[Dkt. Ent. 458]

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

ASTRAZENECA LP and ASTRAZENECA AB,

Plaintiffs,

v.

BREATH LIMITED,

Defendant.

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.

Consolidated
Civil Action No. 08-1512
(RMB/AMD)
Member cases:
09-1518
09-4115
10-5785
11-3626

OPINION

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BUMB, UNITED STATES DISTRICT JUDGE:

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I. INTRODUCTION

Plaintiffs AstraZeneca LP and AstraZeneca AB ("AstraZeneca") bring this consolidated action for patent infringement against the defendants, Breath Limited, Watson Laboratories, Inc. (collectively, "Breath/Watson"[1]), Apotex Corp., Apotex, Inc. (collectively, "Apotex"), and Sandoz, Inc. (all the defendants are collectively referred to as "Defendants"). This case involves AstraZeneca's PULMICORT RESPULES® product, a once-daily nebulized budesonide suspension used to treat asthma in children. AstraZeneca seeks to enjoin Defendants from manufacturing and selling generic versions of this drug, claiming that their products will induce infringement of two of AstraZeneca's patents, U.S. Patent No. 6,598,603 (the "'603 Patent") and U.S. Patent No. 7,524,834 (the "'834 Patent"). Defendants filed counterclaims for declaratory judgment that the patents are invalid and that Defendants do not infringe them.

Previously, in 2009, AstraZeneca moved for a preliminary injunction to prevent Apotex from launching its generic

[1] As reflected in a Stipulation and Order entered on May 11, 2010, Watson Laboratories, Inc., acquired and assumed all rights and obligations of Breath Limited with respect to ANDA 078404. [Dkt. Ent. 191.]

budesonide product. See AstraZeneca v. Apotex, Civ. No. 09-1518. At the time, only Apotex had received approval from the U.S. Food and Drug Administration ("FDA") to market its product. After a hearing, the Court granted AstraZeneca's motion and preliminarily enjoined Apotex.[2] The United States Court of Appeals for the Federal Circuit affirmed. AstraZeneca LP v. Apotex, Inc., 623 F. Supp. 2d 579 (D.N.J. 2009), aff'd, 633 F.3d 1042 (Fed. Cir. 2010). AstraZeneca brought related actions

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[2] AstraZeneca also originally alleged infringement of U.S. Patent No. 6,899,099 and claims 29 and 30 of the '603 Patent, referred to collectively as the "kit claims." In its preliminary injunction orders, the Court found that AstraZeneca had not shown a likelihood of success, and that the kit claims were likely invalid as a matter of law. The Federal Circuit agreed. AstraZeneca LP v. Apotex, Inc., 623 F. Supp. 2d 579 (D.N.J. 2009), aff'd, 633 F.3d 1042 (Fed. Cir. 2010). During a December 15, 2010, hearing before the Court, AstraZeneca withdrew its kit claims. At that time, neither Breath/Watson nor Apotex objected. (Sandoz had not entered as a party.) Federal Rule of Civil Procedure 41(a)(2) provides that after the opposing party has served an answer or motion for summary judgment, an action may be dismissed at the plaintiff's request only by court order on terms that the court considers proper. Because AstraZeneca has represented that it provided covenants not to sue each defendant for infringement of the kit claims and the parties agreed that the counterclaims were to continue, the Court finds dismissal may be proper under those terms. However, because the Court has not been provided with these covenants not to sue, and Defendants argue they are "inadequate", Defs.' FF ¶ 5, n.4, the Court reserves its right to revisit this issue upon motion by Defendants. Accordingly, the kit claims are dismissed without prejudice pursuant to Rule 41(a)(2).

against the other defendants,[3] and the Court consolidated them, with the parties' consent, into the instant action. [Dkt. Ents. 74, 89.] After lengthy discovery and a five-day Markman hearing, the parties filed motions for summary judgment. Shortly thereafter, Breath/Watson received FDA approval to launch its generic product, and AstraZeneca moved for a preliminary injunction to enjoin Breath/Watson from putting its product on the market.[4] [Dkt. Ent. 458.]

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) and dismissed all pending motions for summary judgment without prejudice. [Dkt. Ent. 469.] The Court conducted a 19-day bench trial from November 7, 2012, through December 18, 2012. It then permitted the parties to file post-trial briefing and heard closing arguments on March 6, 2013.[5]

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[3] See AstraZeneca LP v. Breath Ltd., Civ. No. 09-4115; AstraZeneca LP v. Sandoz, Inc., Civ. No. 10-5785; AstraZeneca LP v. Breath/Watson Labs., Inc., Civ. No. 11-3626.

[4] This motion is DISMISSED as MOOT, since the Court now denies AstraZeneca's claim for permanent injunctive relief.

[5] The Court complements counsel for their exceptional advocacy and professionalism throughout this protracted litigation.

After considering all the evidence, and for the reasons set forth below, the Court finds that: (1) Defendants will induce infringement of the '603 Patent; but (2) that Patent is invalid as obvious and anticipated by the prior art; and (3) Defendants will not infringe the '834 Patent. Accordingly, the Court enters judgment against AstraZeneca and in favor of Defendants. This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Rule 52(a).[6]

II. BACKGROUND[7]

A. The Drug Approval Process

The FDA must approve all new drugs before they may be distributed in interstate commerce. 21 U.S.C. § 355(a). To secure approval for a new drug, an applicant may file a New Drug

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[6] The parties' oral motions made during trial for judgment on partial findings pursuant to Federal Rule of Civil Procedure 52(c) are DISMISSED as MOOT. Rule 52(c) permits such motions after "a party has been fully heard on an issue during a nonjury trial". The Court exercised its discretion to reserve on the motions when they were made during trial, Tr. 1878, 3558-72, 4400; except to the extent that the Court granted AstraZeneca's motion for judgment on the Defendants' written description defense as to the '834 Patent [Dkt. Ent. 622] and granted Defendants' motion for judgment as to all claims in the '834 Patent on which AstraZeneca did not present any evidence at trial. [Dkt. Ent. 610.]

[7] Because this civil action arises under the United States patent laws, Title 35 of the United States Code, this Court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a).

Application ("NDA") that includes examples of the proposed label for the drug and clinical data demonstrating that it is safe and effective. Id. at § 355(b)(1)(A, F). "The FDA publishes the names of approved drugs and their associated patent information in the Approved Drug Products with Therapeutic Equivalence Evaluations list, commonly referred to as the 'Orange Book.'" AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1045 (Fed. Cir. 2010).

An applicant seeking approval to market a generic version of a drug that has already been approved may file either an Abbreviated New Drug Application ("ANDA") or a "505(b)(2) application," known as a "paper NDA." Id. (citing 21 U.S.C. § 355(b)(2), (j)). "An ANDA allows an applicant to rely on the safety and efficacy information for the listed drug if the applicant can show that the generic drug is 'bioequivalent' to the listed drug." Id.

Generally, an ANDA applicant must demonstrate that "the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug." 21 U.S.C. § 355(j)(2)(A)(iii). The applicant must also show that "the labeling proposed for the new drug is the same as the labeling approved for the listed drug." Id. at § 355(j)(2)(A)(v). "[F]or each patent listed in the Orange Book

that claims either the listed drug or a use of the listed drug for which the applicant is requesting approval, an ANDA must include either one of four certifications or a 'section viii statement.'" AstraZeneca LP, 633 F.3d at 1046.

If an applicant submits a certification, the applicant must certify "(I) that . . . patent information has not been filed, (II) that such patent has expired, (III) . . . the date on which such patent will expire, or (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug." 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV). The last of these is known as a "paragraph IV certification".

If an applicant seeks approval for an ANDA for a method of use not claimed in a "method of use" patent associated with the listed drug, the applicant must submit a "section viii statement" stating that the patent does not claim such a use. 21 U.S.C. § 355(j)(2)(A). Additionally, the applicant must "remove or 'carve out' any mention of the patented method of use from the proposed label for the generic drug." AstraZeneca, 633 F.3d at 1045 (citing 21 C.F.R. § 314.92(a)(1)).

B. AstraZeneca's Budesonide Drug and Patents

On August 8, 2000, AstraZeneca received FDA approval for its NDA for a budesonide inhalation suspension, which AstraZeneca now markets under the name, PULMICORT RESPULES®.

Its sole active ingredient is budesonide, an anti-inflammatory corticosteroid. It is approved for maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age. Stipulated Facts ¶¶ 50-54, 56 [Dkt. Ent. 700-1].

PULMICORT RESPULES® is available in dosages of 0.25 mg to 1.0 mg/2 mL.[8] The label recommends both once daily and twice daily starting doses, determined by the severity of the asthma and prior medication history of the patient. The label also instructs doses to be titrated down to the lowest effective dose once a patient's asthma stabilizes.

The '603 Patent covers the once-daily use of PULMICORT RESPULES®. AstraZeneca asserts that before the '603 Patent, there were no once-daily nebulized medications for controlling asthma in young children and infants.[9] Trial Transcript ("Tr.") 140:23-141:25 (Dr. Bertil Andersson, an inventor of the '603 Patent). Although nebulized budesonide had been available outside the United States for use twice daily, there were no

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[8] The FDA approved PULMICORT RESPULES® in a 1.0 mg/2 mL strength for marketing in the United States in June 2007.

[9] Unlike other delivery devices available for the treatment of asthma, a nebulizer does not require the patient to time breathing with the device or to inhale forcefully. Rather, a nebulizer turns the drug suspension into a mist, which the patient then inhales. This process is described in more detail infra.

clinical studies showing that it would be effective once daily. Defendants dispute AstraZeneca's claims relating to the '603 Patent on grounds of non-infringement and invalidity.

AstraZeneca further contends that it would not have been permitted to launch PULMICORT RESPULES® in the United States without its '834 Patent, which covers the sterilization of all aqueous-based inhalation solution and suspension products. Specifically, AstraZeneca contends that prior to its '834 invention, no one had ever sterilized budesonide or any aqueous inhalation suspension. AZFF ¶ 3. Defendants dispute this claim as well, and argue that this Patent is invalid. Further, each defendant argues non-infringement on the grounds that their sterilization processes are different from the process required by the '834 Patent.

C. The Defendants' Generic Drugs and FDA Approval

1. Breath/Watson's ANDA

On July 7, 2006, Breath filed ANDA No. 78-404 with the FDA seeking regulatory approval to market budesonide inhalation suspension in 0.25 mg/2 mL and 0.5 mg/2 mL dosages. On December 2, 2009, Breath transferred its rights to Breath/Watson. Breath/Watson's ANDA No. 78-404 identifies the listed drug product that is the basis for the submission as PULMICORT RESPULES®. Breath's ANDA included a paragraph IV certification

asserting that the ‘603 and ‘834 Patents are invalid, unenforceable, or will not be infringed by the manufacture or sale of Breath’s generic budesonide inhalation suspension. On July 31, 2012, FDA approved Breath/Watson’s ANDA No. 78-404.

On February 2, 2011, Breath/Watson submitted ANDA No. 202558 to the FDA seeking regulatory approval to market its budesonide inhalation suspension in the 1.0 mg/2 mL dosage strength. This ANDA also included a paragraph IV certification. It is currently pending.

2. Apotex’s ANDA

On March 31, 2006, Apotex submitted ANDA No. 78-202 to the FDA for approval to market a generic version of PULMICORT RESPULES® in 0.25 mg/2 mL and 0.5 mg/2 mL dosages. Apotex identifies PULIMICORT RESPULES® as the reference listed drug. Apotex’s ANDA included a Section viii certification, asserting that the ‘603 Patent does not claim any indication for which Apotex is seeking approval. On March 30, 2009, the FDA approved Apotex’s ANDA.

