, e.g., DTX 2099 at col.2 ll.1-29, 40-42. More significantly, Purwar utilizes steam sterilization for sterilizing a pharmaceutical formulation of a glucocorticosteroid, hydrocortisone. PTX 2099 at col.2 ll.40-56. These references, filed within months of AstraZeneca's invention, contradict its argument as to the state of the art. See, e.g., Plant Genetic Sys., 315 F.3d at 1344 (Fed. Cir. 2003) ("This court has approved use of later publications as evidence of the state of art existing on the filing date of an application." (citation omitted)).

> A. So I think a person of ordinary skill in the art would -- probably would believe that what's produced here would be sterile.

Trial Tr. 2766:23-2767:8 (Williams).

AstraZeneca contends further that even though O'Neill asserts that dexamethasone avoids decomposition, O'Neill presents no data showing the purity of the final product despite the degradation that would be expected at such temperatures. However, O'Neill plainly states that the analytical studies indicated no decomposition. See DTX 848 at col.4 ll.59-63. AstraZeneca offered the testimony of Dr. Zhanel who opined that O'Neill did not address the degradation problem. Dr. Zhanel opined that if degradation occurred at Step A of O'Neill's example, a POSA would not expect a pharmaceutically acceptable product after Steps B and C. Trial Tr. 1778:2-14. This testimony, however, ignores the fact that O'Neill taught that a POSA could achieve no degradation after autoclaving the steroid-sodium chloride mixture in Step A for even 1 hour at 121°C. See DTX 848 at col.4 ll.59-63.

Plaintiffs also point to U.S. Patent No. 5,540,930, entitled "Suspension of Loteprednol Etabonate for Ear, Eye, or Nose Treatment," filed on Oct. 25, 1993 by Yaacov J. Guy et al. ("Guy"). DTX 853. This patent notes that suspensions of corticosteroids are "frequently hampered by the subsequent formation of cakes resulting from aggregation of the suspended

material." Id. at col.1 ll.14-17. The caking occurs while the suspension is stored – after sterilization and filling. Guy explains that the presence of ions causes caking. Id. at col.3 ll.41-45. Plaintiffs contend that Guy teaches a POSA that the use of sodium chloride in a budesonide aqueous suspension would promote caking and thus teaches away from the O'Neill method. However, Ms. Moldenhauer persuasively explained that, in viewing Guy as a whole, a POSA would understand Guy to be discussing low levels of sodium chloride, e.g. 0.9% sodium chloride (isotonic), in contrast to the saturation or excess of saturation levels discussed in O'Neill. See Trial Tr. 295:22-296:23. AstraZeneca's characterization of Ms. Moldenhauer's testimony as a blanket statement that a POSA reading Guy would be taught away from using sodium chloride in an aqueous budesonide suspension is erroneous.

Notably, the PTO relied upon O'Neill to reject AstraZeneca's claims directed to sterile, dry solids (not suspensions as in claims 50 and 51). DFOF ¶ 107. For its part, AstraZeneca argued that O'Neill discloses a sterile aqueous suspension for parenteral administration which "is not a heat sterilized inhalation powder." DTX 0004 at 017308. There was no reference to O'Neill after the addition of what are now claims 50 and 51. See DFOF ¶ 107. Although the PTO Examiner was technically aware of O'Neill at the time that she addressed

the asserted claims and discussed moist heat sterilization, it is worth noting that the examiner did not discuss O'Neill after claims 50 and 51 were added. Cf. Sciele Pharma, 684 F.3d at 1260.

b) Surfactant

Second, the evidence demonstrated that a POSA concerned with preventing agglomeration and caking could add a surfactant or wetting agent to the product, and this was known and routine as of 1997. Lachman recognized the importance of stabilization of a suspension between manufacture and use to prevent settling and caking, which may prevent redispersion of particles prior to use. DTX 960 at 025814. Lachman suggests the inclusion of a surfactant: "Surface active agents may aid in the preparation and stabilization of a suspension by reducing the interfacial tension between the particles and the vehicle." Id. Ms. Moldenhauer explained that a surfactant covers the particles, making it less likely that they could agglomerate or cake. Trial Tr. 162:10-14. In addition to providing several surfactants used in parenteral suspensions, Lachman provides an example of a specific formulation. DTX 960 at 025814-15. AstraZeneca's expert, Dr. Akers, agreed that Lachman teaches the use of surfactants to prevent agglomeration and that this was known in the art prior to 1997. Trial Tr. 2448:16-23, 2449:2-6. Dr. Williams, AstraZeneca's expert, also agreed that surfactants

or wetting agents can be used by a POSA to prevent agglomeration and caking. See id. at 2770:1-7. (Even O'Neill teaches several steroidal formulations that contain wetting agents. See DFOF ¶ 84.) Moreover, Dr. Williams testified that a POSA could "routinely" calculate the amount of surfactant necessary to prevent agglomeration. See id. at 2770:16-2772:11. And, a POSA would know that the use of surfactants does not render a product pharmaceutically unacceptable. See DFOF ¶ 84.

AstraZeneca's only response to Defendants' evidence is that the use of surfactants may not entirely eliminate agglomeration or caking. AstraZeneca points to Dr. Akers' testimony that the use of surfactants addressed by Lachman was intended only to prevent agglomeration that occurs after the manufacturing process, see PRFOF ¶ 85, thereby suggesting that surfactants could not be used to prevent agglomeration that occurs in the moist heat sterilization process. However, the experts agreed that surfactants can be utilized to prevent agglomeration regardless of the point in the process at which the agglomerates form. Moreover, O'Neill utilizes surfactants prior to steam sterilization in an attempt to address changes in particle size that occur in the steam sterilization process. AstraZeneca further argues that O'Neill discloses that a wetting agent is not sufficient to prevent agglomeration or particle size change as he discloses that "further steps are necessary in order to

overcome the issues that it identifies with moist heat sterilization," such as the use of sodium chloride. PRFOF ¶ 84. This argument is confusing. Even if the addition of a surfactant did not prevent all forms of particle size growth or agglomeration, then a POSA could follow the remaining steps of O'Neill to obtain the claimed products.

c) Sonication

Third, defendants presented evidence that sonication, which is the use of ultrasonic energy to break up agglomerated particles, was "commonly known" to POSAs since the 1970s and "very easy to do." Trial Tr. 162:23-163:5, 166:11-14, 313:10-16 (Moldenhauer). Ms. Moldenhauer testified that it would be known to POSAs to use aseptic sonication if attempting to create a sterilized product. Id. at 166:11-14, 165:4-8 (Moldenhauer). Indeed, as discussed above, in 1997, a POSA routinely conducted several post-sterilization steps aseptically. See also DFOF ¶ 87. Dr. Williams, AstraZeneca's expert, agreed that sonication was commonly known. Trial Tr. 2768:8-25. Dr. Williams testified that he uses sonication routinely in his lab for several purposes including deagglomeration, but that it has been in use since at least the 1980s. Id. Dr. Akers agreed as well. Id. at 2451:6-16 ("Q. Okay. Now, sonication, not only were you familiar with it, but it was well known by those of skill in the art in 1997, right? A. As a technology, yes. Q.

Okay. And indeed, you ran into it in 1960s, if I recall; is that right? A. Maybe not quite that long ago. Q. Needless to say, long before 1997? A. Before 1997. Q. Okay. It's not a new technology, right? A. No, it's not a new technology.").

The only reference in the art to sonication was Steckel. DTX 871. Steckel describes the suspension of particles in an aqueous solution, which was then subjected to ultrasonic treatment. Steckel writes: "The particle size distribution was measured before and after 90 s of ultrasonication treatment. Previous test series have shown that the deagglomeration process was completed after 90 s. This is in agreement with results from (Bleich et al., 1994). The ratio of median particle size (x50%) before ultrasonication to median particle size after ultrasonication was calculated and then termed 'index of agglomeration'." DTX 871 at 018489-90. Ms. Moldenhauer testified that Steckel teaches that "before and after there was no change in particle size when they sonicated." Trial Tr. 163:15-18. However, it also demonstrates, consistent with the testimony of Ms. Moldenhauer and Dr. Williams, that sonication was known in the art as a means of addressing agglomeration as of 1997. See DTX 871 at 018489-90 (citing 1994 reference); Plant Genetic Sys., 315 F.3d at 1344 ("This court has approved use of later publications as evidence of the state of art

existing on the filing date of an application." (citation omitted)).[40]

In rebuttal, AstraZeneca agrees that sonication was widely known but contends that aseptic sonication was not routine. Dr. Akers testified that aseptic sonication would have been "difficult" in 1997 because of the need to sterilize the sonication equipment. Trial Tr. 2183:5-21. However, as discussed at length above, the equipment and technology necessary to prepare the claimed compounds on a laboratory (as opposed to manufacturing) scale existed as of 1997. Indeed, Dr. Akers agreed that sterile isolator technology was available at the time, and an isolator would mitigate the risks associated with micronization of the drug substance. See DFOF ¶ 87; accord Trial Tr. 2242:1-7. Moreover, as noted, Ms. Moldenhauer persuasively testified that it would be known to POSAs to sonicate the drug product aseptically in order to prevent contamination of the sterilized suspension. Trial Tr. 166:11-14, 165:4-8. And, in 1997, POSAs routinely conducted several post-sterilization steps aseptically. See supra; see also DFOF ¶ 87.

[40] Although Dr. Akers takes issue with the fact that "no prior art [] suggests aseptic sonication would solve particle size growth or agglomeration in the first place," Trial Tr. 2183:23-25, he concedes that sonication as a technology was well known before 1997, 2451:6-14.

d) Milling

Fourth, Defendants presented evidence that milling, a mechanical process for reducing particle size, was well-known to a POSA as of 1997. See Trial Tr. 166:17-20 (Moldenhauer); PRFOF ¶ 89. In fact, several prior art references teach aseptic or sterile milling as a method of particle size reduction. In addressing the preparation of parenteral suspensions, Dr. Michael Akers notes that after drying a sterile powder, "it will usually require some method of particle size reduction. Because of the small quantity of powder usually available for development work, fluid energy mills such as the Jet-O-Mizer or Gem Mill are more practical. They are available for sterile milling . . . ." DTX 862 at 018395-96. The 1994 FDA Inspections Guide also recognizes that one of the usual steps in the manufacture of sterile bulk drug substances is aseptic milling. DTX 1000 at 029003. Entitled "Ophthalmic Composition," U.S. Patent No. 5,407,926 issued on Apr. 18, 1995 by Abbot F. Clark ("Clark") discloses in an Example the preparation of a micronized drug suspension consisting of a glucocorticosteroid, like budesonide, that includes the use of sterilized balls to aseptically mill the steroid drug substance. See DTX 160 at col.7 ll.19-26. Specifically, sterilized glass balls are added to a vessel containing the drug substance in sterilized aqueous solution form, "and the contents of the

container are milled aseptically at 225 rpm for 16 hours, or until all particles are in the range of approximately 5 microns." DTX 160 at col.7 ll.19-23; see also Trial Tr. 166:21-167:9 (Moldenhauer). Based upon these teachings, Ms. Moldenhauer testified that a POSA who moist heat sterilized a drug product and wanted to affect the particle size of the resulting sterilized product would have no reason not to utilize the routine process of aseptic milling. See Trial Tr. 167:18-23. Further, she testified that aseptic milling could be employed on either a sterile powder or suspension. Id. at 167:24-168:3. This testimony was convincing.

AstraZeneca does not dispute that milling techniques were well known by 1997 but asserts that they could not be used to create a finely-divided powder. Dr. Akers testified to the distinction between milling and micronization, stating that milling "would not achieve micronization levels of particle size reduction." Id. at 2185:14-20. However, the claims require only "finely-divided" dry particles and do not require that the particles undergo a micronization step. See id. at 2278:12-22 (Akers). In addition, Dr. Akers was asked about Ansel on cross-examination; Ansel discloses that parenteral suspensions "may be prepared by reducing the drug to a very fine powder with a ball mill, micronizer, colloid mill, or other appropriate equipment and then suspending the material in a liquid in which it is

insoluble." DTX 2093 at 030999 (emphasis added). Dr. Akers acknowledged that the equipment and processes set forth in Ansel "could arrive at a powder with a defined particle size to one degree or another" as milling does affect particle size. See Trial Tr. 2305:5-7, 2306:22-23. Dr. Akers does not dispute that milling can be utilized to effect a change in particle size; nor does he dispute that the resultant particle size could fall within a low micron range that would be deemed finely-divided. Id. at 2309:2-25, 2305:5-7, 2306:22-23. Rather, his concern is that the resultant particle size may not be finely-divided enough for certain routes of administration and intended uses.[41] However, the asserted claims are not so limited. Moreover, O'Neill discloses that milling inter alia could be utilized to reduce particle size to 10 microns for use in suspensions. DTX 848 at col.2 ll.37-42. AstraZeneca points out that this step was done prior to moist heat sterilization, but this is a distinction without a difference. The point is that milling could be utilized to achieve a finely-divided powder.