3. Sandoz’s ANDA

On May 28, 2010, Sandoz submitted ANDA No. 20-1966 to the FDA for approval to market its generic version of PULMICORT RESPULES®, 1.0 mg/2 mL. On September 21, 2010, Sandoz submitted a major amendment to its ANDA, which added a request for

approval of the 0.25 mg/2 mL and 0.5 mg/2 mL strengths. Sandoz's ANDA included a paragraph IV certification asserting that the '603 and '834 Patents are invalid, unenforceable, or will not be infringed by the manufacture or sale of the Sandoz product. This ANDA is currently pending.

III. LEGAL ANALYSIS

The Court begins by addressing the '603 Patent. It first determines that Defendants will infringe the asserted claims of this Patent, but also concludes that these claims are invalid as obvious and anticipated by the prior art. The Court then considers the '834 Patent and ultimately determines that Defendants will not infringe the asserted claims of this Patent.

A. The '603 Patent

The '603 Patent is directed to the once-daily use of nebulized budesonide.[10] '603 Patent col. 1, ll. 20-23. AstraZeneca asserts that Defendants will infringe claims 1-3, 7,

[10] The '603 Patent is entitled "METHOD FOR TREATING RESPIRATORY DISEASES" and names Bertil Andersson, Thor-Bjorn Conradsson, and Goran Eriksson as the inventors. It issued on July 29, 2003. It was filed with the United States Patent and Trademark Office ("PTO" or "Patent Office") as U.S. Patent Application Serial No. 09/220,137 (the "'137 application") on December 23, 1998. The '137 application claims priority to provisional U.S. Patent Application Serial No. 60/070,291 (the "'291 application"). The '291 application was filed on December 31, 1997. Stipulated Facts ¶¶ 21-23 [Dkt. Ent. 700-1 (Tab 1)].

8, 12-17 and 24-28.[11] Claim 1, the only independent claim, recites:

> A method of treating a patient suffering from a respiratory disease, the method comprising administering to the patient a nebulized dose of a budesonide composition in a continuing regimen at a frequency of not more than once per day.

The remaining method claims are all dependent on Claim 1, meaning that they include all of the limitations of Claim 1 as well as additional limitations.[12]

1. Infringement

a. Defendants' Product Labels

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[11] Although AstraZeneca originally asserted infringement of claims 6, 11, 18, and 21-23 of the '603 Patent, it presented no evidence of such infringement of those claims. Indeed, at trial AstraZeneca conceded these claims. See Tr. 1115:19-24 (Chipps). They are therefore dismissed with prejudice.

[12] Claim 2 depends from Claim 1 and further recites: "wherein the frequency is once and only once per day." Claim 7 depends from Claim 6 and recites: "wherein the respiratory disease is asthma." Claims 12, 14, and 16 depend from Claim 1 and recite: "wherein the patient is" "one day to fifteen years old", "one month to eight years old" and "six months to five years old," respectively. Claim 24 depends from Claim 1 and further recites: "wherein the budesonide composition contains 0.25 mg to 1.0 mg budesonide." Claim 26 depends from Claim 1 and further recites: "wherein the budesonide composition is a suspension." Claims 3, 8, 13, 15, 17, 25, 27 and 28 depend directly or indirectly from Claim 1 and/or other of the asserted method claims and each further recites: "wherein budesonide is the only active ingredient in the budesonide composition."

AstraZeneca contends that Defendants' labels for their generic products will induce infringement because they instruct once-daily administration.[13] The Court considers each label in turn.

i. Breath/Watson's Labels

Breath/Watson seeks to market its generic product in three dosage strengths, the 0.25 mg, 0.5 mg, and 1 mg strength. Its approved label for the 0.25 mg/2 mL and 0.5 mg/2 mL dosage strengths provides in relevant part:

DOSAGE AND ADMINISTRATION

Previous Therapy	**Recommended Starting Dose**	**Highest Recommended Dose**
Bronchodilators alone	0.5 mg total daily dose administered twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered twice daily in divided doses	1 mg total daily dose
Oral Corticosteroids	1 mg total daily dose administered as 0.5 mg twice daily	1 mg daily dose

The label also contains a "titration down" statement:

> In all patents, it is desirable to downward titrate to the lowest

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[13] AstraZeneca does not assert direct infringement.

> effective dose once asthma stability is achieved.

Ex. DTX 370.

Breath/Watson's proposed label for the 1.0 mg/2 mL strength provides in relevant part:

DOSAGE AND ADMINISTRATION

Previous Therapy	**Recommended Starting Dose**	**Highest Recommended Dose**
Bronchodilators alone	0.5 mg total daily dose administered either once daily or twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered either once daily or twice daily in divided doses	1 mg total daily dose
Oral Corticosteroids	1 mg total daily dose administered either 0.5 mg twice daily or 1 mg once daily	As l mg total daily dose

The label also contains a "titration down" statement:

> In all patents, it is desirable to downward titrate to the lowest effective dose once asthma stability is achieved.

Ex. PTX 151.

ii. Apotex's Label

Apotex's approved dosage label for the 0.25 mg/2 mL and 0.5 mg/2 mL strengths provides in relevant part:

DOSAGE AND ADMINISTRATION

Previous Therapy	**Recommended Starting Dose**	**Highest Recommended Dose**
Bronchodilators alone	0.5 mg total daily dose administered twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered twice daily in divided doses	1 mg total daily dose
Oral Corticosteroids	1 mg total daily dose administered as 0.5 mg twice daily	1 mg total daily dose

The label also contains a "titration down" statement:

> In all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved.

Ex. PTX 171.

iii. Sandoz's Label

Sandoz's proposed label for the 0.25 mg/2 mL, 0.5 mg/2 mL and 1 mg/2 mL provides in relevant part:

DOSAGE AND ADMINISTRATION

Previous Therapy	**Recommended Starting Dose**	**Highest Recommended Dose**
Bronchodilators alone	0.5 mg total daily dose administered either once daily or twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered either once daily or twice daily in divided doses	1 mg total daily dose
Oral	1 mg total daily dose	1 mg total

Corticosteroids	administered either as 0.5 mg twice daily or 1 mg once daily	daily dose

The label contains the following language:

> If once-daily treatment does not provide adequate control, the total daily dose should be increased and/or administered as a divided dose. In all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved.

EX. PTX 110.

b. Infringement by Sandoz & Breath/Watson's 1.0 mg Labels

AstraZeneca contends, first, that Sandoz and Breath/Watson's 1.0 mg labels explicitly instruct once-daily administration for each of the three previous therapy categories of patients. Indeed, neither Sandoz nor Breath/Watson seriously disputes infringement as to these labels. Sandoz's former Director of Regulatory Affairs, Dr. William Kwok, admitted that its label includes explicit instructions for once-daily administration.[14] Although Breath/Watson weakly responds that

[14] Dr. Kwok stated in relevant part:

> Q: Do you have an understanding of whether the label for Sandoz's proposed [budesonide inhalation suspension] product instructs once-daily dosing . . . and the dosing regimen includes once-daily dosing, does it not? A. Yes. . . . At least some patients will

the FDA has not approved labeling for its 1.0 mg product, its proposed labeling explicitly induces once-daily use. Tr. 1142 (Chipps). These labels clearly infringe the only disputed claim limitation (once-daily use). Accordingly, the Court finds that Sandoz and Breath/Watson will induce infringement of the asserted claims with their 1.0 mg labels. Apotex and Breath/Watson's 0.25 mg and 0.5 mg labels require closer analysis.[15]

c. Infringement by Apotex & Breath/Watson's 0.25 & 0.5 mg Labels

To prove infringement, the patentee must show that it is more likely than not that the proposed ANDA product would, if commercially marketed, meet all of the claim limitations of the patent-in-suit. See Adams Respiratory Therapeutics, Inc. v. Perrigo Co., 616 F.3d 1283, 1287 (Fed. Cir. 2010) (en banc);

> ultimately use Sandoz's proposed [budesonide inhalation suspension] product on a once-daily basis according to its label, correct?
>
> A. Yes.

Tr. 522.

[15] In addition to its argument that the FDA has not approved its 1.0 mg product, Breath/Watson also argues that the proposed labeling will not instruct once-daily use for the same reasons cited by the other defendants - because the proposed label is for once-daily or twice-daily administration. These arguments are discussed below.

Abbott Labs. v. TorPharm, Inc., 300 F.3d 1367, 1373 (Fed. Cir. 2002) (infringement analysis turns on whether accused product satisfies every limitation of the claim in question). In other words, the patentee "has the burden of proving infringement by a preponderance of the evidence." Kegel Co., Inc. v. AMF Bowling, Inc., 127 F.3d 1420, 1425 (Fed. Cir. 1997); SmithKline Diagnostics, Inc. v. Helena Labs. Corp., 859 F.2d 878, 889 (Fed. Cir. 1988). Determining whether an accused product infringes the patent involves a two-step analysis. Kegel, 127 F.3d at 1425. The Court first construes the scope and meaning of the asserted patent claim and then compares the accused product to the properly construed claim. Id.

i. Claim Construction

As for the first step, the Court conducted a five-day Markman hearing regarding the disputed claim terms at issue in this litigation. The parties contested only two terms related to the '603 Patent: "budesonide composition" and "suspension". At the Markman hearing, Defendants presented evidence to support the arguments offered by Apotex during the preliminary injunction hearing. For the reasons set forth in this Court's prior Opinion, see AstraZeneca v. Apotex, 623 F. Supp. 2d 579 (D.N.J. 2009), as well as the Federal Circuit's opinion affirming this decision, see AstraZeneca, 633 F.3d 1042, the

Court finds its prior construction proper. As such, it sees no reason to delve into a lengthy analysis. In an Order dated November 29, 2011, the Court entered its Order:

> "Budesonide composition" is defined as "budesonide dispersed in a solvent in the form of a solution or a suspension."
>
> "Suspension" requires no construction and should be accorded its plain meaning, "a liquid in which solid particles are dispersed but undissolved."

[Dkt. Ent. 372.]

ii. Inducement

As for the second step of the infringement analysis, the Court must determine whether the accused product contains every limitation of the properly construed claim. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1467 (Fed. Cir. 1998). Here, to be clear, AstraZeneca does not allege that Defendants directly infringe the '603 Patent. Rather, AstraZeneca claims the Defendants will induce infringement when they launch their generic products. If someone induces another to infringe a patent, that person may be liable for infringement under 35 U.S.C. § 271(b). AstraZeneca, 633 F.3d at 1056 (internal citation and quotations omitted). "In order to succeed on a claim of inducement, the patentee must show, first that there has been direct infringement,' and 'second, that the alleged infringer knowingly induced infringement and possessed specific

intent to encourage another's infringement.'" Symantec Corp. v. Computer Assoc. Int'l, Inc., 522 F.3d 1279, 1292 (Fed. Cir. 2008) (quoting MEMC Elec. Materials, Inc. v. Mitsubishi Materials Silicon Corp., 420 F.3d 1369, 1378 (Fed. Cir. 2005)).

1. Direct Infringement

AstraZeneca contends that Apotex and Breath/Watson's labels for the 0.25 mg and 0.5 mg dosage strengths will induce infringement of claim 1 because the label implicitly instructs patients to administer the generic drug once daily, the critical claim limitation. AstraZeneca presented evidence that the instructions for downward titration to the "lowest effective dose" would instruct once-daily dosing without using the explicit words "once daily".[16] Dr. Bradley E. Chipps testified for AstraZeneca that physicians understand that once-daily dosing of budesonide inhalation suspension is safe and effective. Tr. 1109:19-1110:2, 1110:11-1113:17.