[41] See Trial Tr. 2306:17-22 (Akers) ("And we're talking about a very general piece of equipment, they can arrive at reasonably small particle sizes, whether they could get down to the levels required for some of the products we discussed today, I think is highly unlikely, in fact they wouldn't. But, you know, will milling resize particles? Yes, it will.").

e) Rotary Sterilization

Lastly, Defendants introduced evidence that a POSA would be aware of rotary sterilization, which involves a steam sterilizer equipped with an inner chamber that rotates like a dryer to ensure the contents are constantly agitated throughout the sterilization process. Trial Tr. 168:4-169:1. According to Ms. Moldenhauer, this prevents particles from sticking together and forming agglomerates or cakes. Id. Ms. Moldenhauer credibly testified that rotary sterilization has been known in the pharmaceutical industry since the 1970s and 1980s, and that she was aware of several other pharmaceutical companies that utilized rotary sterilization. Id. at 169:13-22. In support, she cites Dr. Michael Akers, who discloses the characteristics of a well-formulated suspension, which include easy resuspension of drug particles after "mild shaking" and dispersed particles do not settle rapidly after shaking. DTX 862 at 018391. As Ms. Moldenhauer explains, Dr. Michael Akers discusses that agitation or shaking, which is exactly what rotary sterilization is, causes the particles not to settle out of suspension. Trial Tr. 170:1-11.

In rebuttal, Dr. Akers testified that he is not aware of the use of rotary sterilization after a moist heat process to deal with particle size change, agglomeration, or caking; nor would a POSA expect shaking to address these issues. See id. at

2186:2-19. Dr. Akers opines that Dr. Michael Akers' discussion was intended to address shaking as a method of resuspending a suspension after manufacture but does not teach a solution to the problems associated with moist heat sterilization. While Dr. Akers may not have personally been aware of this use, however, Ms. Moldenhauer convincingly testified that other divisions of her employer used rotary sterilization as early as the '70s and '80s. See supra. Moreover, while AstraZeneca contends that rotary sterilization would not be viewed as a "full solution" to the problems associated with moist heat sterilization, a POSA encountering any particle size or agglomeration issues would be able to employ rotary sterilization in conjunction with the other known methods discussed herein to resolve any problems. As such, Defendants have demonstrated that a POSA could use rotary sterilization to address particle growth or agglomeration issues.

AstraZeneca's primary argument in rebuttal is that each of the techniques described above only addresses one or two of the potential problems with moist heat sterilization, but not all of them. However, Defendants need not prove that each individual technique would adequately address all known problems where, as here, all of these methods were available and widely-used to address the known limitations of moist heat sterilization.

AstraZeneca also argued that a POSA in 1997 did not have the ability to conduct many of these techniques aseptically due to the limited technology. However, as addressed in depth in connection with sterile filtration, Dr. Akers candidly acknowledged the availability of the required equipment and knowledge but recognized the impact of human error, especially in the manufacture of large quantities of pharmaceutical drugs. Under ideal aseptic conditions, following the known and routine processes a POSA would have had a reasonable expectation of successfully preparing the claimed compositions using moist heat sterilization and would have been able to routinely optimize the sterilization process to address any particle size, agglomeration, or caking issues by employing the teachings of O'Neill alone or in combination with any of the other known and routine processes discussed above.

f) Conclusion

After considering the evidence set forth above, as well as the evidence of secondary considerations set forth infra, Defendants have presented clear and convincing evidence that a POSA, admittedly motivated to prepare the claimed sterilized budesonide compositions, would have had a reasonable expectation of successfully doing so using moist heat sterilization in combination with known and routine methods of addressing any particle growth, agglomeration, or caking issues.

iii. Ethylene Oxide (EO)

Defendants next argue that a POSA would have had a reasonable expectation of success in creating the claimed sterilized budesonide compositions using conventional ethylene oxide ("EO") sterilization as disclosed in Clark (discussed infra) in combination with a POSA's knowledge as of 1997. Defendants contend, that the asserted claims are invalid as obvious over Clark.

Prior to 1997, a POSA would have understood that EO was a common alternative sterilization method when the material to be sterilized was unable to withstand high temperatures. Trial Tr. 736:15-737:1 (Dalby); DTX 2278 at 0400321; DTX 2274 at 0400617. It was also the standard sterilization method of steroid suspensions in at least the 1950s and 1960s, and continues to be used today. See DRFOF ¶ 66; DFOF ¶ 144.

EO sterilization consists of placing the material to be sterilized in a chamber, which may be preconditioned to a particular temperature and humidity, introducing EO into the chamber until a certain concentration level is reached, and then maintaining that level for a period of time. PRFOF ¶ 136. A POSA understood that the exposure time could be decreased by increasing the relative humidity and temperature, but if the material being sterilized could not tolerate high humidity or temperature, a POSA could increase the exposure time. PRFOF

¶ 138. These were routine optimizations of the sterilization cycle. See Trial Tr. 594:21-595:11 (Miller); see also DTX 285 at 30000106. Although EO sterilization was a standard process as of 1997, a POSA was aware of two concerns with this sterilization technique, elimination of toxic residues and penetration of a product's crystal structure.

a) Toxic Residues

It is undisputed that a POSA knew how to determine the amount of EO residuals after sterilization of a steroid. This is confirmed by a 1965 article published by Norman Adler, entitled "Residual Ethylene Oxide and Ethylene Glycol in Ethylene Oxide Sterilized Pharmaceuticals," 54 J. PHARM. SCI. 735 ("Adler"), in which he describes and applies methods for determining EO residuals in steroids, vitamins, and antibiotics. DTX 2272 at 0400671. It is also undisputed that, as early as 1965, the prior art reflects concerns with the toxic residues left behind after EO sterilization. See id. In 1978, the FDA proposed a rule that would impose restrictions on the amount of EO residuals and byproducts permitted in drug products for human or veterinary use (the "1978 Proposed Rule") because these residues "may produce toxic reactions in patients, and because of the potential risk of mutagenicity from exposure to these residues" if they are not limited. PTX 2059 at 0400681. According to the proposal, EO residuals in parenteral,

ophthalmic, and topical products would be limited to 10 ppm. See Trial Tr. 763:12-23 (Dalby). Notably, the 1978 Proposed Rule did not propose to eliminate this method of sterilization and, in fact the FDA explicitly stated its belief "that there is need for the continued use of ethylene oxide as a sterilant for certain drug products . . . ." PTX 2059 at 0400684. In any event, this rule was never enacted. See DRFOF ¶¶ 68, 70.

Defendants presented evidence that a POSA as of 1997 would know how to remove the EO residuals using aeration or forced ventilation and vacuum purging. Indeed, a document entitled "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products," published in 1994 by the Center for Drug Evaluation and Research and Center for Veterinary Medicine, demonstrates the continued use of EO sterilization even in the mid-90s and also notes the cycle parameters for EO sterilization include degassing, aeration, and determination of residuals. DTX 2273 at 0400661-62. The ophthalmic field, in particular, continued to use EO sterilization during the mid-90s "as a sterilant for the drug used in the formulation of sterile ophthalmic ointments and suspensions." DTX 1000 at 029008. Thus, despite concerns regarding the potential effects of the residuals, Defendants presented evidence that EO sterilization

continued to be used up to the date of the '834 Patent invention and POSAs employed techniques to minimize the residuals.

One such technique, aeration, can be accomplished by exposing the material to air at ambient temperature or subjecting the material to forced ventilation (i.e., forcing air over the material). See PRFOF ¶ 140. Dr. Zhanel, AstraZeneca's expert, agreed that a POSA would know to use aeration to remove EO residuals. Trial Tr. 1589:10-13. Clark, a 1995 reference, teaches a specific aeration cycle consisting of exposure for at least 72 hours at 50°C as a necessary method of reducing EO residuals following sterilization. PRFOF ¶ 142. Notably, Clark discloses EO sterilization of corticosteroids, tetrahydrocortexolone, and dexamethasone; the sterile powder can then be used to make sterile suspensions. See Trial Tr. 589:17-24 (Miller). In addition, Defendants' expert, Dr. Michael Miller, testified that the Portuguese Patent teaches a specific aeration or "degassification" process by which a substance is forcibly ventilated at 50°C for 48 hours, after which the residual EO can be determined. See Trial Tr. 596:24-597:15; DTX 2274. According to the Portuguese Patent and Dr. Miller, the EO content "can be substantially reduced in comparison with conventional methods in which degassification takes place by simply exposing the package to air (open packages) and those perform at ambient temperatures (14°C - 18°C) with forced

ventilation." DTX 2274 at 0400621; see also DFOF ¶ 140. In other words, the forced ventilation process set forth in the Portuguese Patent claims to be more effective than typical aeration cycles employed following EO sterilization.

In addition to aeration or forced ventilation, Defendants presented evidence that a POSA knew that EO residuals could be reduced through vacuum purging as taught by Adler. With vacuum purging, negative pressure is generated by sucking air out of the chamber containing the sterilized material to help remove the residuals. See DFOF ¶ 143. In Table V of his publication, Adler measures the EO residuals for several steroid, antibiotic, and vitamin substances, noting that certain samples underwent poststerilization vacuum treatment for 8 hours, while others underwent treatment for 2 hours. DTX 2272 at 0400673.

Dr. Miller also testified, without impeachment, that EO followed by aeration, as taught by Clark, was actually being used to sterilize ophthalmic glucocorticosteroids. See Trial Tr. 599:1-600:6. In a research article entitled "Sterile Ophthalmic Ointment and Suspension Manufacturing," published in 1986 by Robert Abshire et al. ("Abshire"), Abshire[42] discussed manufacturing methods for sterile ophthalmic ointments and suspensions, which include sterilization by EO followed by

[42] Abshire worked for Alcon, which is the assignee of the Clark patent.

aeration.[43] DTX 163. Dr. Dalby confirmed that even in the '80s and mid-'90s, EO was being used to sterilize products. Trial Tr. 736:3-22. In fact, the 1995 USP recognized that "The choice of gas sterilization as an alternative to heat is frequently made when the material to be sterilized cannot withstand the high temperatures obtained in the steam sterilization or dry heat sterilization process." See id. at 736:3-22 (citing DTX 2278) (emphasis added). And, AstraZeneca's expert acknowledged that EO sterilization is still being used today. See id. at 1580:1-3 (Zhanel). Moreover, the FDA has not required the removal of any EO sterilized products from the market, despite the known concerns with the presence of residuals. See id. at 1580:12-15 (Zhanel).

In addition, as Dr. Zhanel conceded, these steroid suspensions sterilized by EO were pharmaceutically acceptable. Id. at 1580:4-11; PRFOF ¶ 67. This is further confirmed by Clark who utilized EO sterilization in connection with the preparation of ophthalmic suspensions to treat inflammation of the eye. DTX 160.

AstraZeneca's own Preferid® product demonstrates that budesonide can be successfully sterilized using EO to make a pharmaceutically acceptable product. Preferid® was a micronized

[43] Abshire also noted that his company uses dry heat, UV radiation, and membrane filter sterilization. DTX 163 at 0300286.

budesonide suspension in the form of a topical cream that it marketed as sterile and which was 98-102% pure. See DTX 0004 017836-37, 017900-01; see also DTX 2277 at 0400588. From 1980 to 1983 – after the Adler and Portuguese Patent references - , Preferid® was manufactured in Sweden using a process that included exposing the budesonide particles to EO. Id. at 017836, 017908. Test results for three batches of Preferid® demonstrated that the EO residual of the budesonide powder amounted to 12 to 22 ppm, while the suspension would contain less than .006 ppm, which AstraZeneca considered a "low" content that did not "justify establishment of limits and routine analysis for [EO]." Id. at 017931.

According to a declaration of inventor Ann-Kristin Ekelund submitted in connection with the prosecution of the '834 Patent, "[a]round 1983, changes in the regulatory requirements for this product in the Scandinavian countries led to abandonment of the ethylene oxide exposure step and removal of the term 'sterile' from the product description for Preferid® cream." Id. at 017836-37. Although AstraZeneca argues that it ceased marketing Preferid® as sterile because it determined that the residuals rendered the product pharmaceutically unacceptable, see PRFOF ¶ 135, there is no competent evidence in support of this

assertion.[44] Ekelund's declaration provides no description as to the substance of the regulatory requirements that caused AstraZeneca to abandon the EO exposure step. While the declaration proceeds to state that, as of 1997, a POSA understood that EO sterilization would not yield a pharmaceutically acceptable product because of the potential for EO residuals, id., it must be noted that she in no way connects this bare statement with her discussion of Preferid®. Nor does she explicitly state that AstraZeneca determined the EO sterilized Preferid® product to be pharmaceutically unacceptable. In fact, the evidence strongly suggested that the reason AstraZeneca chose to cease using EO sterilization related to a regulation that limited exposure limits for manufacturing personnel – a fact that has nothing to do with the pharmaceutical acceptability of the sterilized powder or suspension. See Trial Tr. 692:3-19 (Miller).[45]

AstraZeneca contends that although a POSA was aware of these well-known techniques for reducing EO residuals (i.e., aeration or forced ventilation and vacuum purging), a POSA would

[44] Dr. Zhanel testified as to the reasons that AstraZeneca chose to cease marketing Preferid® as sterile, but his testimony is based solely upon speculation. See Trial Tr. 1575:3-15.