As other witnesses for AstraZeneca testified, the option of once-daily dosing offers significant advantages because it is more convenient, Tr. 1338:24-1339:14 (Dr. Raoul L. Wolf), and gives physicians the option of prescribing a lower dose. Tr.

[16] As discussed supra, Sandoz and Breath/Watson's proposed 1.0 mg labels explicitly use the words "once daily".

450:10-451:11 (Dr. Kathleen O'Connor Ververeli); Tr. 1103:10-16 (Chipps). Because of these advantages, once-daily treatment is effective for a substantial number of patients. Tr. 1138:7-1142:1 (Chipps); Ex. PTX 963 at 2; Ex. PTX 408 at 359133. In fact, according to Dr. Ververeli, Dr. Chipps and Dr. Christopher A. Vellturo, an economist, most patients use PULMICORT RESPULES® once daily at some point in their treatment. Tr. 431:11-432:8 (Ververeli); 450:20-451:11, Tr. 1108:14-21 (Chipps); Tr. 733:2-6 (Vellturo).[17]

In particular, Dr. Chipps explained why once-daily dosing for young children is especially important.

> Q. And why do physicians use this stepwise approach and downward titration to the lowest effective dose?
>
> A. We want to prevent side effects from excessive dosing of inhaled corticosteroid we want to add the most convenient and efficacious program to allow adherence to therapy. So if once a day dosing can be done, then it allows the whole daily dose to be delivered with one treatment session.
>
> Q. What side effects, when we're talking about young children, are you trying to minimize?

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[17] Notably, AstraZeneca concedes that PULMICORT RESPULES® is more often prescribed twice daily than once daily. AZFF ¶ 38 [Dkt. Ent. 638-26.] The Court addresses this in the context of substantial non-infringing use. See infra.

> A. You want to make sure that the effect on growth is minimized and also weight gain are two [of] the most common things seen.

Tr. 1103:10-21 (Chipps). Dr. Chipps also testified that for many patients with mild and moderate asthma, once-daily dosing is the lowest effective dose. Tr. 1107:10-19 (Chipps).

As to the initial prong of the infringement analysis (whether patients will directly infringe), the Court finds that AstraZeneca has met its burden. Although the accused labels do not explicitly recommend once-daily dosing, they contain titration down language that effectively instructs such use. This will lead some patients to practice the asserted once-daily method and thus infringe claim 1. Tr. 1133:25-1135:25, 1158:1-12159:16 (Chipps).

According to Apotex's label, Breath/Watson's 0.25 and 0.5 mg label, and Sandoz's label,[18] the recommended starting dose for patients previously treated with bronchodilators or inhaled corticosteroids is 0.25 mg twice daily. If the patient titrates down from this starting dose, the only option is 0.25 mg once daily. Tr. 1134:2-25, 1158:1-1159:16 (Chipps). This is because 0.25 mg is the smallest dosage strength available. Physicians

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[18] As discussed, Sandoz's label also clearly states a recommended starting dose of once daily.

will also understand that for patients previously on oral corticosteroids, titration down may include 0.25 mg twice daily or 0.5 mg once daily. Tr. 1134:2-25, 1158:1-1159:16 (Chipps). Moreover, as the Court previously held, the FDA's own statement that titration down "may involve . . . once-daily dosing" also supports a finding of infringement. AstraZeneca v. Apotex, 623 F. Supp. 2d 579, 601 (D.N.J. 2009); FDA Letter, Ex. PTX 162 at 1022341.

Defendants contend that patients could titrate down by using only half of a 0.25 mg ampule twice daily or nebulize for half the time twice daily and thus there would be no infringing use. The record evidence does not, however, support this argument. First, the PULMICORT RESPULES® label as well as the Defendants' labels instruct patients to empty the entire contents of one ampule with the nebulizer. See Ex. PTX 110, at 414882. (Sandoz) ("[S]lowly squeeze all of the medicine from the ampule into the nebulizer medicine cap . . . throw away the empty ampule."); Ex. Ex. DTX 370at 030794 (Breath/Watson)(same); Ex. PTX 151, at 000118 (Breath/Watson)(same); Ex. PTX 151, at 20 (Apotex)(same). Second, Defendants' expert, Dr. Peter J. Barnes, a specialist in respiratory medicine, was unaware of any such studies that 0.125 mg nebulized budesonide administered twice a day is safe and effective. Tr. 2356:6-23 (Barnes).

And, although Dr. Barnes testified that nebulizing only part of the time would not be "prohibited", Defendants introduced no credible evidence of safety and efficacy for such dosage and administration. The Court also rejects Defendants' argument that because their labels state that the ampule must be used "promptly", and that term is not defined, Ex. PTX 110 at 414873, Ex. PTX 171 at 005761, a patient could divide a 0.25 mg ampule and take it twice a day. The record evidence established, however, that each ampule would be given at the time of administration. See Tr. at 1143 (Chipps). Further, the word "promptly" needs no definition, as Defendants argue. Its plain and ordinary meaning is at once or without delay. In fact, Breath/Watson's labels state that the ampule, once opened, should be used "right away." Ex. PTX 151, at 00015; Ex. DTX 370, at 030793.

Defendants also argued that AstraZeneca cannot show infringement because physicians do not prescribe a particular generic drug and do not have control over whether a pharmacist ultimately fills a prescription with a brand or generic drug. The Court finds these arguments unpersuasive. First, a physician's control over the pharmacy is not relevant to inducement. See Akamai Techs., Inc. v. Limelight Networks, Inc., 692 F.3d 1301, 1308 (Fed. Cir. 2012) (en banc)

("[I]nducement does not require that the induced party be an agent of the inducer or be acting under the inducer's direction or control . . . . It is enough that the inducer causes, urges, encourages, or aids the infringing conduct and that the induced conduct is carried out."). Second, contrary to their position, physicians can control whether or not a prescription may be substituted with a generic product. Tr. 1200:8-16 (Chipps); Tr. 426:6-25 (Ververeli).

2. Specific Intent

As for the specific intent prong of the inducement analysis, Defendants assert several arguments. Apotex and Breath/Watson (as to its 0.25 mg and 0.5 mg label) urge that they removed all references to "once daily" and that they have never intended for their products to be prescribed or used on a once-daily basis. Apotex presses the same arguments as it did before at the preliminary injunction stage. When Breath/Watson became aware of the prior litigation before this Court and AstraZeneca's citizen's petition,[19] it sought to remove the titration language from its products, like Apotex did, but the FDA rejected these efforts as well. See Ex. DTX 417; Ex. DTX

[19] The FDA permits private entities to provide comments and opinions on draft guidelines by filing citizen's petitions. 21 C.F.R. § 1030.

432; Tr. 2611:21-25, 2614:18-2675:13 (Dr. James C. Morrison). Thus, Defendants argue that they had no choice but to comply with the FDA's class labeling, and therefore the Court should not infer an intent to induce infringement. They further argue, as Apotex did, that they have exhausted all regulatory avenues, and there is nothing more they can do. Yet as the Federal Circuit observed, that is not so. They could have waited until the '603 Patent expired before distributing their generic drug. AstraZeneca, LP v. Apotex, Inc., 633 F.3d 1042, 1061 (Fed. Cir. 2010).[20]

The relevant question is whether the Defendants' labels instruct the patient to perform the patented method. If so, these labels may evidence an intent to induce infringement. Id. at 1060 (quoting Vita-Mix Corp. v. Basis Holding, Inc., 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009) ("The question is not . . . whether a user following the instructions may end up using the device in an infringing way. Rather, it is whether [the] instructions teach an infringing use of the device such that we

[20] Although there is evidence in the record that the Defendants could have formally appealed the FDA's decision regarding the inability to remove the downward titration statement, that does not appear to be a realistic avenue. See Tr. 305 (Dr. Thomas Q. Garvey, III).

are willing to infer from those instructions an affirmative intent to infringe the patent."). For the reasons discussed above and set forth in this Court's prior Opinion, the labels at issue would cause many patients to adopt a once-a-day dosing regimen. AstraZeneca, 623 F. Supp. 2d at 603. Defendants know this and are aware that these labels present infringement problems. They have nevertheless decided to proceed with their planned distribution of the generic drugs.[21]

Lastly, Defendants argue that specific intent is lacking because their generic drugs will be used for a substantial non-infringing use, that is, twice daily dosing. "Especially where a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when the defendant has actual knowledge that some users of its product may be infringing the patent." Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1365 (Fed. Cir. 2003).

The evidence at trial presented by all parties demonstrated that PULMICORT RESPULES® is prescribed more often on a twice-daily dosing regimen. See Tr. 4406:20-4407:6, 4408:16-4409:2 (Christopher Spadea, Defendants' expert on evaluation of patents

[21] There is no dispute that each Defendant was aware of the '603 Patent and AstraZeneca's position that the generic labels would infringe.

and their effect on the market); Tr. 715:5-21 (Vellturo). According to evidence presented by Defendants, over 60% of all budesonide inhalation suspension prescriptions are for a non-once-daily dosing regimen. See Ex. PTX 1521D; Ex. PTX at 16220. AstraZeneca's expert, Dr. Vellturo, testified that 36.1% of PULMICORT RESPULES® prescriptions were written for once-daily dosing. Tr. 715. AstraZeneca disputes the significance of this data.

The Court agrees with AstraZeneca. "The existence of a substantial non-infringing use does not preclude a finding of inducement." Toshiba Corp. v. Imation Corp., 681 F.3d 1358, 1364 (Fed. Cir. 2012). Indeed, Defendants' reliance on Warner-Lambert is misplaced. There, only a nominal 2.1% of prescriptions were written for the infringing use. 316 F.3d at 1365. Furthermore, AstraZeneca has proved that Defendants include instructions in their labels that will teach many patients to use the patented once-daily method. Defendants are aware of this infringement problem and have nevertheless decided to proceed with their plans to distribute these generic drugs. This evidence demonstrates Defendants' purposeful, culpable conduct. It overcomes the law's reluctance to find liability when a defendant sells a commercial product suitable for some lawful use. See Metro-Goldwyn-Mayer Studios, Inc. v. Grokster,

Ltd., 545 U.S. 913, 936 (2005) ("Evidence of active steps taken to encourage direct infringement . . . such as advertising an infringing use or instructing how to engage in an infringing use, show an affirmative intent that the product be used to infringe[.]"); AstraZeneca, 633 F.3d at 1059-61 (affirming this Court's prior finding of specific intent for the same reasons discussed here).

For these reasons, AstraZeneca has established by a preponderance of the evidence that Breath/Watson and Apotex will induce infringement of the asserted claims of the '603 Patent with their 0.25 mg and 0.5 mg labels. Specifically, AstraZeneca has proved that (1) others will directly infringe the '603 Patent; and (2) Breath/Watson and Apotex possessed the specific intent to encourage this infringement.

2. Invalidity

Defendants' infringement is a moot point, however, because the Court finds the '603 Patent invalid. Defendants assert three grounds for invalidity of the '603 Patent: obviousness, anticipation, and lack of enablement. Because the Court finds the obviousness argument the most persuasive, it addresses this issue first.

As an initial matter, the Court notes two things. First, the parties agree that the difference in how they define a

person of ordinary skill in the art with respect to the '603 Patent is immaterial to the invalidity analysis. Tr. 3936 (Chipps), Tr. 2201 (Defendants' expert, Dr. Peter J. Barnes), Tr. 1994 (Defendants' expert, Dr. Paul B. Myrdal). The Court therefore adopts AstraZeneca's definition:

> A person of ordinary skill in the art ["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.

Tr. 3935:24-3936:13 (Chipps).

Second, the Court notes that the claims of a patent are invalid, regardless of any alleged "invention date", if the invention described by those claims was already in the public domain (i.e., in a printed publication) more than a year before the earliest effective "filing date" of the patent. 35 U.S.C. § 102(b). This one-year deadline is called the patent's "critical date." Velander v. Garner, 348 F.3d 1359, 1363 (Fed. Cir. 2003). Here, the parties agree that the earliest possible effective filing date of the '603 Patent is December 31, 1997, and that the "critical date" of the '603 Patent is therefore December 31, 1996.

a. Obviousness

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 Inc. v. Lupin Ltd., 684 F.3d 1253, 1259 (Fed. Cir. 2012) (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.[22] In re

[22] The Court notes that "[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.

Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1068-69 (Fed. Cir. 2012) (internal citations omitted).

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 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

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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).

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).

Although patents are presumed valid, a party can rebut this presumption with clear and convincing evidence of invalidity. Sciele Pharma, 684 F.3d at 1260 (citing 35 U.S.C. § 282 and Microsoft Corp. v. i4i Ltd. P'ship, -- U.S. --, 131 S. Ct. 2238, 2245 (2011)).

Since the parties' disagreement as to the level of ordinary skill in the art does not affect the analysis, the Court begins by addressing the first two Graham factors: (i) the scope and content of the prior and (ii) the differences between the claimed invention and the prior art. Next, the Court assesses (iii) whether a skilled artisan would have been motivated to try

nebulized budesonide once daily, and (iv) whether such a person would have had a reasonable expectation of success in doing so. The Court then addresses (v) the last Graham prong, secondary considerations, and then sets forth its (vii) conclusion of law. Finally, the Court considers (vii) the dependent claims.

i. Scope and Content of the Prior Art

By 1997, inhaled corticosteroids such as budesonide were known to effectively treat asthma. In fact, AstraZeneca's PULMICORT RESPULES® product was already on the market outside the United States for twice-daily dosing. See PULMICORT RESPULES adver., 49 Thorax: J. of British Thoracic Soc'y (April 1994), Ex. DTX 1026, ("Thorax Ad"); Astra Draco, Int'l Patient Package Leaflet, PULMICORT® Suspension for Nebulisation (Aug. 18, 1994), Ex. DTX 751 ("IPPL"). It was approved for adults and children from three months to twelve years. Ibid. To be clear, the only invention claimed by the '603 Patent is the reduction in dosage frequency of nebulized budesonide from twice daily to once daily.[23] The question now before the Court is whether such

[23] The parties agree that the IPPL discloses every element of claim 1 of the '603 Patent except dosing "at a frequency of not more than once per day." Defs.' Proposed Findings of Fact ("Defs.' FF") & AZ's Resp. ¶ 153 [Dkt. Ent. 675-95].

once-daily dosing would have been obvious to a person of ordinary skill in the art.

The parties agree that at the time of invention, there existed a known problem:

> There is significant difficulty in the treatment of young children, including infants, who suffer from respiratory disease, e.g., asthma. In light of the requirement for frequent and repeated administration of appropriate drugs, issues of compliance and convenience are major aspects of this problem.

'603 Patent col. 1, ll. 11-15. Defendants argue that in light of the prior art, once-daily dosing of nebulized budesonide was the obvious solution to this problem. The prior art established the safety and efficacy of inhaled budesonide once daily. See infra n.24. While these studies used delivery devices other than a nebulizer, Defendants argue that a skilled person in the art would have understood that the effectiveness of budesonide in permitting once-daily dosing stemmed from the inherent properties of the drug and did not depend on the delivery device used. Thus, a skilled artisan would have interpreted the prior art to predict such success with nebulized budesonide. Defendants further argue that in addition to issues of compliance and convenience, a person of ordinary skill in the art would have been motivated to reduce the dosage to once per day based on the prevailing approach to treating asthma, known as the "stepwise" approach, which taught doctors to titrate down

to the lowest effective dosage and frequency. Defendants presented the following evidence to support their position.

1. Once-Daily Studies

Defendants established that prior to 1997, several journal articles taught the safety and efficacy of once-daily inhaled budesonide.[24] As AstraZeneca correctly points out, however, none of these studies used a nebulizer to administer the drug. Rather, the studies cited in these articles used two other delivery devices: (1) a dry powder inhaler ("DPI") and (2) a

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[24] See T.P. McCarthy, The Use of a Once Daily Inhaled Glucocorticosteroid (Budesonide) in the Management of Childhood Asthma, 4 Brit. J. Clinical Res. 55 (1993) (DTX 815, "McCarthy"); C. Möller, et al., Administration of Budesonide via Turbuhaler® (200 µg and 400 µg) Once Daily Is as Effective as when Given Twice Daily in Children with Asthma, 9 Eur. Respiratory J. 115s (Sept. 1996) (DTX 816, "Möller"); A.H. Jones, et al., Pulmicort® Turbohaler® Once Daily as Initial Prophylactic Therapy for Asthma, 89 Respiratory Med. 293 (1994) (DTX 830, "Jones"); Goran Stiksa & Christer Glennow, Once Daily Inhalation of Budesonide in Treatment of Chronic Asthma: A Clinical Comparison, 55 Annals of Allergy 49 (July 1985) (DTX 814, "Stiksa"); L.M. Campbell, et al., Once Daily Budesonide Turb[u]haler Compared with Placebo as Initial Prophylactic Therapy for Asthma, 2 Brit. J. Clinical Res. 111 (1991) (DTX 873, "Campbell I"); L.M. Campbell, et al., Once Daily Budesonide: Effective Control of Moderately Severe Asthma with 800 µg Once Daily Inhaled via Turb[u]haler When Compared with 400 µg Twice Daily, 7 Eur. J. Clinical Res. 1 (1995) (DTX 1045, "Campbell II") (collectively, the "once-daily studies").

metered-dose inhaler ("MDI"[25]) with a spacer device known as a Nebuhaler. Defendants respond that a person skilled in the art at the time would have understood that the effectiveness of once-daily budesonide by DPI and MDI rendered obvious such success with a nebulizer. A brief description of these delivery devices is helpful here.

2. Delivery Devices

By 1997, there were three devices for administering inhaled budesonide to patients: the DPI, MDI, and nebulizer. Defs.' FF 139. Defendants introduced expert testimony from Dr. Raoul L. Wolf, a practicing allergist and immunologist, who testified as to how each of these devices works and whose testimony is undisputed on this point.[26] Tr. 1315, 1319-1320 (Wolf); Ex. DTX 623.

The MDI uses a canister, which contains the medication in the form of a solution or suspension. Tr. 1996 (Myrdal). When the patient presses down on the canister, the medication is propelled into a gaseous suspension in the form of a cloud, which the patient then inhales. Tr. 1319-20 (Wolf); Tr. 1996-97

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[25] An MDI is sometimes also known as a pressurized metered-dose inhaler or "pMDI". Tr. 1352-53 (Wolf).

[26] The Court notes that none of the parties objected to the qualifications of any of the experts at trial.

(Myrdal). The primary difficulty with this device is that the patient must time the dose so that he or she inhales the medication properly. This requires considerable coordination. Tr. 1320 (Wolf). A Nebuhaler is a "spacer" that facilitates this. Id. at 1330. It creates a space between the MDI and the patient's mouth, so that when the MDI sprays the medication, it acts as a "holding chamber" from which the patient can inhale it, thus reducing the coordination required by the MDI. Id. at 1330-32.

The DPI contains dry powder medication and works in a similar manner as the MDI, but rather than using a propellant, the patient uses the force of her own inhalation to propel the medicine. Id. 1320; Tr. 1996-97 (Myrdal). This can be problematic for small children. Tr. 1320 (Wolf).

Nebulizers aerosolize a drug from a liquid solution or suspension to create a fine mist of droplets, which the patient then inhales. Tr. 1997:25-1998:19 (Myrdal). Unlike the MDI and DPI, it is a "completely passive device", that is, it does not require any force or effort on the part of the patient, who simply breathes at a normal respiration. Tr. 1320 (Wolf). This makes the nebulizer easy to use for patients, especially small children, who do not have the coordination required for the MDI or the "negative force" needed for the DPI. Id. The

nebulizer's disadvantage is its inefficiency; a lot of the medication is lost in the air or swallowed by the patient. Id. at 1321. To compensate for this, the patient runs the nebulizer over a longer period of time and uses a higher dose of the medication. Id.

3. Expert Testimony

Defendants proffered considerable evidence that a person of ordinary skill in the art would have deemed it obvious that delivery devices are interchangeable for purposes of once-daily dosing of budesonide. They presented expert testimony from Dr. Wolf, Dr. Barnes, who, as discussed above, is a specialist in respiratory medicine, and Dr. Paul B. Myrdal, an expert in the development of inhalation pharmaceuticals. These witnesses all opined that in light of the prior art, once-daily dosing of nebulized budesonide would have been obvious to a person of ordinary skill in the art at the time of the alleged invention. Tr. 1317:7-12 (Wolf); Tr. 2184:10-20 (Barnes); 1992:2-8 (Myrdal); Ex. DTX 623, 85, 620. Since their testimony was at times cumulative, the Court addresses each expert's testimony as it becomes relevant to the discussion of the prior art.

4. Brattsand & Selroos: The Inherent Properties of Budesonide

Dr. Myrdal testified that from a formulation perspective, a person of ordinary skill in the art would have understood that

so long as the budesonide particle size is sufficiently small for delivery to the lungs, it is irrelevant which device delivers the drug. Tr. 1998-99.

Dr. Myrdal explained that in 1997, a person of ordinary skill in the art would have understood that the physico-chemical properties of budesonide make it amenable to delivery by any of the three delivery methods described above. Tr. 2055. He supported this proposition by citing to a chapter from the book, Advances in Clinical Pharmacology: Drugs and the Lung, which was published in 1994 and is clearly prior art.[27] Tr. 2054-55 (Myrdal). This chapter - the "Brattsand & Selroos" reference – states in relevant part:

> [T]he physicochemical properties of budesonide (notably its relatively high solubility in water – 14 mcg/ml), means that this drug can be delivered by CFC aerosol, by a novel type of multidose dry powder inhaler without additives (Turbuhaler), as well as by nebulization.

DTX 912, at BB024376.

Dr. Myrdal further opined that a person skilled in the art in 1997 would understand, based on the prior art, that airway cells would not respond differently to budesonide based on the

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[27] Ralph Brattsand & Olof Selroos, Current Drugs for Respiratory Diseases – Glucocorticosteroids, in Drugs and The Lung 101 (Clive P. Page & W. James Metzger eds., 1994), DTX 912.

delivery device. Tr. 2053, 2056-57. He cited the following passage from Brattsand & Selroos to support this proposition:

> It seems logical that when [glucocorticosteroids] are slowly released from these still-unidentified binding sites (phospholipid-rich membranes?) they produce prolonged stimulation at local GCS receptors. This type of local depot may explain the possibility of using budesonide even once daily in treatment of stable mild asthma.

Id. at 129, Ex. DTX 912 (footnotes omitted); Tr. 2056. Dr. Myrdal explained that a person of ordinary skill in the art would understand "depot" to mean "some kind of extended release or long release." Tr. 2056. He opined that based on Brattsand & Selroos, a person of ordinary skill in the art would have understood that budesonide can be administered using any of the three delivery devices discussed above, and that once delivered to the lung, its physico-chemical properties "come into play" and the depot effect, which permits once-a-day dosing, occurs regardless of the delivery device used. Id. at 2056-57.