[45] AstraZeneca's assertion that it chose to make Preferid® non-sterile "[o]nce toxicity and other problems with [EO] were discovered," PFOF ¶ 15, is also questionable because of the fact that the concerns with residuals were expressed in the art more than a decade prior to its manufacture of Preferid®.

have no reasonable expectation of successfully reducing the residuals to a pharmaceutically acceptable level. Dr. Zhanel testified that a POSA's tolerance for EO residuals, as of 1997, would have been "near zero," as evidenced by a 1993 recommendation of the European Union that EO residuals in a steroid powder be limited to 1 ppm. See id. at 1568:16-18, 1572:10-21. Looking to the budesonide powder used in Preferid®, Dr. Zhanel stated that a POSA would believe EO residuals amounting to 12 to 22 ppm would yield a pharmaceutically unacceptable product. Id. at 1865:1-9. As such, because a POSA would know based upon the proposed limits that the EO residual limits were gradually moving towards zero, a POSA would have no reasonable expectation of successfully preparing the claimed compositions using EO. See id. at 1865:21-1866:21 (Zhanel).

However, the European guidelines would not have applied in the United States. See id. 1854:7-9. The FDA's 1978 Proposed Rule would only have limited residuals to 10 ppm, but these were never enacted in the more than 30 years since, and EO sterilization continued – and still continues – to be used. Dr. Zhanel's testimony also appears to be based upon his opinion that the EO residual amounts in the Preferid product would be unacceptable in a product intended for injection or nebulization. See id. at 1575:16-1576:4. But these are not limitations of the claim and thus the Court accords less weight

to Dr. Zhanel's opinion. Regardless, as the evidence amply demonstrated, a POSA concerned with achieving a specific level of EO residuals could employ known techniques for reducing residuals and optimize the parameters of any degasification process used in order to achieve the desired level. See infra.

Dr. Zhanel also testified that a POSA reviewing Table V in Adler would not only expect high residues of EO in steroid powders but also understand that the techniques for lessening residuals are ineffective. Trial Tr. 1343:6-12, 1344:7-21. Defendants' expert, Dr. Dalby, acknowledged that Adler reflects that even after 8 hours of vacuum treatment, hydrocortisone tert-butyl acetate (a steroid) still contained 0.51% EO residue as compared to 1.61% EO residue for a sample of the same steroid vacuum treated for only 2 hours. DTX 2272 at 0400673. Dr. Zhanel's conclusion, however, seems to be undermined by the significant reduction in residuals after only 6 hours of vacuum treatment. Id. The Court was persuaded by Dr. Dalby's perspective of the chart: "my characterization would be that more than half of the time it is possible to reduce the level to a reasonably low concentration, but sometimes that's difficult." Trial Tr. 774:21-23.

While recognizing the difficulty, Dr. Dalby testified that the parameters for vacuum purging provided in Adler could be adjusted to achieve the desired level of residuals. See id. at

740:5-741:1, 773:19-24. Notably, the vacuum treatment utilized by Adler consists of significantly less time than the "at least" 72 hour aeration cycle recommended by Clark, or the 48 hour forced ventilation cycle recommended by the Portuguese Patent; even so, the treatment demonstrates a considerable reduction in EO residuals when compared to the 2 hour treatment. It would thus stand to reason that a longer cycle, more consistent with the lengthy cycles taught by the other prior art, would result in even greater reduction in EO residuals as suggested by Dr. Dalby. Further, the experts agree that when a sterilized powder is incorporated into a suspension, any EO residuals would be further diluted. See DRFOF ¶ 71. Thus, the evidence clearly and convincingly demonstrates that a POSA would have known how to reduce potentially toxic residuals to acceptable levels.

b) Penetration of the Crystalline Structure

Defendants also introduced evidence demonstrating that a POSA would not be concerned with the ability of EO to penetrate water insoluble drug crystals like budesonide. Some prior art references suggest that EO is only a surface sterilant and may be unable to penetrate the crystal core of a sterile powder. See, e.g., PTX 2054 at 3. For example, the 1994 Inspection Guide provides

> As a primary means of sterilization, [EO] is questionable because of lack of assurance of penetration into the crystal core of a sterile powder.

> Ethylene oxide has also been utilized in the 'treatment of sterile powders. Its principal use has been for surface sterilization of powders as a precaution against potential microbiological contamination of the sterile powder during aseptic handling.

DTX 1000 at 029008.

Dr. Miller testified that he does not agree that EO is unable to penetrate the crystal core of a sterile powder. First, he is unaware of any scientific evidence demonstrating that spores are trapped within crystals and are not sterilized by EO. Trial Tr. 607:24-608:3. Ms. Moldenhauer similarly testified that she is unaware of any data as of 1997 demonstrating that EO fails to penetrate the crystal core of budesonide. Id. at 315:7-10. Second, Dr. Miller testified that a POSA would have known of Preferid®, a sterile micronized budesonide suspension that had undergone EO treatment but retained purity levels in excess of 98%. Id. at 608:3-9; accord DTX 0004 at 017893, 017901, 017927. Had EO been ineffective in penetrating the budesonide particle, Dr. Miller testified that it would not have been able to pass the sterility test requirements and could not have been marketed as sterile.[46] Third, Dr. Miller testified to a number of sterile ophthalmic corticosteroid suspensions that were on the market that could

[46] While Preferid® was no longer marketed as sterile after 1983, there is no evidence that this was the result of AstraZeneca's discovery that the EO process failed. See supra.

not have met the USP sterility test if occluded spores were not inactivated by EO sterilization. Trial Tr. 608:25-609:7; see also DFOF ¶ 177-92. In other words, if those products contained spores, Dr. Miller testified that a POSA would expect that they would not have been approved in the first place, or that there would have been recalls of the product. But he is not aware of either any recalls due to contamination or lack of sterility issues, or any scientific data suggesting that those sterile ophthalmic glucocorticosteroid suspensions were contaminated. Trial Tr. 609:3-15, 609:23-610:3. The Court finds this testimony to be credible and persuasive and consistent with the teachings of the prior art, specifically Clark.

Contrary to Dr. Miller's testimony, Dr. Akers opined that EO sterilization would not be effective because of its inability to penetrate solid crystalline material. Id. at 2178:7-14. In support, he cited a 1968 article by Charles L. Mullican et al., entitled "Dry Heat or Gaseous Chemical Resistance of Bacillus subtilis var. niger Spores Included Within Water-soluble Crystals," which teaches that EO does not decrease the count of viable bacterial spores encased inside intact crystals of either sodium chloride or glycine. See id. at 2176:17-21 (discussing DTX 0004). However, this experimental research paper does not address sterilization of glucocorticosteroids. Accord id. at 2372:25-2374:6 (Akers). Moreover, Dr. Akers candidly conceded

that he is not aware of any prior art that concludes that EO does not penetrate the core of either budesonide or other corticosteroids. Id. at 2366:1-5. Accordingly, the Court finds this opinion not probative of the issue at hand.

c) Conclusion

In sum, the Court finds that Defendants have clearly and convincingly demonstrated that a POSA, who is admittedly motivated to create sterile budesonide compositions, had a reasonable expectation of successfully creating the claimed compositions using EO sterilization. And, while a POSA was aware that such a sterilization technique may result in potentially toxic EO residuals, a POSA could employ known techniques for reducing those residuals to a pharmaceutically acceptable limit based upon the teachings of the prior art and the knowledge of a POSA. Indeed, a POSA would be aware of not only several sterile ophthalmic suspensions prepared using EO sterilization that continued to be marketed as of 1997 with no evidence of contamination or sterility issues, but also of AstraZeneca's Preferid® product. Thus, after consideration of all of the evidence, including the evidence of secondary considerations addressed below, the Court finds that the asserted claims are invalid as obvious.

iv. Irradiation

Defendants next presented evidence that a POSA would have had a reasonable expectation of success in creating the claimed sterilized budesonide compositions using conventional irradiation sterilization as disclosed in Guy. Defendants contend that the asserted claims are invalid as obvious over Guy in view of Robertson (defined below).

Irradiation consists of using a type of ionizing radiation to kill microorganisms, including beta irradiation, which is an electron beam, or gamma irradiation, which is a radioisotope such as cobalt 60. PRFOF ¶ 155. Prior to 1997, irradiation sterilization processes were well known, a POSA would have understood how to optimize them, and it would be routine for one to do so. Specifically, a POSA would have considered the specific type of irradiation (i.e., beta, gamma), as well as the dose, energy level, and power output for irradiation sterilization. PRFOF ¶ 157.

Guy, filed in 1993 and issued in 1996, discloses pharmaceutically acceptable, sterile, aqueous, ophthalmic glucocorticosteroid suspensions, and teaches each element of the asserted claims except for budesonide. See DFOF ¶¶ 148-54. As a prior art patent, Guy is presumed to be enabled.[47] Amgen, 314

[47] Thus, while Dr. Zhanel takes issue with Guy because it fails to disclose data showing the product was actually

F.3d at 1354-55. Guy explicitly discloses that irradiation can be used to sterilize the glucocorticosteroid used to make the sterile suspensions. DFOF ¶ 154. He further notes that other steroids such as beclomethasone, betamethasone, fluocinolone, fluorometholone, or exednisolone may be employed. DTX 853 at col.4 ll.2-4. In fact, a sterile ophthalmic suspension of loteprednol etabonate was subsequently made and approved for pharmaceutical use. See DFOF ¶ 161.

Moreover, Guy discloses that "[p]urity levels of all materials employed in the suspensions of the invention exceed 98%." DTX 853 at col.3 ll.61-63 (emphasis added); see also PRFOF ¶ 152. The asserted claims of the '834 Patent require that the budesonide be at least 98.5%, and thus it falls within the range disclosed by Guy. The Federal Circuit has held that "'when the difference between the claimed invention and the prior art is the range or value of a particular variable,' then a patent should not issue if 'the difference in range or value is minor.'" Iron Grip Barbell Co., Inc. v. USA Sports, Inc., 392 F.3d 1317, 1321-22 (Fed. Cir. 2004) (quoting Haynes Int'l v. Jessop Steel Co., 8 F.3d 1573, 1577 n.3 (Fed. Cir. 1993); Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 783 (Fed. Cir. 1985)). If the claimed invention falls within the range

---

achieved, a prior art patent is presumed to be valid and enabled.

disclosed by the prior art, the claims are presumed obvious. Id. That presumption may be rebutted if it can be shown: "(1) That the prior art taught away from the claimed invention, In re Geisler, 116 F.3d 1465, 1471 (Fed. Cir. 1997); or (2) that there are new and unexpected results relative to the prior art, In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990)." 392 F.3d at 1321-22. No such showing has been made here with respect to the purity levels.

Although Guy does not disclose the specific irradiation parameters such as type or dosage, Dr. Miller convincingly testified that these parameters were known to a POSA who would engage in routine optimization to determine the specific parameters required to irradiate budesonide. See Trial Tr. 627:13-17. As Dr. Miller explained, other well-known treatises discussed the successful use of irradiation for sterilization of steroids. Id. at 627:18-628:8. For instance, "Remington's Pharmaceutical Sciences" published in 1975, discloses that "[i]onizing radiation has been successfully used for the sterilization of . . . steroids . . . ." DTX 147 at 030060-61. It then describes the irradiation process in more detail, explaining that a POSA must consider the dose, the amount of radiation absorbed by the material, the energy level, and the material's density, inter alia. Trial Tr. 627:18-628:8 (Miller). Similarly, a 1974 publication entitled "Surface area

stability of micronized steroids sterilized by irradiation," published by Lisbeth Illum & Niels Moller ("Illum"), also taught that irradiation could be successfully used on steroids. PTX 513 at 1332166. Illum taught that "degradation of hydrocortisone acetate and prednisone was less than 1 per cent, while for hydrocortisone, prednisolone, and prednisolone hydrate it was about 2-4 per cent." Id. Despite this, Illum concluded "that the steroid powders in question are physically stable when irradiated with doses realistic for irradiation sterilization." Id. Dr. Miller acknowledged that irradiation can but does not always result in undesirable degradation products that could render the product pharmaceutically unacceptable. Trial Tr. 647:8-13. However, the prior art clearly indicates that degradation for some steroids may be minimal. See, e.g., PTX 513 at 1332166. Notably, the inventors of the '834 Patent note that Illum recommends the use of beta or gamma irradiation to sterilize glucocorticosteroids. See PTX 0004 at col.1 ll.62-65.

The only element of the asserted claims that is missing from Guy is budesonide. Dr. Miller persuasively testified that to arrive at a pharmaceutically acceptable, sterile budesonide suspension, a POSA would combine the teachings of Guy with those of U.S. Patent No. 5,589,184, filed March 16, 1995 by Stella M. Robertson et al. ("Robertson"), and entitled "Pharmaceutical Compositions and Methods of Treatment of the Cornea Following

Laser Treatment." See DTX 2298. Robertson, like Guy, is directed to ophthalmic, pharmaceutical compositions and teaches the use of some of the same glucocorticosteroids taught by Guy, such as betamethasone, fluorometholone, and beclomethasone. Id. at col.5 ll.1-22. But, Robertson also teaches that budesonide can be used. DFOF ¶ 164. According to Dr. Miller, these disclosures would cause a POSA to expect to be able to successfully use budesonide in the sterilization process taught in Guy. See also DFOF ¶¶ 149, 163, 188-91.

AstraZeneca argues that a POSA as of 1997 would not have had a reasonable expectation of successfully using irradiation to sterilize budesonide as the prior art taught that irradiation would unacceptably degrade the drug substance and thus it would not meet the purity or pharmaceutical acceptability limitations of the asserted claims. Dr. Zhanel testified that Illum discloses that irradiation of steroids causes degradation of 2% to 4% and a POSA would, therefore, expect reduced purity and degradation products with irradiation sterilization. Trial Tr. 1417:2-16. But, as noted above, Illum concludes that steroid powders remain stable under irradiation and demonstrates certain of the tested steroids experience only minimal degradation, i.e., less than 1%. A POSA would not be dissuaded from using irradiation simply because some prior art references acknowledge that there may be associated degradation. This is because, as

Dr. Miller testified, every sterilization method may cause some level of degradation. Id. at 658:23-25. Even the FDA recognized that irradiation of budesonide was a viable option. During the pre-NDA meeting with the FDA on November 20, 1996, AstraZeneca informed the FDA that gamma irradiation produced degradation, with substances exhibiting 95% potency. See DTX 760 at 1335703. In response, the FDA commended that "lower irradiation doses may be used to reduce bioburden with less degradation." Id. Thus, the evidence supports Dr. Miller's opinion that a POSA would have a reasonable expectation of successfully using this method to sterilize budesonide.

AstraZeneca also argues that other art, as well as the failures of AstraZeneca and the Defendants, demonstrate that irradiation of budesonide is not successful. In the '834 Patent, the inventors conclude "that micronized budesonide can not be satisfactorily sterilized with β- or γ-irradiation, due to significant chemical degradation." PTX 0004 at col.11 ll.43-45. In Comparative Example 8, however, the inventors provide the results of their attempts to irradiate budesonide. Table 8 reflects that when budesonide was exposed to beta irradiation at levels from 2.5 to 25 kGy, the budesonide content exceeded 98.8%. Id. at col.11 ll.10-35. Thus, as Dr. Miller persuasively testified, the inventors' data does not support the conclusion that irradiation unacceptably degrades budesonide.

Trial Tr. 629:13-630:18.[48] The data also shows an increase in the amount of unknown foreign steroids, which Dr. Zhanel testified would be of concern to a POSA. Id. at 1416:19-25. But Dr. Miller credibly testified that a POSA would understand that a pharmaceutical powder can include impurities, id. at 687:4-7, and indeed, the reference sample of budesonide tested by the inventors contained unknown foreign steroids even before irradiation.[49] The amount of unknown foreign steroids for certain irradiation dosages appear quite similar to those in Table 1, which provides data regarding AstraZeneca's heat treatment process. DTX 0004 at col.7 ll.18-33 (examples 7, 10). Moreover, there was no credible evidence, and Dr. Zhanel pointed to none, demonstrating that these levels would be considered pharmaceutically unacceptable. Finally, it is worth noting that even as to AstraZeneca's irradiation experiments, Dr. Elkins testified that these showed "feasibility" but that the amount of

[48] In its Findings of Fact, AstraZeneca stated that Ms. Moldenhauer confirmed that Table 8 "shows an unacceptable amount of unknown foreign steroids . . . ." PFOF ¶ 89. However, it cites no testimony in support of this bare statement. It further cites testimony of Dr. Miller but it does not support AstraZeneca's conclusion. Dr. Miller merely confirmed the amounts of unknown foreign steroids reflected in that table.

[49] When AstraZeneca met with the FDA in 1996, it provided chemical properties for its proposed budesonide product. Those properties provide for total impurities/degradants not to exceed 2.0% and any individual unknown degradants not to exceed 0.3%. DTX 760 at 1335719. Thus, the mere presence of unknown degradants would be insufficient to conclude that irradiation is unsuccessful.

work required to create a commercial process was more than would be required of dry heat. 2012 Trial Tr. 655:11-21. She further stated that she "would not classify [the irradiation experiments] as unsuccessful." Id.

AstraZeneca points to Defendants' purported failures to produce the claimed product through irradiation sterilization. Any such post-art failures are irrelevant to this Court's obviousness analysis. Even if relevant, the evidence does not demonstrate that either Apotex or Crystal Pharma failed to make the claimed products; nor does the evidence demonstrate a failure to use irradiation. At most, the evidence suggests that Apotex failed to sterilize by irradiation the final product, or suspension. See DTX 131 at 021099-100. The Crystal Pharma decision tree on which AstraZeneca relies was uncorroborated by any testimonial evidence by individuals with personal knowledge regarding either that document or Crystal Pharma's efforts to sterilize budesonide. See DTX 475; DRFOF ¶ 12. As such, AstraZeneca's conclusions are based solely upon speculation.

Finally, although the PTO Examiner considered Guy during patent prosecution, she focused on Guy's teaching that disodium edentate ("EDTA") could be added to a suspension to prevent microbial growth. See, e.g., DTX 0004 at 017496; see also id.

at 017534.[50] She does not appear to have the addressed Guy in conjunction with the arguments set forth herein.

Accordingly, after considering the evidence set forth above, as well as the evidence of secondary considerations set forth infra, Defendants have presented clear and convincing evidence that a POSA, admittedly motivated to prepare the claimed sterilized budesonide compositions, would have had a reasonable expectation of successfully doing so using the conventional sterilization technique of irradiation based upon the teachings of Guy in view of Robertson.

v. Dry Heat

Finally, Defendants argue that a POSA would have had a reasonable expectation of success in creating the claimed sterilized budesonide compositions using conventional dry heat sterilization, as disclosed in Clark, in combination with the knowledge of a POSA. Defendants contend that the asserted claims are invalid as obvious over Clark.

In addition to disclosing the use of EO, Clark also discloses that dry heat may be used to sterilize the

[50] The Examiner repeatedly rejected other sterile powder claims as obvious to make by irradiation. See, e.g., DTX 0004 at 017325, 017594. In addressing the Examiner's rejection, AstraZeneca made several arguments to overcome the other cited references, including arguments based upon the presence of irradiation byproducts and the fact that the sterile composition would be distinct from one that contained heat-killed bacteria. See, e.g., DTX 0004 at 017628. These are not applicable here.

glucocorticosteroid used to make the sterile ophthalmic suspensions that are the subject of his patent. PRFOF ¶ 118. Dry heat sterilization consists of placing a material to be sterilized into a chamber that functions like an oven, closing the chamber, introducing filtered air into the chamber, and raising it to a high temperature for an exposure period sufficient to sterilize. PRFOF ¶ 119.

As of 1997, a POSA understood that there is an inverse relationship between temperature and time, and that one can decrease the temperature and increase the time required for sterilization. See DFOF ¶ 121. The proper time and temperature would be based upon the characteristics of the drug product itself. PRFOF ¶ 122. However, the parties agree that a POSA would have understood that typical or conventional dry heat sterilization cycles as of 1997 run at temperatures from 140-180°C. See PRFOF ¶ 123.

Defendants contend that a POSA, understanding the inverse relationship between time and temperature, and knowing that some substances cannot withstand the typical temperatures, would have known to use temperatures lower than the typical temperatures and it would have been routine to do so. Dr. Miller testified that a POSA attempting to sterilize budesonide in 1997 would have tried lower temperatures. Trial Tr. 594:10-14. In support, he cites Remington, which provides that "[i]n dealing

with pharmaceutical preparations, however, it must be emphasized that long experience has shown that many preparations cannot be subjected to such temperatures and other dry heat sterilization cycles have been established according to the nature of the various products." See id. at 593:18-23 (quoting DTX 147 at 0300155). According to Dr. Miller, Remington thus taught lower temperatures than 140°C for those pharmaceutical preparations that may not be able to withstand higher temperatures. Id. at 594:3-7.

Although Dr. Miller's testimony was credible, it is difficult to find that it was not influenced by what the inventors did here. None of the prior art references addressing dry heat provide a dry heat sterilization cycle with temperatures below 140°C. Dr. Zhanel testified that a POSA was aware that these unconventional temperatures were considered to be sublethal temperatures at which a product could not be sterilized. Id. at 1297:18-20. Moreover, by 1997, the trend was to use higher – not lower – temperatures. Ansel, published 20 years after the Remington reference on which Dr. Miller relies, teaches "Because dry heat is less effective in killing microorganisms than is moist heat, higher temperatures and longer periods of exposure are required." DTX 851 at 018243. While Ansel also recognizes that temperatures and times may be tailored to the particular substance sought to be sterilized, he

provides only the typical temperature range. Id. ("For example, if a particular chemical agent melts or decomposes at 170°C, but is unaffected at 140°C, the lower temperature would be employed in its sterilization, and the exposure time would be increased over that required to sterilize another chemical that may be safely heated to 170°C.").

The Court questioned from time to time whether AstraZeneca's invention consisted of simply turning down the heat on the oven. It seemed to be common sense to do so, especially for a POSA taught to optimize a dry heat cycle by altering the time and temperature so as to achieve sterilization. The prior art, however, clearly taught that any such optimization should occur with a specific temperature range, 140 to 170°C, with a trend toward higher temperatures. AstraZeneca's heat sterilization process is directed to temperatures ranging from 100 to 130°C, preferably between 110 to 120°C. Thus, the Court finds that Defendants have failed to clearly and convincingly demonstrate that a POSA would have had a reasonable expectation of successfully creating the claimed budesonide compositions using dry heat temperatures below the conventional range.[51]

[51] During closing arguments, Plaintiffs conceded that their secondary consideration argument as to unexpected results is relevant only to the dry heat sterilization method. See Trial Tr. 3504:12-24. Because the Court finds that Defendants failed

c. Secondary Considerations

Turning to the final Graham factor, the Court considers the significance and relevance of any secondary considerations. "[S]econdary considerations [such] as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented" and "may have relevancy" as indicia of obviousness or nonobviousness. Graham, 383 U.S. at 17-18. "A nonmovant may rebut a prima facie showing of obviousness with objective indicia of nonobviousness." Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311 (Fed. Cir. 2006) (citing WMS Gaming, Inc. v. Int'l Game Tech., 184 F.3d 1339, 1359 (Fed. Cir. 1999); In re Kahn, 441 F.3d 977, 990 (Fed. Cir. 2006)). "Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." In re Huai-Hung Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (quoting Pfizer, 480 F.3d at 1372).

---

to submit sufficient evidence demonstrating a reasonable expectation of success using dry heat, even in the absence of evidence of the unexpected results of such a process, it need not address the parties' arguments regarding this secondary consideration. See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1363 (Fed. Cir. 2007) ("In light of our conclusion that Alphapharm failed to prove that the claimed compounds would have been prima facie obvious, we need not consider any objective indicia of nonobviousness."); Otsuka Pharm. Co., Ltd. v. Sandoz, Inc., 678 F.3d 1280, 1296 (Fed. Cir. 2012) (same).

Secondary considerations must be "reasonably commensurate" with the scope of the claims. In re Huai-Hung Kao, 639 F.3d at 1068. "This does not mean that an applicant is required to test every embodiment within the scope of his or her claims. If an applicant demonstrates that an embodiment has an unexpected result and provides an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner, this will generally establish that the evidence is commensurate with scope of the claims." Id. (citations omitted).

In addition, the Federal Circuit requires the patentee to demonstrate a nexus "between the claimed features of the invention and the objective evidence offered to show non-obviousness." WMS Gaming, 184 F.3d at 1359 (citing Cable Elec. Prods., Inc. v. Genmark, Inc., 770 F.2d 1015, 1027 (Fed. Cir. 1985)). "[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent." Ormco Corp., 463 F.3d at 1312; see also In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990); Tokai Corp. v. Easton Enters., Inc., 632 F.3d 1358, 1369 (Fed. Cir. 2011).

AstraZeneca urges this Court to evaluate seriously the objective indicia of nonobviousness, which AstraZeneca contends will prevent this Court from employing a hindsight bias in consideration of the prior art. Specifically, AstraZeneca

points to (a) industry skepticism, (b) long-felt, unmet need, (c) the failure of AstraZeneca and others, and (d) commercial success. For the reasons discussed below, the Court rejects each of these considerations as insufficient to overcome the strong evidence of obviousness.

i. Industry Skepticism

"[S]kepticism of skilled artisans before the invention" can demonstrate nonobviousness. Santarus, Inc. v. Par Pharm., Inc., 720 F. Supp. 2d 427, 456 (D. Del. 2010), aff'd in relevant part, 694 F.3d 1344, 1358 (Fed. Cir. 2012); see also In re Hedges, 783 F.3d 1039, 1041 (Fed. Cir. 1986) (proceeding contrary to the accepted wisdom can be "strong evidence of unobviousness"). AstraZeneca contends that the industry and POSAs believed the sterilization of budesonide was impossible, and that AstraZeneca and the FDA were skeptical that the patented product could be made.