Dr. Myrdal testified that the Jackson reference[28] is consistent with this opinion. Id. According to Dr. Myrdal, and as discussed in detail below, Jackson teaches that budesonide has the same clinical effectiveness and side effects regardless

[28] William F. Jackson, Nebulised Budesonide Therapy in Asthma – A Scientific and Practical Review 39 (1995), DTX 826A, 826, PTX 1650 ("Jackson").

of whether the delivery device used is the MDI or nebulizer. Tr. 2058-59, 2072 (citing Jackson at 39-40). According to Dr. Myrdal, Jackson teaches that, "regardless of delivery device, if you can get the drug to the lung, then budesonide will do naturally whatever it's going to do in the lung." Tr. 2059.

Dr. Myrdal also testified that the Campbell II reference supports his opinion about the inherent properties of budesonide. Tr. 2059.[29] The Campbell II study established that once-daily dosing of budesonide was equally as effective as twice-daily dosing. Ex. DTX 1045; Tr. 2061 (Myrdal). Although this study used a DPI, Dr. Myrdal pointed out that it relied upon previous studies (i.e., Stiksa, McCarthy, and Jones) involving once-daily budesonide by MDI, thus suggesting an understanding that delivery devices are interchangeable. Id. Dr. Myrdal ultimately opined that it would have been obvious to a skilled artisan in 1997 that budesonide could be dosed once per day via nebulization. Tr. 2081.

[29] Campbell II was published in 1995 and is undisputedly prior art. Ex. DTX 1045. That study involved 229 patients with moderate asthma. It compared treatment with 800 mcg of budesonide given once daily by Pulmicort Turbuhaler (a DPI) and treatment with 400 mcg given twice daily by Turbuhaler. Id. The study concluded that once-a-day dosing of budesonide was "equally as effective" as twice-a-day dosing. Tr. 2061 (Myrdal); Campbell II at 9.

On cross-examination, AstraZeneca challenged Dr. Myrdal's reliance on Brattsand & Selroos, pointing out that the statement regarding the depot effect of budesonide was speculative and incorrect as to the location of the binding site. Tr. 2127-28. On re-direct, Dr. Myrdal stated that this distinction as to the location of the binding site was irrelevant. Tr. 2177-78. He testified that the important point, which a person of ordinary skill would have appreciated, is that Brattsand & Selroos discloses that budesonide can be dosed once daily because of its inherent properties, which was consistent with the once-daily studies. Id.

AstraZeneca introduced expert testimony from its consultant, Dr. Chipps, Tr. 4016-18, who challenged Dr. Myrdal's reliance on Brattsand & Selroos. Dr. Chipps opined that a person of ordinary skill in the art would not find the statement in Brattsand & Selroos – "This type of local depot may explain the possibility of using budesonide even once-daily in the treatment of stable and mild asthma" – to be credible. Tr. 4047-48. He acknowledged on cross-examination, however, that the authors of this paper were employed by an affiliate of AstraZeneca's, AB Astra Draco, and that Brattsand is the original inventor of the budesonide molecule. Tr. 4048. Dr. Chipps then qualified his earlier statement, saying, "That

statement does not explain the depot effect to me." Id. However, whether Brattsand & Selroos accurately described the actual depot effect is beside the point. Rather, the relevant inquiry is how a person of ordinary skill in the art in 1997 would have viewed this statement, and as to that inquiry, Dr. Myrdal's testimony was persuasive.

Dr. Myrdal's testimony comports with the rest of the evidence in the record. Indeed, Dr. Wolf and Dr. Barnes both corroborated this. Dr. Wolf testified that from a clinical standpoint, "there is no difference whatsoever" between the three devices in the sense that they are all used to propel medication into the lungs. Tr. 1319. According to Dr. Wolf, so long as the device effectively delivers the medication to the lungs, "how it gets there is relatively unimportant." Tr. 1319-20. He cited to the McCarthy and Jackson references, discussed below, to support this proposition.

5. McCarthy: The Effectiveness of Once-Daily Budesonide by DPI and MDI

The McCarthy article was published in 1993, and is undisputedly prior art. Tr. 1335 (Wolf); Ex. DTX 815. It discusses a study of asthmatic children who were switched from twice-daily to once-daily dosing of budesonide. Ex. DTX 815 at 000947. The key teaching of McCarthy, according to Defendants'

experts, is that the participants used different delivery devices but experienced the same success with once-a-day budesonide. Some used an MDI with a Nebuhaler, while others used a DPI (the Pulmicort Turbohaler). Ex. DTX 815. The study concluded that,

> [B]udesonide may be administered on a once daily basis without reducing its effect in controlling asthma symptoms. The evidence for the use of once daily budesonide as effective prophylactic medication in the management of asthma can be considered to extend from adults to children. The previous evidence has studied the Turbohaler as the delivery device, but in this study some children used a Turbohaler and others used a metered dose inhaler with a Nebuhaler. The Nebuhaler appears to be equally effective as a device for delivering once daily glucocorticosteroids.

Id. at 000951-52. McCarthy then commented on the author's success with once-daily budesonide in small children via Nebuhaler and facemask:

> The author has frequently found once daily budesonide to be effective in the management of asthma in small children. This has been found to be of considerable use when stepping down treatment with inhaled glucocorticosteroids in children. It is also of use in the administration of inhaled glucocorticosteroids to infants via a chamber device [Nebuhaler] and mask when the child resists treatment[.] [I]n these cases the parent may administer the medication once daily at night when the child is asleep.

Id. at 000952.

Dr. Wolf testified that McCarthy's conclusion that the DPI and MDI with Nebuhaler were equally effective would have reinforced what a skilled artisan would have already believed –

that the delivery device itself is irrelevant to the effectiveness of the budesonide so long as it delivers the medication to the lungs. Tr. 1329-30. Dr. Wolf also opined that a person of ordinary skill in the art would conclude from the McCarthy paper, that once-daily dosing of budesonide "is a step that could readily be taken [] that [] is effective and is in keeping with good medical practice of reducing to the minimum amount of medication required." Id. at 1333. Dr. Wolf reiterated that the once-daily studies, such as McCarthy, predicted success with once-daily nebulized budesonide, because "what is important is [that] the drug is delivered, the actual mechanism whereby it's delivered is unimportant." Tr. 1344. The Court was persuaded by Dr. Wolf's testimony, which was credible and consistent with the evidence as a whole.

Dr. Barnes confirmed Dr. Wolf's interpretation of McCarthy. He testified that this reference shows the interchangeability of delivery devices.

> So once it's known that inhaled budesonide works by once-daily administration, I think anyone who understood this area, a person of ordinary skill in the art, would expect it to work once daily whichever inhaled delivery system you use. Because what's important is not how the drug is delivered to the lung but the fact that the drug gets to the lung . . . . So once the drug is in the lung, it's going to work exactly the same way to control asthma, whichever type of inhale[r] device you use to get the drug into the right place.

Tr. 2231 (Barnes). To support this opinion, Dr. Barnes first cited to the introduction of the McCarthy article, which refers to the use of once-daily budesonide generally and never limits its discussion to a specify delivery method. Tr. 2231 (citing McCarthy at 000948). He then pointed to McCarthy's conclusion that the MDI with Nebuhaler is equally as effective as the DPI (Turbohaler). Id.

Dr. Barnes further opined that a person of ordinary skill in the art would have understood that one could use a nebulizer with a mask instead of the MDI with a Nebuhaler and mask, which McCarthy discussed in reference to once-daily treatment of small children. Tr. 2233. Dr. Barnes acknowledged, again, that "there was a general understanding that changing the type of inhaled delivery device didn't [a]ffect the efficacy of the drug, because as long as you get the drug into the lung . . . it doesn't matter how you got it there." Tr. 2233-34. Dr. Barnes testified that while McCarthy and certain other pieces of prior art – i.e., the Barnes[30] and Boutin & Boulet[31] references,

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[30] See Peter J. Barnes, Inhaled Glucocorticoids for Asthma, 332 NEW ENG. J. MED. 868 (1995) (DTX 875) ("Barnes article").

[31] See Helene Boutin & Louis-Philippe Boulet, UNDERSTAND AND CONTROL YOUR ASTHMA (McGill-Queen's Univ. Press 1995), DTX 1048A ("Boutin & Boulet").

discussed in the anticipation context below - do not cite specific clinical trials establishing the once-daily effectiveness of nebulized budesonide, "it's implicit in the discussion that [nebulized] budesonide would be effective on a once-daily basis," because these references discuss budesonide in general. Tr. 2292. The Court found Dr. Barnes credible and his testimony consistent with the record as a whole.

Dr. Barnes further noted that "there is a huge amount of literature" showing that the MDI with Nebuhaler and face mask are interchangeable with the nebulizer and face mask. Tr. 2234. By way of example, Dr. Barnes pointed to a book written by William F. Jackson on behalf of AstraZeneca, entitled Nebulised Budesonide Therapy in Asthma – A Scientific and Practical Review.[32] Id.

6. Jackson: The Comparability of Nebulized Budesonide and Budesonide by MDI

Jackson was published in 1995 and is prior art to the '603 Patent. It includes a section entitled "Relative Efficacy of Budesonide Nebulising Suspension", with a subsection entitled "Comparison with pMDI". Jackson at 37. This section provides a

[32] William F. Jackson, Nebulised Budesonide Therapy in Asthma – A Scientific and Practical Review 39 (1995), DTX 826A, 826, PTX 1650 ("Jackson").

summary of various studies comparing the administration of budesonide by pMDI and by nebulizer. Tr. 2235-36 (Barnes) (citing id.). Jackson cites a study of 18 children, ages 6 to 15, which compares nebulized budesonide with budesonide by pMDI and Nebuhaler. The study concluded: "The effect of budesonide 0.2 mg b.d., by pMDI was slightly less than that of nebulized budesonide, 0.5 mg b.d., though the difference was not statistically significant." Jackson at 37. Jackson describes another study in adults with moderately severe asthma, who were given nebulized budesonide and budesonide by pMDI and a Nebuhaler. Id. at 38. At the conclusion of this section, Jackson states: "In terms of efficacy, nebulised budesonide suspension, 1000 mcg, seems to be as effective as budesonide, 400-800 mcg by pMDI, depending on the nebulisation technique used."[33] Id. at 39 (emphasis added). On the following page,

[33] In cross-examining Dr. Barnes, Dr. Myrdal, and Dr. Wolf, AstraZeneca highlighted the last phrase of this sentence – "depending on the nebulisation technique used" – although none of the experts explained its significance. Defendants inexplicably failed to address the issue on redirect. Nevertheless, it is clear that none of these experts' opinions were swayed by this phrase, since they all based their opinions on this reference with particular emphasis on this sentence. Moreover, the plain language of the sentence suggests that it pertains to equivalent dosage amounts between the nebulizer and pMDI, which may vary depending on the nebulization technique used.

Jackson also concluded: "There is no difference between clinically equivalent doses of budesonide given by nebuliser and by pMDI in terms of systemic side-effects." Id. at 40 (emphasis added).

Dr. Barnes testified that the teachings in Jackson – that nebulized budesonide and budesonide by pMDI have "similar efficacy and side effects" - would have motivated a person skilled in the art to apply the once-daily teachings of McCarthy to nebulized budesonide. Tr. 2237. In fact, Dr. Barnes testified that in the mid-1990's, he himself prescribed nebulized budesonide once daily to patients even though the PULMICORT label did not indicate such dosing. Tr. 2380. He did this "[b]ecause it was known that once-daily budesonide via other inhaled routes was effective and therefore nebulized budesonide would certainly be as effective. Because once the drug is in the lung it will work in exactly the same way whichever inhaler device you use to deliver the drug to the airways." Tr. 2380. Dr. Barnes testified that he did not write such prescriptions very often, however, because he does not generally treat children. Id.