As an initial matter, whether or not AstraZeneca's employees believed that a budesonide suspension could be sterilized using dry heat or any other known method is not the proper inquiry. The focus of this consideration is skepticism of others, not skepticism of the inventors. Santarus, 720 F. Supp. 2d at 456. Nonetheless, the evidence did not demonstrate universal skepticism even within AstraZeneca. AstraZeneca relies upon slides that its scientists created in preparation

for its November 1996 pre-NDA meeting, which provide "Sterilization of BNS [budesonide nebulizing suspension] is not required and not feasible." PTX 530 at 1337011. However, these slides reflect only "potential" disadvantages of each sterilization technique and were created prior to the FDA's instruction that AstraZeneca prepare a sterile product or prove that it could not be done.

Moreover, subsequent internal documents reflect opinions that the preliminary data collected in preparation for further meetings with the FDA do not support the conclusion that the drug substance cannot be sterilized. See, e.g., PTX 516 at 1334613 ("The documents do not provide conclusive evidence that the drug substance cannot be sterilized. In fact, in several instances the statements made are not supported by the data presented."); see also PTX 515 ("I don't think we can produce a sterile product!"); 2012 Trial Tr. 689:6-17. As mentioned earlier, even inventor Elkins admitted irradiation and EO were not unsuccessful at producing sterilized budesonide. 2012 Trial Tr. (Elkins) 655:11-18 ("I would not classify [attempts at irradiating the micronized budesonide] as unsuccessful. I think that they were feasible . . . ."); id. at 657:2-9 ("[T]hese were feasibility experiments, they were not further pursued. The initial result of those experiments indicated that residuals from the ethylene oxide treatment would require further

development to see whether or not a successful process could be developed."); see also id. at 655:22-656:2.

AstraZeneca also contends that as of 1997, it was generally believed in the industry that budesonide powder compositions and suspensions could not be sterilized in a way that preserved purity and pharmaceutical acceptability. See PFOF ¶ 24. In support, however, it cites only to itself. Id. For example, it cites a statement within Defendant Breath's McAffer Patent that "the sterilization of budesonide is generally considered by the market to be impossible," but that statement cites an AstraZeneca document that provides the basis for the '834 Patent. See PTX 507 at col.4 ll.45-49; accord DTX 0004 at 017807. Hence, as this Court has previously held, AstraZeneca's attempt to cast the statements in the McAffer Patent as Breath's independent description of the state of the art is rejected. See AstraZeneca LP v. Breath Ltd., No. 08-1512, 2014 WL 2526909, at *10 (D.N.J. June 4, 2014). The patentee, Ian McAffer, explained that this statement was also based upon communications from a few pharmaceutical companies that had failed to sterilize budesonide in which they expressed their belief that it was impossible.[52] See Trial Tr. 2540:23-2541:5. However, in those same communications, the companies requested that Breath make

[52] The record contains no evidence as to the nature of these companies' efforts to sterilize budesonide.

sterile budesonide for them, id., suggesting, it seems, that they did not actually believe such a task was impossible. Finally, McAffer testified consistently that the scientific community, as opposed to the market, did not believe that the sterilization of budesonide was impossible. See 2012 Trial Tr. 3551:11–3552:9 ("there was a belief in the marketplace, not necessarily the scientific community, that the sterilization of budesonide was generally considered by the market to be impossible"); Trial Tr. 2540:13-17; see also DRFOF ¶ 23. Thus, the evidence does not demonstrate the industry-wide skepticism AstraZeneca describes.

As for AstraZeneca's contention that the FDA exhibited skepticism that budesonide could be sterilized, there is simply insufficient evidence to support this contention. In fact, the evidence is to the contrary. During the pre-NDA meeting with the FDA on November 20, 1996, the FDA acknowledged the technical difficulties associated with the sterilization of suspensions but in no way expressed its belief that it could not be done. DTX 760 at 1335702. Rather, the FDA commented that it "expects sterile products for both solutions and suspension for inhalation." Id. The agency further stated that "it would be precedent-setting to approve a nonsterile inhalation product" and thus "the first goal should be a sterile product." Id. at 1335703. These statements to AstraZeneca are consistent with

statements the FDA had made to POSAs as early as the mid-'90s: any aqueous-based inhalation products must be sterile. See DFOF ¶¶ 234-35.

Most notably, during the pre-NDA meeting the FDA queried AstraZeneca as to what sterilization methods it had tried and actually offered suggestions for alternative methods of sterilization. See, e.g., DTX 760 at 1335703 ("G. Poochkian commented that lower irradiation does may be used to reduce bioburden with less degradation and this should be considered."). The FDA told AstraZeneca that it was "their [AstraZeneca's] burden to make the product sterile or justify why it can't be."[53] See PFOF ¶ 18. These statements are hardly indicative of the FDA skepticism AstraZeneca describes. The FDA simply placed the onus on AstraZeneca to prove impossibility (or otherwise) because, as AstraZeneca's own witness, Mr. Peter Mathers, testified,[54] the FDA does not conduct its own testing or

[53] See also DTX 760 at 1335703 ("J. Jenkins repeated and strongly urged that the first goal should be a sterile product. If a sterile product can be proven to be unfeasible, these attempts should be discussed with the Division. Otherwise attempts should be made to reduce the bioburden as much as possible. However, FDA is not in favor of accepting a nonsterile product.").

[54] During the trial, Defendants objected to the introduction of Mr. Mathers' testimony under Federal Rules of Evidence 702 and 403, and also as untimely offered to rebut the opinions of Mr. Muhvich, which were at issue in the first trial. The Court reserved on the objection but permitted the testimony. See Docket No. 1074. The Court now overrules Defendants' objections. Defendants contend that Mr. Mathers' opinion is

research. The Court questioned Mr. Mathers whether, in his experience, the FDA asks a manufacturer to do what it knows is impossible, to which Mr. Mathers responded:

---

based only upon his experience as an attorney reading and interpreting regulations and thus he is not competent to testify under Federal Rule of Evidence 702. Docket No. 1072 at 7. Under Federal Rule of Evidence 702:

> A witness, qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if: (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert has reliably applied the principles and methods to the facts of the case.

Dymnioski v. Crown Equip. Corp., No. 11-3696, 2013 WL 2297035, at *2 (D.N.J. May 24, 2013). The Court finds that Mr. Mathers, a regulatory lawyer who has practiced before the FDA for over 35 years, possesses specialized knowledge that can assist the Court in understanding the manner in which the FDA issues rules and regulations. Accordingly, his testimony is admissible under Rule 702.

Defendants also argue that Mr. Mathers' testimony is cumulative in violation of Rule 403 as it merely rebuts the same opinions that Mr. Muhvich proffered in the first trial and thus impermissibly provides Plaintiffs with a "redo". See Fed. R. Evid. 403 (permitting Court to exclude evidence where there is "a danger of . . . undue delay, wasting time, or needlessly presenting cumulative evidence"). For similar reasons, Defendants argue that Mr. Mathers' report was untimely disclosed in violation of Federal Rule of Civil Procedure 27(a)(2)(B). In response, AstraZeneca argues that Mr. Mathers' opinions rebut a new issue first raised by Dr. Muhvich in his 2014 responsive expert report, i.e., whether the FDA's Final Rule in 2000 was affected by AstraZeneca's apparent successful sterilization of an inhaled suspension product. Because the Court ultimately finds Mr. Mathers' opinions to be unpersuasive, it need not address these objections.

> No. But often they ask people to do things that they don't know are possible in order to find out if it's possible. Because it's the manufacturer that has to generate the data, FDA doesn't do any -- almost any tests, all the tests that are done are done by the sponsors of the products at the behest of FDA or as part of an effort to convince the FDA that what is possible is possible and what -- what they've done is adequate.

Trial Tr. 1167:12-19. In other words, the FDA was not skeptical as to whether budesonide could be sterilized; it simply did not know whether it could be done or not because it did not have sufficient data. Mr. Mathers confirms this finding:

> Q. Are you rendering any opinion on the ultimate conclusion of whether FDA was skeptical as to whether an inhalation suspension product could be prepared as sterile by 1997? A. I don't know whether they were skeptical, I just know what they said. THE COURT: . . . . You said that FDA was unsure whether it could be done, that's how you read the document, is that another way of saying that the FDA thought it might be possible that it could be done? THE WITNESS: Yes. Well, yes, that it's possible that it could be done. And it's also possible that Astra could go to sufficient lengths to try and yet still fail to have an acceptable sterile product so that it could also not be possible.

See id. at 1166:16-1167:7 (emphasis added). Thus, the FDA instructed AstraZeneca to perform the tests and collect sufficient data.

AstraZeneca places great emphasis on the fact that the FDA did not impose a regulatory requirement on the industry that inhaled aqueous suspensions be made sterile until after AstraZeneca had demonstrated that this was possible with

budesonide. See PFOF ¶ 11. Specifically, AstraZeneca argues that in the interim between the 1997 Proposed Rule (directed to inhalation solutions) and the 2000 Final Rule (covering all aqueous-based oral inhalation products), the FDA completed its microbiology review of AstraZeneca's Pulmicort Respules NDA. The review was signed on September 2 and September 15, 1998, thereby indicating as of those dates that the microbiologists were satisfied with the sterility assurance set forth in AstraZeneca's NDA. See PTX 2305 at 0166959; Trial Tr. 1147:3-22 (Mathers). From this, AstraZeneca urges the Court to conclude that the FDA believed sterilization of a suspension could not be done, and that it only imposed a regulatory requirement (i.e., the 2000 Final Rule) that required both solutions and suspensions be sterilized in response to AstraZeneca's purportedly unexpected success. The evidence does not support this finding.

As discussed above, the 1997 Proposed Rule explicitly required only that aqueous inhalation solutions be sterile. DTX 872. Mr. Mathers testified that the FDA is very deliberate in their choice of words and thus the 1997 Proposed Rule intentionally did not cover suspension products. Trial Tr. 1128:11-16. Dr. Muhvich persuasively testified, however, that the Proposed Rule was intended to apply to both solutions and suspensions. Id. at 1053:21-1054:2. Moreover, the parties

agree that at the time of the 1997 Proposed Rule there was a motivation to make all aqueous-based products, solutions and suspensions, sterile. POSAs understood this. See supra.

As discussed supra, on December 1, 1997, Dr. Muhvich submitted a written comment to the FDA encouraging it to require inhalation suspensions, as well as solutions, be made sterile because of the similar contamination risks for both product types. PTX 3076. Dr. Muhvich's comment, submitted after he left the FDA, appears to have been intended to clarify the scope of the rule for the industry. The FDA stated that it had received a total of 61 comments on the 1997 Proposed Rule. "The majority of comments requested clarification of the scope of the rule and the drug products intended to be covered . . . . In response to these comments, the agency has revised the final rule to state [that all aqueous-based drug products must be sterile]." DTX 915 at 024786 (emphasis added). Hence, on May 11, 2000, the FDA published the Final Rule, which explicitly requires all "aqueous-based drug products for oral inhalation be manufactured sterile." Id. at 024785. The FDA's explanation that it clarified the Final Rule ***as a result of the comments*** submitted negates AstraZeneca's speculation that its own invention prompted an expansion of the scope. Indeed, when asked about the "impetus" for changing the language in the Final Rule to explicitly cover suspensions, Mr. Mathers, AstraZeneca's

witness, opined that it was Dr. Muhvich's comment that motivated the change – and not AstraZeneca's successful sterilization of budesonide:

> THE COURT: I just want to know what's the language. When you say the impetus, what language are you referring to?
>
> THE WITNESS: Well, the impetus -- well, the impetus was originally stated -- the impetus originally stated in the proposed rule was that there were safety issues with having oral inhalation solution products that were unsterile and that were leading to adverse experiences and recalls because of those products being contaminated. The point was made and addressed in the final rule where FDA refers to a comment that was received which points out that suspension products are potentially subject to similar concerns and that suggested that FDA expand the rule to encompass suspension products because of that. The impetus -- I take that to be the impetus, the safety concern that FDA is addressing here in imposing a sterility requirement.

Trial Tr. 1177:23-1178:12. Finally, it is noteworthy that Mr. Muhvich's comment – dated December 1, 1997, only a few weeks after the critical date - also informed the FDA that he was "personally aware of several inhalation **suspension** products which are now in development for human use." PTX 3076. Because POSAs knew from the FDA that it expected any inhalation products, including suspensions, to be sterile, Muhvich's statement certainly indicates that entities other than AstraZeneca were creating sterile suspensions which further

undermines AstraZeneca's position.[55] In the end, AstraZeneca's contention that the FDA changed its Final Rule in response to the allegedly novel '834 Patent is just hype and speculation.

As such, the evidence does not demonstrate skepticism on the part of the industry, the FDA, or even AstraZeneca, and thus does not demonstrate the nonobviousness of the asserted claims.

ii. Long-felt, Unmet Need

"Evidence that an invention satisfied a long-felt and unmet need that existed on the patent's filing date is a secondary consideration of nonobviousness." Perfect Web Techs., Inc. v. InfoUSA, Inc., 587 F.3d 1324, 1332 (Fed. Cir. 2009). If prior art products were effective for the purpose of the claimed invention, there is no long-felt need. See, e.g., B.F. Goodrich Co. v. Aircraft Braking Sys. Corp., 72 F.3d 1577, 1583 (Fed. Cir. 1996) (discounting long-felt need because invention "was similar to the teachings" of prior art).

Evidence of the long-felt need factor must squarely address the need satisfied by the asserted claims themselves. AstraZeneca proffered evidence of a long-felt, unmet need for an aqueous, sterile, nebulized, inhaled corticosteroid for the long-term maintenance treatment of asthma in young children. See PRFOF ¶ 220. The evidence here clearly demonstrated,

[55] No party examined Muhvich on this statement.

however, that a nonsterile Pulmicort Respules® would have satisfied the long-felt, unmet need.

It is true, as AstraZeneca has claimed, that a sterile product may have been preferred based on health risks. Yet, the evidence conclusively established that, had the FDA determined that Pulmicort Respules® could be sold in the United States without being sterile, the unmet need would have been met. For example, several physicians testified that nonsterile Pulmicort Respules® would have addressed their patients' needs. Dr. Raul Wolf, a treating physician with a clinical practice who testified on behalf of Defendants, stated:

> Q. [I]f there was a need for a treatment, an asthma treatment for young children by 1997, would the non-sterile product have met that need?
>
> A. Yes, it would have.

Trial Tr. 1955:25-1956:3. He subsequently confirmed:

> Q. In your opinion, if the European Pulmicort or Canadian Pulmicort products had been available in the United States by 1997, would those products have met the need of those patients who would not use MDIs [metered-dose inhalers] or DPIs [dry powder inhalers]?
>
> A. They certainly would have.
>
> Q. And do you agree that those products would have met that need even if they were in nonsterile form?
>
> A. Yes, they would have.

Id. at 2019:23-2020:5.

Dr. Peter Barnes, a treating physician, testified that the European Pulmicort Respules® satisfied the need to treat young

children under the age of three who were unable to use effectively the other inhalation devices. See id. at 2549:4-18. That need was the same for children of similar age in the United States. AstraZeneca's own witness, Dr. Kathleen O'Connor Ververelli, testified that physicians treating pediatric asthma in young children, "really needed a product that was safe and approved by the FDA for that particular grouping of children" in a nebulized delivery form. Id. at 893:20-24. But, importantly, she acknowledged that the need was really the nebulized budesonide. Id. at 894:13-18. That need was satisfied by the nonsterile Pulmicort Respules available in Europe and the only thing that stood in the way was FDA approval. See id. at 895:1-16. Yet, had the FDA approved a nonsterile Pulmicort Respules product, Dr. Ververelli candidly admitted, it would have satisfied the need:

> Q. If FDA had approved non-sterile Pulmicort®, would that have met your unmet need that you've been testifying about?
>
> A. I think that's kind of playing Monday morning quarterback because it's hard to say, but if the FDA felt that even though the solutions had to be sterilized and the suspension did not have to be sterilized, then yes.
>
> Q. Yes, that would have met the need?
>
> A. Yes.

Id. at 973:22-974:5. Dr. Zhanel, a microbiologist, also testified as to the long-felt need.

> Q. Now, Dr. Zhanel, could you summarize for the Court what the long-felt need was and your position about whether that need was met as of 1997?
>
> A. Yes. So as I said, there may have been a need for sterile steroid suspensions in the injectable world and in the ophthalmic world, but the driving need, and a person of ordinary skill knew that, was for a **sterile** steroid suspension, that would be of high purity and it would be acceptable pharmaceutically to be used as a nebulizing suspension in these young kids with asthma, when other things didn't work.

Id. at 1292:6-16 (emphasis added); see also id. at 1306:7-14. This testimony, however, contradicts Dr. Ververelli's testimony that the need was for nebulized budesonide and would have been satisfied by a nonsterile product. The Court affords more weight to the opinion of Dr. Ververelli, a treating physician, as it is consistent with the other evidence of record. Thus, while sterility may have been important, it was not the long-felt need. Rather, physicians wanted the nebulized corticosteroid that had demonstrated efficacy overseas.[56]

Accordingly, AstraZeneca's attempt to equate the FDA's need[57] for sterile aqueous-based inhalation products with the

[56] Dr. Ververelli testified that doctors were asking about bringing Pulmicort Respules® to the United Sates "because we had been seeing the evidence from the European literature about the benefits of this medication." Trial Tr. 886:12-17; see also id. at 887:20-888:2 (doctors were desperately seeking Pulmicort Respules in the United States because they became aware of the nonsterile European product around 1994-1995 and "how well it was doing," but they were told the FDA required sterility).

[57] The evidence of this "need" is debatable as the FDA left open the possibility that it would approve a nonsterile product

community's long-felt need for a nebulized suspension is misplaced. While AstraZeneca argues that Federal Circuit case law, and specifically Knoll Pharm. Co., Inc. v. Teva Pharm. USA, Inc., 367 F.3d 1381 (Fed. Cir. 2004), "compels the conclusion" that there is a nexus between the asserted claims and the long-felt need, the Court disagrees. There, the patent was directed to methods and compositions for pain treatment through administration of a combination of hydrocodone and ibuprofen. Id. at 1382-83. The patentee had proffered evidence on summary judgment of the failure of two pharmaceutical companies to obtain FDA approval for other opioid-NSAID combinations. In concluding the district court erred by failing to view the evidence in the light most favorable to the patentee, the Federal Circuit briefly noted that "the conflicting evidence reinforces the patentee's argument that the activity observed for the patented combination is not routinely present for all opioid-NSAID combinations," thereby suggesting the nonobviousness of the patented invention. Id. at 1385. Contrary to Plaintiffs' assertion, there is no "significant overlap" between the facts of Knoll and the instant matter as, here, there is no evidence of any attempts or failures to obtain FDA approval. To the contrary, Defendants received FDA approval

---

if AstraZeneca made a convincing demonstration that such was necessary.

for their ANDA products. See generally Docket No. 843.[58] Accordingly, for the reasons stated above, AstraZeneca has failed to demonstrate a nexus between the novel feature of the '834 Patent (i.e., sterility) and the long-felt, unmet need.

In addition, AstraZeneca's evidence as to the long-felt, unmet need is not reasonably commensurate with the scope of the claims as it goes to only a single embodiment of the claims – Pulmicort Respules®. See In re Huai-Hung Kao, 639 F.3d at 1068 ("Evidence of secondary considerations must be reasonably commensurate with the scope of the claims. . . . If an applicant demonstrates that an embodiment has an unexpected result and provides an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner, this will generally establish that the evidence is commensurate with scope of the claims."). None of the asserted claims are directed to a nebulized inhalation product that is used in the long-term treatment of asthma in young children. Rather, they are much broader in scope. See In re

[58] AstraZeneca's reliance on Leo Pharmaceutical Products, Ltd. v. Rea, 726 F.3d 1346, 1358 (Fed. Cir. 2013), is similarly unavailing. There, the court held "While FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness. Here, FDA approval highlights that Leo Pharmaceutical's formulation is truly storage stable, something that the prior art formulations did not achieve." In this matter, however, there were a number of sterile pharmaceutically acceptable corticosteroids on the market and thus the reasoning of Leo is inapposite.

Greenfield, 571 F.2d 1185, 1189 (C.C.P.A. 1978) (finding evidence of secondary considerations was not commensurate with the scope of the claims where evidence related to only one compound and there was no adequate basis to conclude that other compounds included within the scope of the claims would behave in the same manner); see also Dome Patent, L.P. v. Rea, No. 07-1695, 2014 WL 2948927, at *27 (D.D.C. July 1, 2014) ("Evidence of secondary considerations 'is not commensurate with the claims if the claims are broader than the scope' of such evidence. . . . 'The claims are broader in scope than the objective evidence if a limitation or element recited in the claim is broader than the limitation or element in the objective evidence . . . or if the objective evidence contains limitations or elements not recited in the claims.'" (citations omitted)). Because AstraZeneca's evidence of a long-felt, unmet need relates in large part to limitations or elements that do not form part of the asserted claims, there is no evidence to infer that other embodiments of the asserted claims would satisfy that long-felt, unmet need.

iii. Failures of AstraZeneca and Others

Evidence that others within the field have tried and failed to make the claimed invention can demonstrate that the invention was nonobvious. See, e.g., Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1285 (Fed. Cir. 2000). "Failure of

others 'to find a solution to the problem which the patent[] in question purport[s] to solve' is evidence of non-obviousness." Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 923 F. Supp. 2d 602, 680 (D. Del. 2013), aff'd 752 F.3d 967 (Fed. Cir. 2014), (quoting Symbol Techs., Inc. v. Opticon, Inc., 935 F.2d 1569, 1578 (Fed. Cir. 1991)). The purpose of this evidence "is to show 'indirectly the presence of a significant defect in the prior art, while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan.'" In re Cyclobenzaprine, 676 F.3d at 1082 (citation omitted). "In the pharmaceutical industry, the failure of others to develop a safe and effective drug often supports the nonobviousness of a drug that finally achieves success." Teva Pharma. USA, Inc. v. Sandoz, Inc., 876 F. Supp. 2d 295, 417 (S.D.N.Y. 2012).

AstraZeneca introduced evidence of its own failures to create the claimed budesonide compositions using conventional sterilization techniques other than dry heat. Defendants argue, however, that evidence of AstraZeneca's failures is legally irrelevant as it is only the failures of others that indicate nonobviousness. The Court agrees that the focus of this secondary consideration should be the failure of others and not the failure of the inventors, see, e.g., Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 759 (N.D. W. Va. 2004) ("In the context of secondary considerations, the Federal

Circuit has generally focused on the prior failures of others in the industry, not the inventors."), aff'd 161 F. App'x 944 (4th Cir. 2005); In re Cyclobenzaprine, 676 F.3d at 1081 ("Evidence that others tried but failed to develop a claimed invention may carry significant weight in an obviousness inquiry."); Bristol-Myers Squibb Co. v. Teva Pharma. USA, Inc., 923 F. Supp. 2d 602, 681-82 (D. Del. 2013) (same); Advanced Display Sys., 212 F.3d at 1285 (citing cases), but nonetheless the Court has considered AstraZeneca's evidence of its own failures.[59]

AstraZeneca has consistently contended that its own failures at sterilizing, other than low dry heat sterilization, are compelling evidence of nonobviousness. But the record is not as compelling as AstraZeneca makes it out to be. The record demonstrates that AstraZeneca created and marketed a pharmaceutically acceptable sterile product with Preferid® as early as the 1980s. There was no evidence that any EO residues rendered Preferid® pharmaceutically unacceptable or that AstraZeneca experienced problems with penetration of the crystal core of the budesonide molecule. Moreover, Dr. Elkins testified that AstraZeneca's irradiation experiments showed "feasibility" but that the amount of work required to create a commercial

[59] Several of the cases on which AstraZeneca relies to demonstrate the relevance of its own failures did not explicitly consider the inventor's failures in the context of secondary considerations. See, e.g., Sanofi-Sythelabo v. Apotex, Inc., 550 F.3d 1075, 1088 (Fed. Cir. 2008).

process was more than would be required of dry heat. 2012 Trial Tr. 655:11-21. She further stated that she "would not classify [the irradiation experiments] as unsuccessful." Id. And, importantly, like Defendants, AstraZeneca ultimately prepared sterilized budesonide compositions; AstraZeneca did so using its patented low dry heat process within months of being instructed to do so by the FDA.[60]

Although failures of others may demonstrate nonobviousness, there must be some understanding of the nature of those failures. See Advanced Display Sys., 212 F.3d at 1285; Orthopedic Equip. Co. v. All Orthopedic Appliances, Inc., 707 F.2d 1376, 1382 (Fed. Cir. 1983) (finding while claimed invention made it possible to decrease inventories, there was "no evidence of any previous, unsuccessful attempts to reduce inventories"), abrogated on other grounds by Therasense, Inc. v. Becton, Dickinson & Co., 649 F.3d 1276 (Fed. Cir. 2011). Here, there is insufficient evidence of the extent or nature of any of Defendants' attempts to make a sterilized budesonide suspension from which this Court could make the finding AstraZeneca urges. AstraZeneca introduced an internal decision tree prepared by Crystal Pharma, Breath/Watson's supplier of sterile micronized

[60] Cf. Gusmer v. Parker, No. 79-2119, 1980 WL 30238, at *8 (D.D.C. 1980) (considering inventor's years of research activity in which he tested over 180 research items involving multiple configurations supported court's conclusion of nonobviousness).

budesonide, that purportedly shows Crystal Pharma chose filter sterilization after it determined the product could not be sterilized using conventional methods such as dry heat and ionizing radiation. See DTX 475 at 000148. However, there was no competent evidence that Crystal Pharma considered or even performed each of the listed steps.[61] See Trial Tr. 2341:2-6 (Akers) ("Q. So the fact is you don't know whether Crystal Pharma performed any methods other than sterile crystallization, correct? A. I don't absolutely know. No, I don't know with an absolute degree of certainty."). Dr. Akers acknowledged that he would not expect the Drug Master File he reviewed to contain any feasibility studies regarding any other sterilization methods, and in fact there were none. Id. at 2341:10-21. He further agreed that it was plausible that Crystal Pharma did not perform the other sterilization methods and that it did not do so because it focuses its business on sterile crystallization. Id. at 2342:15-19. Moreover, Dr. Akers testified that the Crystal Pharma decision tree is taken "verbatim" from a decision tree published by the European Medicines Agency, which was designed "to assist in the selection of the optimal sterilisation method." See id. at 2343:2-5 (Akers); PTX 1888 at 029930,

[61] AstraZeneca chose not to depose a Crystal Pharma representative. See Docket No. 144.