The Court found Dr. Barnes to be very well qualified as an expert in the treatment of asthma and respiratory diseases. Tr. 2183-84. He is currently a professor of thoracic medicine at

the National Heart and Lung Institute, head of respiratory medicine at the Imperial College London, and honorary consultant physician at the Royal Brompton Hospital in London. Ex. DTX 85. He has been practicing medicine for forty years and is a specialist in respiratory medicine with a particular focus in the treatment of asthma. Tr. 2182. He has also consulted with AstraZeneca on the topic of asthma treatment. Tr. 2182-83. The Court found him credible in his assessment of how a skilled artisan would have viewed the McCarthy and Jackson references.

Despite a skillful cross-examination, AstraZeneca did not impeach Dr. Barnes in any material way. It merely pointed out that the studies cited in Jackson did not actually involve a Nebuhaler with a facemask, as Dr. Barnes had originally indicated. Tr. 2300 (Barnes). Dr. Barnes then explained that the study cited by AstraZeneca involved adults, who would not need such facemasks, which are used by children who cannot use "the normal mouthpiece." Tr. 2300-02 (Barnes). AstraZeneca also pointed out that one particular study involved adults, who used an "intermittent nebulizer," which would not be appropriate for children. Id. Dr. Barnes explained on redirect, however, that Jackson also cited studies involving children. Tr. 2377 (Re-Direct); Jackson at APO0300760. In any event, this last

point is only relevant to the dependent claims, which include age limitations. See infra.

Dr. Myrdal corroborated Dr. Barnes' testimony. He testified that a person of ordinary skill in the art would understand the teachings in Jackson to be consistent with Brattsand & Selroos; i.e., that "regardless of delivery device, if you can get the drug to the lung, then budesonide will do naturally whatever it's going to do in the lung." Tr. 2059 (Myrdal).

7. AstraZeneca's Rebuttal

AstraZeneca argues that the Patent Office considered McCarthy, so the Court should give that reference less weight. The Court notes, however, that the Patent Office did not consider Jackson or Brattsand & Selroos, which link the teachings of McCarthy and the other once-daily studies to nebulized budesonide. Without these references, the Patent Office may not have appreciated the critical fact that delivery devices are interchangeable for purposes of once-daily dosing.

AstraZeneca also counters that a person of ordinary skill in the art in 1997 would not extrapolate data from one device to another. AZ's Resp. to Defs.' FF ¶ 214 [Dkt. Ent. 675]. Citing

the Expert Guidelines[34] and Dr. Chipps' testimony, AstraZeneca argues that the delivery devices differ in efficiency, which affects efficacy. AZ's Resp. FF ¶ 140 [Dkt. Ent. 675]. The Court gives little weight to the portion of the Expert Guidelines relied upon by AstraZeneca, since it did not present any expert testimony or other evidence to support its interpretation of this passage.[35] This section of the Guidelines explains the chart on the previous page, which compares dosing

[34] Nat'l Asthma Educ. & Prevention Program, Expert Panel Report II: Guidelines for the Diagnosis & Mngmt. of Asthma 89 (NIH Nat'l Heart Lung & Blood Inst. July 1997), DTX 845 ("Expert Guidelines"). Both parties rely on the Expert Guidelines, suggesting that they stipulate that it is prior art to the '603 Patent.

[35] Indeed, this appears to be an argument raised for the first time in AstraZeneca's post-trial briefing. The full paragraph cited by AstraZeneca states:

> Data from in vitro and clinical trials suggest that the different inhaled corticosteroid preparations are not equivalent on a per puff or microgram basis. However, it is not entirely clear what implications these differences have for dosing recommendations in clinical practice because there are few data directly comparing the preparations. Relative dosing for clinical comparability is affected by differences in topical potency, clinical effects at different doses, delivery device, and bioavailability. The Expert Panel developed recommended dose ranges (see figure 3-5b) for different preparations based on available data and the following assumptions and cautions about estimating relative doses needed to achieve comparable clinical effect.

Expert Guidelines, DTX 845 at BB16860 (emphasis in original).

amounts across various corticosteroids (i.e., beclomethasone diproprionate, flunisolide, and budesonide). Expert Guidelines, Ex. DTX 845 at BB16859. The only language specific to delivery devices and budesonide states:

> Delivery systems influence comparability. For example, the DPI delivery device for budesonide delivers approximately twice the amount of drug to the airway as the MDI, thus enhancing the clinical effect.

Id. at BB16860. Without expert testimony explaining the significance of this statement, the Court accords it limited weight. The Court notes, however, that it appears to address the undisputed fact that the three delivery devices available have different levels of efficiency in delivering the drug to the airway. Dr. Wolf testified to this, explaining that the patient compensates for the relative inefficiency of the nebulizer by running it over a longer period of time and using a higher dose of medication. Tr. 1321. Similarly, in comparing nebulized budesonide to budesonide by pMDI, Jackson addressed the issue of giving "clinically equivalent" doses of budesonide. Jackson, supra, at 39-40. The fact that the Expert Guidelines highlights this point seems to have little bearing on the obviousness analysis. Rather, the critical issue, as framed by Dr. Barnes, is whether a person of ordinary skill in the art would have understood that clinically equivalent doses of budesonide would have the same effect in the lung regardless of

the delivery device used.

AstraZeneca relies heavily on Dr. Chipps' testimony. Dr. Chipps stated that dosing in one delivery device would not predict dosing in another device because they have different "deposition patterns" and "penetration." Tr. 3951 (Chipps). Dr. Chipps did not explain the meaning of these terms but cited to examples of other drug products (the relevance of which was unclear to the Court) and vaguely stated that one cannot extrapolate clinical effectiveness of one delivery device to another "until the appropriate studies are done." Tr. 3953. On cross-examination, however, Dr. Chipps conceded that the PULMICORT RESPULES® label itself relies on data concerning the Pulmicort Turbuhaler, a DPI. Tr. 4046-47.

In any event, the Court gives little weight to Dr. Chipps' opinions. First, they did not comport with the record evidence as a whole. Second, he seemed unclear as to the standard for obviousness. On cross-examination, he admitted that he did not apply the correct legal standard. He admitted that he did not consider that a person of ordinary skill would also have ordinary creativity. Tr. 4002 (Chipps). He also conceded that he did not know whether the law required a randomized, placebo-controlled study establishing the effectiveness of once daily nebulized budesonide before a person of ordinary skill in the

art would have had a reasonable expectation of success in trying it. Tr. 4043-44 (Chipps). At first, he indicated that such a study would be required but then stated that he was not sure. Id. Finally, the Court appreciates the fact that he was testifying for a company that has been his longtime benefactor. He testified that he has worked as a consultant for AstraZeneca since 1999, that AstraZeneca has paid him over $100,000 to give lectures, and that he has never provided testimony in support of a generic product. Tr. 4016-18. He also testified that he has been paid to serve on multiple advisory boards for AstraZeneca and that his practice does ongoing research for AstraZeneca. Tr. 4017 (Chipps). For these reasons, the Court did not find Dr. Chipps persuasive and thus gives limited weight to his opinions on this issue.

ii. Differences between Prior Art & Claimed Invention

The essential teaching of the '603 Patent is the once-daily dosing of nebulized budesonide. Defendants have established that a person skill in the art would have understood the prior art to disclose that: (1) budesonide can be administered effectively once per day using the two other delivery devices available, the DPI and MDI; (2) the once-a-day effectiveness of budesonide results not from the delivery device but from the inherent properties of the budesonide particle itself; and (3)

budesonide administered by nebulizer has similar efficacy and side effects as budesonide by MDI. Clearly, the distinction between the claimed invention and the teachings of the prior art is slight. It concerns whether a skilled person in the art would have been motivated to draw the obvious conclusion: once-daily, nebulized budesonide.

iii. Motivation to Try Once-Daily Nebulized Budesonide

Defendants proffered considerable evidence showing that a person of ordinary skill in the art would have been motivated to titrate down to once-daily dosing of nebulized budesonide in 1997. First, Dr. Myrdal testified that the general understanding of the inherent properties of budesonide and the successful once-daily dosing of budesonide in other delivery devices would have prompted this application. Tr. 2072. As discussed above, the Court finds Dr. Myrdal's testimony credible and persuasive.

Second, Defendants presented evidence that a nebulizer was the most practical delivery device for certain patients like young children, who could not handle other devices. They relied on the expert testimony of Doctors Wolf, Barnes, and Myrdal, the IPPL, the Jackson reference, and the pre-NDA package, in which AstraZeneca recognized the problems with the use of holding chamber devices – such as Nebuhalers – for small children, i.e.,

that it still requires some degree of coordination. Defs.' FF 189 (citing Ex. DTX 751 (IPPL); Ex. DTX 826A (Jackson); 1320-21 (Wolf); 2240-2241 (Barnes); 2080-81 (Myrdal); Ex. DTX 627 at 0000534 (AstraZeneca's Pre-NDA Package)). The Court finds this evidence persuasive as well.

Indeed, although AstraZeneca argues to the contrary, Jackson clearly teaches that nebulized therapy "continues to have an important role in infants and young children, in patients of all ages with acute severe asthma, and in other selected patients." Jackson at 14 (emphasis added). Jackson states that "[n]ebulized budesonide is effective in controlling severe, steroid dependent asthma in infants and children under 3 years of age [and] has an emerging role in adults." Id. at 55. Jackson further states, "nebulized budesonide is particularly appropriate in infants with very severe asthma, either before resorting to oral steroids or as a means of reducing the oral steroid requirement." Id. at 59. Dr. Chipps testified that he had no reason to disagree with these statements in Jackson. Tr. 4014.

Dr. Chipps testified that while the nebulizer with facemask and the MDI with Nebuhaler are recommended delivery devices for children under four, the nebulizer is the easiest and most effective delivery device for young children, and doctors thus

prefer it. Tr. 4076:9-20, 4076:24-4077:9 (Chipps). Dr. Wolf confirmed that it was well-known that nebulized suspension formulations were often used to treat children. Tr. 2080-81.

AstraZeneca's argument that the prior art teaches away from using a nebulizer because it was cumbersome, expensive, time-consuming, and inefficient lacks support in the record. Indeed, it runs counter to the testimony by AstraZeneca's own expert, Dr. Chipps, and ignores the express teachings of Jackson, as discussed above.

Third, Defendants reiterate that there was a known problem in 1997: that the dosing frequency for young children with asthma created issues of compliance and convenience. Tr. 4003 (Chipps); '603 Patent, col. 1, ll. 10-17, Ex. PTX 1; Tr. 1339-40 (Wolf). Defendants argue that in light of the extensive prior art establishing the effectiveness of once-daily budesonide, a person skilled in the art would have been motivated to solve this problem by trying nebulized budesonide once daily. They contend that this would not only improve patient compliance and convenience for patients and caregivers, but it would also comport with the prevailing "stepwise" approach to asthma therapy. Defs.' COL 48 (citing Tr. 1337:22-1338:6). Defendants introduced more than sufficient evidence to prove this.

1. Compliance & Convenience

The parties agree that compliance and convenience played important roles in the treatment of asthma. Defendants' expert, Dr. Wolf, testified that a person skilled in the art would understand that simplifying the treatment regimen would improve compliance. Tr. 1338. He explained that convenience and compliance are interrelated concepts, noting that "if the medication is easy to take, someone is more likely to do it." Id. at 1339. He stated that once-daily dosing would be particularly convenient for children taking nebulized budesonide, "because a squirming child may not sit still for the use of the nebulizer and it is actually essential for the nebulizer to work that it be firmly attached to the child's face." Tr. at 1339.