029933. Thus, the chart was not even designed by Crystal Pharma.

As for Apotex, the evidence shows that it attempted to use irradiation to terminally sterilize the final suspension. An Apotex progress report reflects that "Samples sent out for alternate way to sterilize FP. FP subjected to various dose 5, 10, 15, 20 and 25 Kgry) of Gamma and E-Beam for sterilization resulted in extensive degradation of the active. Sterilization post manufacturing is not possible so far." DTX 131 at 021099-100. Dr. Jiang testified that "FP" meant final product or budesonide suspension.[62] See Trial Tr. 1383:18-19. Apotex never attempted to sterilize the budesonide powder. Nor is there any other evidence of its attempts to sterilize budesonide.[63]

AstraZeneca also maintains that Sandoz failed in its initial efforts to make a pharmaceutically acceptable, sterile budesonide due to particle size changes. It cites Mr. Madsen.

---

[62] Dr. Zhanel explained that he initially believed the document to reflect an attempt to sterilize the powder, but he agreed that it could have been an attempt to sterilize the final product, or suspension. In the end, he had no firm understanding as to the meaning of the Apotex notation. See Trial Tr. 1593:3-19.

[63] Evidence of a single failed experiment (assuming such is demonstrated here) provides little persuasive evidence of nonobviousness. Even Dr. Zhanel acknowledged that "[w]e frequently don't succeed on our first attempts. I don't think it's an expectation. . . . So, it wouldn't surprise an individual that you may get some failures." Trial Tr. 1594:6-11.

2012 Trial Tr. 3146:22-3147:2, 3186:21-3187:25. But Mr. Madsen persuasively clarified that Sandoz's process uses a sterilized slurry, which is not pharmaceutically acceptable because of particle size changes, which is why Sandoz then uses sonication – a well-known process as of 1997 – to break up the particles and thus create a pharmaceutically acceptable product.

As such, there is no competent evidence demonstrating the nature and extent of Defendants' purported failures. The Court finds this lack of evidence to be particularly relevant here, where each of the Defendants (and Teva Pharmaceuticals USA, Inc. ("Teva"))[64] succeeded in preparing a pharmaceutically acceptable, sterile budesonide composition (powder or suspension) using one of the conventional sterilization techniques. DFOF ¶ 237.[65] Bristol-Myers, 923 F. Supp. 2d at 680 ("Failure of others 'to

[64] Teva markets a budesonide inhalation suspension pursuant to an agreement with AstraZeneca. See PTX 927.

[65] AstraZeneca has also suggested throughout this litigation that the fact that Defendants failed to sterilize budesonide until the mid-2000s somehow confirms the novelty of AstraZeneca's own invention. This argument also fails in light of the dearth of evidence regarding Defendants' attempts to create the claimed products. Indeed, the Apotex progress report relied upon by AstraZeneca notes that Apotex is "re-visit[ing]" the sterilized budesonide project, thereby suggesting that Apotex abandoned the project for some time for unknown reasons. To conclude that because Defendants took so long to sterilize budesonide that this is evidence of nonobviousness would require this Court to engage in speculation - not fact-finding - as to the reasons for the delay. Cf. Trial Tr. 2229:1-14 (Akers) (agreeing there may be many reasons such as resources, cost, or marketing strategy to explain why a company chooses not to make a product sterile).

find a solution to the problem which the patent[ ] in question purport[s] to solve' is evidence of nonobviousness." (citation omitted)); see also Cubist Pharm., 2014 WL 6968046, at *17 ("The weight of the 'failure of others' factor becomes considerably more limited when it is acknowledged that others had only failed with respect to [treatment of one infection].").

AstraZeneca also presented evidence, in the form of hearsay testimony from Mr. McAffer, that two or three other companies failed to sterilize budesonide. See PFOF ¶ 23. Here, again, because there was no evidence as to the nature of those purported failures, it is of little value. This is especially so in light of the evidence presented that there were several glucocorticosteroid ophthalmic suspensions on the market by 1997, thus demonstrating other companies' successful sterilization of glucocorticosteroids. See DFOF ¶ 246.

iv. Commercial Success

"Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art. Thus, the law deems evidence of (1) commercial success, and (2) some causal relation or "nexus" between an invention and commercial success of a product embodying that invention, probative of whether an invention was non-obvious." Merck & Co., Inc. v. Teva Pharma. USA, Inc., 395

F.3d 1364, 1376 (Fed. Cir. 2005). "Commercial success of an invention over the prior art also implies that the difference between an invention and the prior art is significant or substantial." Dome Patent, 2014 WL 2948927, at *24. However, commercial success may be the result of something other than the "patentable inventiveness," such as "skillful marketing of the product embodying the invention." Ritchie v. Vast Resources, Inc., 563 F.3d 1334, 1336 (Fed. Cir. 2009). Thus, it is important to ensure an adequate nexus to the patented claims.

AstraZeneca submitted evidence in support of the commercial success of Pulmicort Respules®. From 2000 to May 2014, AstraZeneca has sold more than 44 million packages of Pulmicort Respules®, and net sales in the United States have totaled $5.6 billion. DFOF ¶ 40. There is no question that Pulmicort Respules® has been very profitable for AstraZeneca in the United States.

However, AstraZeneca again attempts to create a nexus between its success and the '834 Patent by relying on FDA approval. It argues that its success is due to its ability to obtain FDA approval of its product, which could only be obtained because it was able to sterilize the budesonide suspension. Dr. Vellturo testified that, prior to AstraZeneca's invention, there was an opportunity to provide nebulized corticosteroids for use as an asthma treatment in small children, and only because of

AstraZeneca's invention was AstraZeneca able to take advantage of that opportunity. Trial Tr. 2045:15-2046:13, 2052:16-23 (Vellturo). As AstraZeneca puts it, "If AstraZeneca had not been able to develop the claimed invention, it would either face significantly more competition (because the FDA would have permitted non-sterile products to enter the market), or would not be in the market at all (because FDA would have demanded sterility without AstraZeneca having achieved it)." PFOF ¶ 41.

As this Court has previously cautioned, AstraZeneca "cannot equate regulatory compliance with evidence of commercial success." In re OxyContin Antitrust Litig., 994 F. Supp. 2d 367, 399-400 (S.D.N.Y. 2014) ("Purdue emphasizes that the low-ABUK process allowed the Rhodes facility to obtain FDA approval and that Rhodes could not have been successful without FDA approval. The Court cannot equate regulatory compliance with evidence of commercial success.").[66] Under AstraZeneca's theory, there would likely always be commercial success when a pharmaceutical product experiences substantial sales because the product must comply with FDA requirements in order to be sold in the United States. Sterility is an FDA requirement; it is not driving demand for Pulmicort Respules®. See infra. AstraZeneca conflates the two. Whether or not there is a nexus between the

[66] See also Ex Parte Gary R. Delduca, Appeal No. 2009-1245, 2009 WL 726769, at *14 (B.P.A.I. 2009) ("Further, the lack of FDA approval is not sufficient to show a long-felt need.").

novel features of the patented product and the commercial success must be evaluated in terms of what is driving sales, not what is allowing the product to reach the shelf in the first place. See Trial Tr. 2668:21-2669:17, 2729:10-25 (Spadea).

Here, it cannot reasonably be concluded that sterility is the reason Pulmicort Respules® experiences substantial sales because nonsterile European Pulmicort Respules experienced significant sales overseas. In many senses, the Patent is creating its own isolation: AstraZeneca is using its Patent to enjoin other companies, like Defendants, from coming onto the market with their own budesonide inhalation suspension products. In an attempt to circumvent this logic, AstraZeneca argues that sterility is clearly the nexus because the '834 Patent has not prevented other nonbudesonide products from entering the market, such as fluticasone or beclamethasone. In doing so, it relies heavily on hearsay evidence from Defendants' expert, Ms. Moldenhauer, but that testimony was taken out of context. Ms. Moldenhauer explained that certain individuals employed by the companies that market fluticasone and beclomethasone nebulizing suspensions overseas "told [her] that they just weren't going to pursue sterility." Trial Tr. 286:12-19. Thus, even assuming that this evidence goes to any nexus, there was no evidence as to the reason these companies chose not to pursue sterility.

Dr. Zhanel admitted that the reasons these companies chose not to pursue sterility is unknown.

> Q. . . . You are not suggesting that beclomethasone and fluticasone are not on the U. S. market because the makers of those drugs couldn't make them sterile, are you?
>
> A. I don't know what the researchers in the beclomethason and fluticasone companies are doing. . . .
>
> Q. The fact of the matter is you don't know why the makers of fluticasone and beclomethasone decided not to seek approval to the get on the U.S. market, correct?
>
> A. I do not know exactly what they were doing and what they decided, yes.

Id. at 1711:12-1712:5. In fact, it is certainly plausible that the potential sales of their products in the United States does not outweigh the expense of making them sterile. Cf. id. at 2229:1-14 (Akers).

In addition, the evidence does not demonstrate a connection between the sales of Pulmicort Respules® in the United States and sterility. Dr. Vellturo testified that the sterility of Pulmicort Respules® helped it to achieve commercial success by addressing doctors' concerns about safety. PFOF ¶ 42. Dr. Vellturo explained that FDA approval is connected to sterility because the FDA considered sterility an important requirement for a suspension. See Trial Tr. 1016:16-21. Dr. Vellturo testified in 2012, however, that he was "not aware of direct evidence that tie[d] the sterility of [Pulmicort Respules®] to

specific demands of physicians." Id. at 2071:7-13. Rather, he relied solely on Dr. Ververelli's testimony that, after the difficulties with contaminated albuterol around 1992, sterility of nebulized suspensions became important to doctors because they treat small children. See id. at 895:21-896:23. But Dr. Ververelli repeatedly acknowledged that what was important was safety – not sterility. Indeed, she agreed that "if the FDA felt that even though the solutions had to be sterilized and the suspension did not have to be sterilized, then yes," nonsterile Pulmicort would satisfy the unmet need. See, e.g., id. at 973:22-974:5 (Ververelli).[67] This statement illustrates the fact that doctors prescribe Pulmicort Respules® for reasons other than its sterility. In addition, even if FDA approval constitutes an important assurance of safety for a prescribing physician, as Dr. Ververelli suggests, had the FDA approved a nonsterile product, then the physician would still feel assured of the product's safety and, importantly, would still have

[67] Dr. Zhanel testified that sterility impacts the ability to deliver Pulmicort Respules® via a nebulizer: "If you have a sterile steroid suspension, you now have the confidence that you can instill this particular sterile nebulized suspension of a steroid and you will not have a risk of pneumonia, you will not have a risk of the patient developing a pneumonia and potentially a bacteremia and potentially getting very sick and dying. So it gives you that confidence that this is the -- an optimal suspension, nebulizing suspension in terms of safety." Trial Tr. 1306:5-14. Once again, Dr. Zhanel's testimony is contradicted by the testimony of Dr. Ververelli, a treating physician, whose testimony demonstrates that sterility does not equate to safety. See supra and infra.

written prescriptions for the nonsterile product, thereby contributing to its success.

The Court finds Dr. Vellturo's foregoing testimony regarding the commercial success of Pulmicort Respules® to be based upon a flawed analysis and, therefore, unhelpful and unpersuasive. Dr. Vellturo agreed that "there are multiple attributes that drive the commercial success of Pulmicort Respules®." Trial Tr. 2056:12-18. These include: (1) efficacy; (2) safety; (3) nebulized method of delivery; and (4) once-daily dosing. Id. at 2056:19-2057:7. However, he made no effort to compare the relative impact of each of these attributes on the success of Pulmicort Respules®, as he determined they were not "germane" to the inquiry. Id. at 2057:8-2060:20 (Vellturo).

Mr. Spadea, Defendants' expert, testified that while sterile Pulmicort Respules® has enjoyed significant sales in the United States, it is not due to a nexus between the commercial success and the patented invention. More specifically, Mr. Spadea opined that the commercial success of Pulmicort Respules® has been driven by factors unrelated to the '834 Patent: efficacy, safety of the budesonide molecule, and nebulized delivery. Id. at 2668:8-13. Sterility is not a marketed feature of the product, nor is it a driver for physicians' prescriptions. Id. at 2668:13-17.

Mr. Spadea persuasively explained that companies, especially pharmaceutical companies, promote features of their products that are important to consumers, and they test whether the features they are marketing are resonating with their audience. Id. at 2685:5-21. The evidence was firm that, while AstraZeneca promotes Pulmicort Respules®, the marketing materials do not extol the sterility of the product. Id. at 2067:25-2068:12 (Vellturo). Rather, AstraZeneca's marketing focuses on other features such as the safety and efficacy of the budesonide molecule. See DFOF ¶ 248. For instance, a 2001 marketing study of the reasons that physicians prescribed Pulmicort Respules® recommended that AstraZeneca promote its differentiating aspects, i.e., nebulizing delivery mechanism and efficacy. DTX 673 at 154898. Later, in a 2006 strategic plan for Pulmicort Respules®, which contains an internal analysis of strengths, weaknesses, opportunities, and threats, lists the historical safety of budesonide as a strength of the product. See Trial Tr. 2675:20-2677:1 (Spadea).