AstraZeneca's expert, Dr. Chipps, corroborated this testimony, stating that a logical solution to the problems of compliance and convenience would be to give the drug as few times per day as possible. Tr. 4005. He agreed that the fact that patients are more compliant with once-per-day dosing provides a motivation to achieve such a regimen. Tr. 4004. He also testified that a skilled artisan would have known that patients and caregivers preferred once-a-day dosing, because it is more convenient. Id. Dr. Chipps further stated that once-daily dosing is particularly advantageous for nebulized medicine

as compared to a DPI and MDI, because a nebulizer takes longer to administer medication than such other devices. Id.

The prior art supports this testimony. The Stiksa reference, for example, states: "The decrease of inhalation frequency to once daily would be easier for the patient to perform and might improve patient compliance." Ex. DTX 814 at 2. Similarly, the McCarthy reference states: "By using the medication on a once daily basis, compliance, and therefore prophylaxis, with this inhaled glucocorticosteriod, may be improved." Ex. DTX 815 at 60. McCarthy further provides:

> The number of times that a medication has to be taken during the day affects the degree to which the patient conforms to the recommended regime, and patients have shown a preference for a once daily inhaled medication. It seems, therefore, reasonable to administer a therapy as few times as possible during the day, and once daily medication would seem to be preferable . . . .

Ex. DTX 815 at 56. Likewise, Jackson states:

> At this stage, many patients and parents find the need for nebulisation twice a day to be time-consuming and irksome. The reduction of dose (and thus of nebulising time), and the ultimate transfer to other inhaler systems, may thus have important compliance advantages in adequately controlled asthma, in addition to lessening the risk of side-effects.

Jackson at APO0300784; Tr. 4015 (Chipps).

The evidence persuades this Court that a person of ordinary skill in the art would have been motivated to try nebulized budesonide once daily to achieve compliance and convenience.

2. "Stepwise" Approach to Asthma Therapy

Defendants also argue that the "stepwise" approach to asthma treatment would have motivated a person of ordinary skill in the art to reduce the administration of nebulized budesonide to once daily. The parties agree that the stepwise approach to asthma therapy was well known by 1997, and, in fact, was "drilled" into the heads of doctors during their fellowships. 1321:8-1322:5 (Wolf); 4006:13-4008:12 (Chipps); 2229:16-2230:6 (Barnes); 423:3-15, 440:25-441:15 (Ververeli). This approach involves starting a patient with a higher dose of medication twice a day, then stepping down the dose and then the frequency of administration, titrating to the lowest dose that is effective for that patient, which is hopefully a once-a-day strategy. 1322:17-1323:2 (Wolf); 1103:3-16 (Chipps); Expert Guidelines Ex. DTX 502A at 147. Physicians use this approach to prevent side effects from excessive dosing of inhaled corticosteroids and to achieve the most convenient and effective program. Tr. 1103 (Chipps).

The parties only dispute whether a person of ordinary skill in the art would have been motivated to reduce the dose of nebulized budesonide to once daily. Defendants argue in the affirmative and rely on the McCarthy reference, which states that reducing the administration of inhaled budesonide to once-

daily is consistent with "stepping down treatment according to the recommendations of the most recent guidelines." Ex. DTX 815 at 60. McCarthy expressly recognized that the stepwise approach teaches once-daily dosing of budesonide:

> The recommendations of the British Thoracic Society Guidelines both in their original form and the revised version put emphasis on the importance of prophylactic therapy in the management of asthma, and stepping down medication as a means of reducing drug intake when control has been achieved. It therefore seemed appropriate to examine the effects of reducing the dose of an inhaled glucocorticosteroid (budesonide) in stable, well controlled asthmatic children from twice daily to a once daily regime.

McCarthy at 000948 (internal footnotes omitted) (emphasis added); Tr. 2229-30(Barnes). Dr. Wolf corroborated McCarthy's approach. He noted that the National Heart, Lung, and Blood Institute Guidelines "put an official stamp on what was good medical practice and certainly advocated for reducing to the least amount of medication needed to control asthma." Tr. 1339, 1332-33 (commenting on McCarthy). Defendants also cite to the 1997 Expert Guidelines, which states: "Step-down therapy is essential to identify the minimum medication necessary to maintain control." Ex. DTX 502 at 145.

AstraZeneca first counters that a person of ordinary skill in the art would know that for some drugs, once-daily dosing is not an effective dosing regimen. The Court rejects this out of hand, since the overwhelming evidence shows that it was well

known in 1997 that budesonide was effective when given once daily.

AstraZeneca next argues that a person of ordinary skill in the art would have known that the stepwise approach required downward titration to the lowest known effective dose, which was twice daily, and would not have experimented with unproven dosing regimens, particularly with infants and young children. AZ's Resp. to Defs.' FF 200. The record does not support this position. As set forth above, the Court has credited the evidence proffered by Defendants that a person of ordinary skill in the art would have understood that (1) budesonide is safe and effective when given once daily in other delivery devices; and (2) the delivery devices are interchangeable for purposes of achieving once-daily dosing.

Moreover, for the reasons already discussed, the Court gives limited weight to Dr. Chipps' testimony that a person of ordinary skill in the art would not have administered budesonide once daily, because there were no clinical studies to support this.

iv. Reasonable Expectation of Success

Defendants presented ample evidence to establish that a person of ordinary skill in the art in 1997 would have had a reasonable expectation of success that once daily nebulized

budesonide would work. Doctors Myrdal, Wolf, and Barnes, all testified to this. Tr. 2071-73, 2079 (Myrdal); 1340-31 (Wolf); 2286-87 (Barnes). The evidence establishes that a person of ordinary skill in the art in 1997 would have understood that: (1) budesonide administered through a nebulizer was already safe and effective at twice-daily dosing (PULMICORT RESPULES was already on the market outside the United States); (2) inhaled budesonide was effective once daily when administered by either DPI or MDI, the other two delivery devices available besides the nebulizer, see supra n.24 (once daily studies); (3) budesonide's effectiveness as a once-a-day medication likely stemmed from its inherent properties rather than the specific delivery device used; and (4) nebulized budesonide is comparable to budesonide by MDI in terms of efficacy and side effects. The evidence is clear and convincing. Putting these pieces together, a person of ordinary skill and creativity would have reasonably expected nebulized budesonide to be effective once daily. Indeed, the prior art clearly pointed to this conclusion.

v. 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 v. John Deere Co., 383 U.S. 1, 17-18 (1966). "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)).

AstraZeneca presented evidence purporting to show the commercial success of PULMICORT RESPULES® and the unexpected results and skepticism within its company about pursuing a once-daily indication.

To support the commercial success factor, AstraZeneca submitted testimony that (1) PULMICORT RESPULES® has netted over $5 billion in sales, Tr. 4180 (AstraZeneca executive Dr. Gerard J. O'Malley); (2) 36.1% of prescriptions were for once-daily dosing, Tr. 715 (Vellturo); and (3) the once-daily dosing feature was an "important sales driver" and "prominently" included in sales aids used with physicians, Tr. 4186-87 (O'Malley).

The record evidence does not support the third prong. The sales aid cited by AstraZeneca includes the relevant language

("Once- or twice-daily dosing") at the bottom of the page, underneath small print stating: "PULMICORT RESPULES and Pulmicort Turbuhaler are registered trademarks of the AstraZeneca group of companies. . . ." Ex. DTX 716 at AZ 1007167. Rather, the aid focuses on the fact that PULMICORT RESPULES is the exclusive medication for very young children; it prominently displays a chart comparing various products with the heading, "The only inhaled corticosteroid for children under age 4." Id.

Further, the record does not support the contention that the drug's once-daily indication served as an "important sales driver." As AstraZeneca itself noted, little more than one third of PULMICORT RESPULES prescriptions were given for the once-daily indication. Additionally, Defendants introduced testimony from Christopher H. Spadea, an expert in the evaluation of patents and their effect on the market, who testified that patients under the age of four use PULMICORT RESPULES because they have no other choice, regardless of the once-daily indication. Tr. 4420-25 (Spadea); Ex. DTX 715 at 1007167; Ex. DTX 1215 at 1123255. Mr. Spadea also testified that AstraZeneca did not prominently display the once-daily dosing indication in sales aides, instead showcasing the product's safety, efficacy, and ease of use, particularly its

position as the only inhaled corticosteroid for patients under four and the only nebulized formulation for patients under eight. Tr. 4404-06, 4424-25, 4411-13, 4416-24 (Spadea); Ex. DTX 716; Ex. DTX 1212. Mr. Spadea also cited a survey of physicians, showing that the once-daily indication was ranked 43rd out of 46 performance attributes in terms of importance. Id.; Ex. DTX 731 at AZ 1168224-26. The record supports Mr. Spadea's opinion. Moreover, AstraZeneca did not submit any evidence that the sales of PULMICORT RESPULES® would have been any different if the product was indicated only for twice-daily dosing.

Thus, the Court agrees with Defendants that AstraZeneca has not established a nexus between the novel aspects of the patent and the sales of the product as required by the case law. Ormco Corp., 463 F.3d at 1311-12 ("Evidence of commercial success . . . is only significant if there is a nexus between the claimed invention and the commercial success. . . . [I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent.").

To establish the "unexpected results and skepticism" prong, AstraZeneca submitted testimony from one of the inventors of the '603 Patent, Bertil Andersson, who stated that certain people at AstraZeneca believed it was risky to pursue a once-daily

indication. Tr. 149-51. Dr. Andersson explained, however, that AstraZeneca had good reason to be cautious – if the once-daily studies did not show clinical efficacy, it might risk the "provability" of the entire NDA, including the twice-daily indication. Tr. 153-54. Accordingly, AstraZeneca conducted a third study to show clinical efficacy of both the once-daily and twice-daily regimens. AstraZeneca did this so that even if once-daily dosing proved clinically ineffective, it would still have two studies – as required by the FDA – to support the NDA for a twice-daily indication. Id. This suggests to the Court not that AstraZeneca seriously doubted the effectiveness of once-daily dosing but, rather, took a relatively simple precaution to guard against the possibility that the once-daily dosing would not work and thus risk the entire NDA. Additionally, the Court gives limited weight to Dr. Andersson's testimony, given his inherent bias as an AstraZeneca employee and the inventor of the '603 Patent, and the fact that he provided very few specifics on who showed the alleged skepticism and why.

Moreover, even assuming that AstraZeneca has properly established commercial success and skepticism, which it has not, the Court notes that such secondary considerations of non-obviousness cannot overcome the strong prima facie case of

obviousness here. Sundance, Inc. v. DeMonte Fabricating Ltd., 550 F.3d 1356, 1368 (Fed. Cir. 2008) (collecting cases).

vi. Conclusion of Law

Upon careful consideration of the four Graham factors, the Court concludes as a matter of law that claim 1 of the '603 Patent would have been obvious to a person of ordinary skill in the art in 1997. In reaching this decision, the Court is guided by three principles from the Supreme Court's decision in KSR Int'l. Co. v. Teleflex, Inc., 550 U.S. 398, 417-21 (2007): (1) that in many cases a person of ordinary skill will be able to fit the teachings of multiple pieces of prior art together "like pieces of a puzzle"; (2) that a person of ordinary skill in the art is not an automaton, but a person of "ordinary creativity"; and, most importantly, (3) that "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."