Mr. Spadea also examined physician surveys conducted by AstraZeneca that showed efficacy, nebulized delivery, and safety were the reasons why physicians prescribed Pulmicort Respules®. DFOF ¶ 247; see also DTX 673 at 0154887 ("Physicians choose to prescribe PR because it is efficacious and has a delivery system that is more compatible for young children."); PTX 174 at

0021513 (acknowledging "safety data associated with the budesonide molecule" was one reason for prescribing). In one third-party study, doctors connected safety with the safety of the budesonide molecule or pregnancy Category B labeling safety. See Trial Tr. 2670:1-3, 2673:5-2675:2 (Spadea). In another study, 91% of physicians chose efficacy over dosing as most influencing their choice of asthma controller. DTX 1210 at 0246188. Dr. Spadea found it telling that sterility was not raised in this questionnaire, which was consistent with his conclusion that AstraZeneca did not view sterility as a driver of the sales of Pulmicort Respules®. Trial Tr. 2681:9-17. In yet another physician survey comparing Pulmicort Respules® to its competitors, Singulair, Floven, Advair, and Ciclesonide,[68] AstraZeneca evaluated performance based upon 46 separate features. DTX 731 at 1168224-26. None of these 46 features relate to sterility.[69]

[68] AstraZeneca's assertion that it has no competitors for its Pulmicort Respules® product is belied by its own internal documents. See, e.g., DTX 1215 at 1123256 ("Protect PULMICORT RESPULES Business from the Emerging Threat of Increased Flovent use in Younger Children (1-3 years)"); id. at 1123267, 1123269 (listing as threats "[i]mpending ciclesonide launch" and Singulair's growing presence); DTX 731 at 1168224-26.

[69] Trial Tr. 2687:15-25 (Spadea) ("What I mentioned here, in my review again when we go back to try to test for sterility of Budesonide powders and suspensions, there is no mention of sterility at all from these 46 features. So there is -- in my experience that's -- you would not expect to see no mention if it were actually driving the sale of the product. And in my prior testimony, of course, I use the same document when we

AstraZeneca's attempt to connect "sterility" to physician's desire for "safety," and therefore create a nexus to the patented feature of the '834 Patent, fails. As the above discussion demonstrates, the "safety" factor prized by physicians related to long-term safety data on the budesonide molecule or pregnancy Category B elements.[70] In any event, the record shows that the nonsterile versions of Pulmicort Respules sold overseas, and particularly in Europe and Canada, enjoyed great success because they were safe and effective drugs. American physicians began contacting AstraZeneca after learning how well the nonsterile European Pulmicort was doing, demanding that it be made available in the United States. See Trial Tr. 886:12-17, 887:20-888:2. Dr. Ververelli acknowledged that she provided nonsterile Canadian Pulmicort Respules® to a small percentage of her patients due to its unavailability in the United States. Id. at 889:16-19. She considered the Canadian product safe and effective. Id. at 950:20-23. Moreover, nonsterile European Pulmicort® was economically successful.

---

talked about once daily dosing, you know, to note that it was a low contributor, a 40 score, but at least it was on the document, at least the feature was tested and results were produced that you could measure the impact.").

[70] In one physician survey, physicians were asked to rank the top three reasons they do or would prescribe Pulmicort Respules. The results show 77.9% prize the nebulized delivery, 73.7% the effective anti-inflammatory properties, and 52.1% its proven safety. See PTX 174 at 0021506. Again, sterility is not mentioned.

DFOF ¶ 250. Dr. Barnes testified, "I think it's been successful because doctors have found it to be a useful treatment for some patients with asthma, particularly young children under the age of three, and for some patients with severe asthma who require high doses of steroid."[71] Id. at 2548:7-20.

In short, the evidence shows the lack of a nexus between the allegedly novel feature of the '834 Patent (i.e., sterility) and the commercial success of the product. Because the evidence shows that the commercial success of Pulmicort Respules® is attributable to aspects of the invention that were known in the art (i.e., the budesonide molecule), AstraZeneca has failed to satisfy its burden of establishing the requisite nexus. See, e.g., Ormco Corp., 463 F.3d at 1312 (finding patentee failed to demonstrate that the commercial success was "was due to the claimed and novel features"); see also Tokai Corp., 632 F.3d at 1370 (finding no nexus between commercial success and patented feature where marketing and sales data did not refer to purportedly distinguishing feature of patented product); MRC Innovations, Inc. v. Hunter Mfg., LLP, 747 F.3d 1326, 1336 (Fed.

[71] As for the characteristic making it most useful, Dr. Barnes attributed it to the nebulized delivery system that rendered it useful in the treatment of very young children. Id. at 2548:21-2549:3.

Cir. 2014) (finding patentee failed to establish nexus between secondary considerations and patented invention).[72]

v. Conclusion

For the reasons set forth above, the evidence clearly and convincingly demonstrates that a POSA would have had a reasonable expectation of successfully preparing the claimed sterile budesonide compositions (the powder set forth in claims 1 and 2, and the suspensions set forth in claims 50 and 51) using four of the five conventional sterilization techniques (i.e., sterile filtration/crystallization, moist heat, EO, and irradiation). Moreover, there is insufficient evidence of secondary considerations of nonobviousness. See Wyers v. Master Lock Co., 616 F.3d 1231, 1246 (Fed. Cir. 2010) ("[S]econdary considerations of nonobviousness . . . simply cannot overcome a strong prima facie case of obviousness."). As such, the asserted claims are invalid as obvious.

[72] For similar reasons, the evidence proffered by AstraZeneca is also not commensurate in scope with the patent claims, and thus fails to demonstrate nonobviousness. Dome, 2014 WL 2948927, at *28 ("[E]vidence that commercially desirable properties are not commensurate with the patent claim suggests that the commercial success of one particular embodiment results from something different (or more specific) than the claim. . . . Where it appears that commercially desirable properties appear only in a subset of a patent's embodiments, however, a court may not extend evidence of commercial success to the entire patent range.").

3. Anticipation

"[T]he dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from a prior art reference that every claim element is disclosed in that reference." AstraZeneca v. Apotex, 633 F.3d 1042, 1055 (Fed. Cir. 2010) (quoting In re Baxter Travenol Labs., 952 F.2d 388, 390 (Fed. Cir. 1991)) (internal quotations and brackets omitted). In other words,

> Claimed subject matter is "anticipated" when it is not new; that is, when it was previously known. Invalidation on this ground requires that every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a [POSA] in possession of the invention. See Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1379 (Fed. Cir. 2003); Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1267-69 (Fed. Cir. 1991).

Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1082 (Fed. Cir. 2008), cert. den'd, 130 S. Ct. 493 (2009). Anticipation is a question of fact, and the party invoking this defense must establish it at trial by clear and convincing evidence. AstraZeneca, 633 F.3d at 1055 (citing Sanofi-Synthelabo, 550 F.3d at 1082; Purdue Pharma L.P. v. Boehringer Ingelheim GmbH, 237 F.3d 1359, 1365 (Fed. Cir. 2001)).

Anticipation requires that "all limitations of the claimed invention are described in a single reference, rather than a single example in the reference." Net MoneyIN, Inc. v.

VeriSign, Inc., 545 F.3d 1359, 1369 n.5 (Fed. Cir. 2008). The court must look at the reference "as a whole" and determine whether it discloses all elements of the claimed invention as arranged in the claim. Id.; see also Cellectis S.A. v. Precision Bioscis., Inc., 937 F.Supp.2d 474, 487 (D. Del. 2013) ("As noted above, a prior art reference must disclose all of the limitations of the claim, 'arranged or combined in the same way as in the claim,' to anticipate a claim." (quoting Net MoneyIN, Inc., 545 F.3d at 1370)).

Defendants argue that the asserted claims are anticipated by U.S. Patent No. 3,992,534, entitled "Compositions and Method of Treating with Component B of Stereoisomeric Mixtures of 2'-Unsymmetrical 16,17-Methylenedioxy Steriods [sic]," filed Nov. 6, 1975 by Ralph Lennart Brattsand et al. ("Brattsand"). DTX 849. Dr. Paul Myrdal, Defendants' expert, testified that Brattsand was looking at isomers of various glucocorticosteroids as well as certain compositions of them. Trial Tr. 450:15-17. The parties agree that Table 1 discloses budesonide. See id. at 451:9-11 (Myrdal); id. at 1700:9-19 (Zhanel). Brattsand notes "The present application also relates to pharmaceutical formulations or compositions containing new physiologically active steroids of the present invention." DTX 849 at col.12 ll.43-52. Dr. Myrdal testified that a POSA would understand this to disclose pharmaceutical formulations of different

steroids. Trial Tr. 451:18-24. Brattsand discloses formulations intended for the treatment of asthma and other inflammatory conditions. PRFOF ¶ 257. In addition, Brattsand teaches that steroids "intended for oral or nasal inhalation" should contain "particles basically less than 5 µm, which are suspended in the propellant mixture by the aid of a surfactant." PRFOF ¶ 259. Brattsand noted that due to the separation process set forth in the patent, "it is possible . . . to prepare in a pure form new stereoisomeric components . . . ." DTX 849 at col.2 ll.15-19. Brattsand further discloses a suspension for injection. PRFOF ¶ 260. According to Mr. Zaccheo, it was known in the art that a parenteral suspension must be sterile and of a reduced particle size. Trial Tr. 2567:13-16.

Dr. Zhanel testified that Brattsand reflects research studies looking at budesonide's therapeutic effectiveness, but it does not disclose sterility, purity, and pharmaceutical acceptability. Id. at 1329:19-1330:4. The Court agrees that Brattsand does not disclose any particular purity level, much less a purity level of 98.5%. See PRFOF ¶ 258; Trial Tr. 1786:22 (Zhanel). At best, Brattsand discloses that the process of his invention permits the preparation of stereoisomers in "pure form." See DTX 849 at col.2 ll.15-19. The testimony did not demonstrate a connection between this statement and the purity limitation of the asserted claims. As such, Defendants

have failed to demonstrate by clear and convincing evidence that the asserted claims are anticipated by Brattsand.

4. Enablement

Defendants also argue that the asserted claims are invalid under 35 U.S.C. § 112 for lack of enablement as the specification fails to provide information sufficient to enable a POSA to make the full scope of the claimed compositions without undue experimentation and, specifically, a suspension containing nonsterile budesonide powder. Defendant Sandoz previously asserted this argument in its opposition to AstraZeneca's motion for a preliminary injunction and the Court rejected it in its June 4, 2014 Opinion. See Docket No. 980 at 15-20. Accordingly, for the same reasons set forth therein, the Court finds that Defendants have failed to demonstrate by clear and convincing evidence that the asserted claims are invalid for lack of enablement.[73]

[73] For the first time, after trial, Defendants argue that a POSA would have been unable to prepare a micronized budesonide composition (powder or suspension) in accordance with the asserted claims that was "synthesized as sterile in the first instance" without undue experimentation. Because they did not preserve these arguments in the Pretrial Order, however, the Court finds that they have waived them. See Pretrial Order, Docket No. 1041, at ¶¶ 709-18; Schering Corp. v. Apotex Inc., No. 09-6373, 2012 WL 2263292, at *14 (D.N.J. June 15, 2012) ("When an issue, argument, claim or defense is not raised in the pretrial order, it is deemed waived." (citing Briglia v. Horizon Health Care Servs., Inc., No. 03-6033, 2010 WL 4226512, at *4 n. 5 (D.N.J. Oct.21, 2010))).

5. Written Description

Finally, Defendants argue that the asserted claims are invalid under 35 U.S.C. § 112 for lack of sufficient written description, in that it fails to convey to a POSA that the inventors possessed a suspension consisting of a nonsterile budesonide product. Here, again, the Court previously addressed this argument in its June 4, 2014 Opinion. See Docket No. 980 at 10-15. Accordingly, for the same reasons set forth therein, the Court finds that Defendants have failed to demonstrate by clear and convincing evidence that the asserted claims are invalid for lack of a sufficient written description.

IV. CONCLUSION

Accordingly, for the foregoing reasons, the Court finds that the '834 Patent is invalid as obvious under 35 U.S.C. § 103 and, therefore, unenforceable. Judgment of non-infringement is hereby entered in favor of Defendants. See TypeRight Keyboard Corp. v. Microsoft Corp., 374 F.3d 1151, 1157 (Fed. Cir. 2004) ("invalidity operates as a complete defense to infringement for any product, forever") (citation omitted). AstraZeneca's

request for a permanent injunction against each Defendant is denied. Finally, AstraZeneca's request for judgment declaring this to be an exceptional case is dismissed as moot. A trial shall be held on the issue of damages.

Date: February 13, 2015

s/Renée Marie Bumb
RENÉE MARIE BUMB
UNITED STATES DISTRICT JUDGE