Here, the prior art disclosed all of the elements of the invention. A person of ordinary skill and creativity could have easily fit these teachings together like pieces of a puzzle. Reduced to its simplest form, the evidence essentially shows:

Budesonide by MDI & DPI = Effective Once Daily

> Budesonide's Inherent Properties = Once Daily Effectiveness
>
> Budesonide by MDI = Nebulized Budesonide
>
> Therefore:
>
> Nebulized Budesonide = Effective Once Daily

In other words, a simple application of the transitive property results in the once-daily administration of nebulized budesonide (if A=B and B=C, then A=C). This was not an act of innovation or creativity, but of common sense. Moreover, Defendants have established that several motivating factors would have driven a person skilled in the art to apply the known once-daily technique to nebulized budesonide in 1997; i.e., it addresses compliance and convenience concerns and comports with the prevailing "stepwise" approach to asthma therapy.

At the very least, Defendants have established that it would have been obvious to a person of ordinary skill in the art to try nebulized budesonide once daily. In KSR, the Supreme Court held,

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. Here, Defendants established a need for reducing the frequency of doses, particularly with the nebulizer, which takes the longest time to administer. Since it was known that inhaled budesonide could be given effectively once daily using the other two delivery devices available and that at least one of these delivery devices was comparable to the nebulizer in terms of efficacy and safety, there was a simple and predictable solution to the problem – administering budesonide once daily by nebulizer. Accordingly, the Court concludes that claim 1, the only independent claim of the '603 Patent, is invalid as obvious. The Court now considers the remaining dependent claims.

vii. Dependent Claims

Because dependent claims contain additional limitations, they are not necessarily invalid merely because the independent claims on which they depend are invalid. Sandt Tech., Ltd. v. Resco Metal & Plastics Corp., 264 F.3d 1344, 1356 (Fed. Cir. 2001); 35 U.S.C. § 282(a) ("[D]ependent claims shall be presumed valid even though dependent upon an invalid claim."). As set forth above, the dependent claims at issue are claims 2, 3, 7, 8, 12-17, and 24-28.

Claim 2 invokes the method of claim 1 "wherein the frequency is once and only once per day." Defendants introduced

testimony from Dr. Wolf, stating that the McCarthy reference discloses this limitation. Tr. 1346 (citing McCarthy, Ex. DTX 815). The Court agrees that McCarthy discloses the effectiveness of inhaled budesonide only once per day, and the prior art, as set forth above, establishes that it would have been obvious to apply this technique to a nebulizer.

Claim 7 applies the additional limitation that the respiratory disease being treated is asthma. The IPPL and all of the once daily studies involved the treatment of asthma. See supra. Dr. Wolf confirmed that the IPPL disclosed this limitation, and the Court agrees that it is obvious.

Claims 12, 14, and 16 include age limitations. Claim 12 is limited to patients "one day to fifteen years old." Claim 14 is limited to patients "one month to eight years old." Claim 16 is limited to patients "six months to five years old." Defendants proffer the IPPL, which disclosed that nebulized budesonide could be used for "children." Ex. DTX 751 at 1326445. Dr. Wolf testified that a person of ordinary skill in the art would understand "children" to mean patients under the age of 16. Tr. 1327:10-16, 1349:20-24. The Court found Dr. Wolf's testimony to be credible and sees no reason to doubt it. Defendants also produced evidence showing that by 1994, PULMICORT RESPULES was already on the market and approved for children ages 3 months to

12 years. Thorax Ad, Ex. DTX 1026. Dr. Wolf confirmed this. Tr. 1373-74. Additionally, Defendants introduced testimony from Dr. Barnes stating that a person of ordinary skill in the art would not have any concerns about using nebulized budesonide once daily in children under the age of five, because the principles for treating this patient group and for treating older children and adults are the same. Tr. 2287:3-7. Dr. Barnes also testified that the Boutin & Boulet reference, see infra, discloses the age ranges identified in claims 12, 14, and 16, because it refers to "children," which would be understood to cover the range from birth to "about 16" or 17. Tr. 2317, 2373. Defendants also point to the Moller and McCarthy references, which teach the use of inhaled budesonide once daily in children ranging in age from 5 to 13 (Moller) and 7 to 13 (McCarthy). Ex. DTX 816, 815. Moreover, McCarthy explicitly teaches the use of once-daily inhaled budesonide in "small children" and "infants" (using a "chamber device and mask," which, as discussed above, is interchangeable with a nebulizer, see infra). Defendants also cite to the Jackson reference, which, as set forth in detail above, establishes that nebulized budesonide is effective in controlling asthma in infants and children under three years of age and that the nebulizer is similar to the MDI with Nebuhaler in terms of efficacy and

safety. Ex. DTX 826 at 55, 39-40, 60. Finally, Defendants point to the fact the '603 Patent itself only relies on studies involving children from six months to eight years of age and extrapolates to the ages listed in the claims – including adults - based on this data. '603 Patent, col. 4, l. 40, col. 7, l.36.[36] Dr. Chipps conceded this on cross-examination. Tr. 4055-56.

AstraZeneca counters that a person skilled in the art would not have understood that nebulized budesonide could effectively treat children in a once-daily dose. It proffers the testimony of its expert, Dr. Kathleen O'Connor Ververeli, an allergist and clinical immunologist, who testified that she would not prescribe once-daily budesonide although patients asked for it, because at the time, there was no literature to support it. Tr. 429-30, 445-46. Significantly, however, Dr. Ververeli also admitted that she was dealing with children with severe asthma.

[36] Indeed, the Court notes that the prior art references involving adults cite to and build off of studies involving children and vice versa, suggesting that a person of ordinary skill in the art would consider adult studies when treating children. See Campbell II at 10-11, DTX 1045 (asthma study in adults that explicitly "aimed to extend" the teachings of prior studies done in both adults and children [Stiksa, McCarthy, and Jones]); McCarthy at 56 (study of children relying on data from studies in adults).

Id. ("These patients . . . were so severe prior to getting them going on [PULMICORT RESPULES], that they weren't going to experiment and try to do it once a day."). Thus, the Court gives her testimony limited weight, since it does not resolve whether she would have prescribed once-daily dosing had her patients had "stable and well controlled" asthma, which is what the McCarthy and Moller references taught. See McCarthy at 55 (involving children "whose asthma was stable and well controlled"); Moller at 115s (involving children with "well-controlled" asthma).

AstraZeneca also proffers Dr. Chipps' testimony that a person of ordinary skill in the art would lower a dosing frequency from twice daily to stopping the medication completely, but would not try a once-a-day dose because it had not been "shown to be safe and effective" to do so. Tr. 4083:13-4084:17. However, as set forth above, the Court did not find Dr. Chipps' testimony persuasive. It did not comport with the evidence as a whole, and he admittedly did not consider that a person of ordinary skill in the art is also one of ordinary creativity.

Finally, AstraZeneca cites to the 1995 Canadian label for Pulmicort Turbuhaler®, a dry powder inhaler, which reflects that it was not recommended for children under 6 "due to limited

clinical data." Pulmicort Turbuhaler Label, Compendium Pharma. & Specialties: The Canadian Reference for Health Professionals 1129 (30th ed. 1995), Ex. DTX 1012. This point has little relevance, however, since the Turbuhaler is not at issue here. As Dr. Wolf testified on re-direct, it was well-established that PULMICORT RESPULES, was safe and effective in children three months to twelve years. Tr. 1373-74 (citing Thorax Ad, Ex. DTX 1026). The Court therefore concludes that the age limitation claims are obvious as a matter of law.

Claim 24 includes the additional limitation that the budesonide composition must contain 0.25-1.0 mg budesonide. Defendants cite to the IPPL, which discloses a composition containing 0.25, 0.5, and 1.0 mg budesonide. Ex. DTX 751 at 2(8). Dr. Wolf confirmed that the IPPL disclosed this limitation, Tr. 1349:25-1350:3, and the Court finds that it therefore would have been obvious to a person of ordinary skill in the art at the relevant time.

Claim 26 requires a suspension. The IPPL also discloses such a suspension. Ex. DTX 751; 1350:4-7 (Wolf).

As for claims 3, 8, 13, 15, 17, 25, 27, and 28, these claims require, in addition to the other limitations already cited, that the budesonide be the only active ingredient. The IPPL discloses a product wherein budesonide is the only active

ingredient, Ex. DTX 751; 1346:23-1347:1 (Wolf), so the Court agrees with Defendants that these claims would have been obvious to a skilled artisan in 1997.

b. Anticipation

The Court notes that even if the '603 claims were not obvious, the Court would still find them invalid on anticipation grounds.

"[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 person of ordinary skill 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 and Purdue Pharma L.P. v. Boehringer Ingelheim GmbH, 237 F.3d 1359, 1365 (Fed. Cir. 2001)).

i. Barnes Article

Defendants argue that an article written by their expert, Dr. Barnes, anticipates all of the asserted claims of the '603 Patent.[37] The Barnes article was written in 1995 and is undisputedly prior art under 35 U.S.C. § 102(b). The Patent Office did not consider it during prosecution of the '603 Patent.

Dr. Barnes testified that his article is a "review article about the use of inhaled steroids for treating asthma." Tr. 2211:9-11. He explained that such a review brings together all available evidence in a particular area and then interprets it. Tr. 2378:19-21. He testified that when read as a whole, his article discloses all of the elements of the asserted claims. Id. at 2378:12-19. Specifically, he stated that his article discloses the use of nebulized budesonide to treat asthma in a sub-section of the article entitled "Studies in Children". Tr. 2211 (citing Barnes at 869). The relevant sentence reads: "For

[37] See Dr. Peter J. Barnes, Inhaled Glucocorticoids for Asthma, 332 NEW ENG. J. MED. 868 (1995) (DTX 875) ("Barnes article").

example, nebulized budesonide reduced the need for oral glucocorticoid therapy and also improved lung function in children under the age of three years." Barnes at 869 (citing Ilangovan, P., et al., Treatment of severe steroid dependent preschool asthma with nebulized budesonide suspension, Arch. Dis. Child 68:356-9 (1993) ("Ilangovan")).

As for the once-daily element, Dr. Barnes pointed to a section of the article entitled "Frequency of Administration", which states:

> When inhaled glucocorticoids were first introduced it was recommended that they be given four times daily. . . . For patients with mild asthma, one dose per day may suffice.

Barnes at 870 (internal footnote omitted). Dr. Barnes testified that a person of ordinary skill in the art would have read this article "as a whole" and would have understood it to be teaching once-daily dosing of nebulized budesonide. Tr. 2378. The Court found him credible and persuasive. His expertise in this area and the fact that he authored the article lends further support to his interpretation of how a person of ordinary skill in the art would have interpreted it.

AstraZeneca makes several arguments in rebuttal. First, it argues that the sentence discussing nebulized budesonide does not disclose once-daily dosing; in fact, it refers to the Ilangovan reference, which is a study that only involves twice-

daily dosing. AZ's Resp. to FF 73 [Dkt. Ent. 675]. Dr. Barnes and Dr. Chipps both confirmed that the Ilangovan reference involves twice-a-day dosing. Tr. 2304 (Barnes); Tr. 3979-80 (Chipps). Second, AstraZeneca argues that the Barnes article does not disclose all of the elements of claim 1 as arranged in the claim, because the language discussing nebulized budesonide and once-daily dosing are in different sections. Dr. Chipps testified to this. Tr. 3983. Third, AstraZeneca argues that a person of ordinary skill in the art would not infer that the once-daily language referred to nebulized budesonide because it (1) does not specify any particular delivery device; and (2) cites the Jones reference, which studied once-daily budesonide using the Pulmicort Turbuhaler, which is a DPI. AZ's Resp. to FF 73 (citing Tr. 3981 (Chipps))[Dkt. Ent. 675].

While the question is close, the Court finds that Defendants have satisfied their burden of showing by clear and convincing evidence that the Barnes reference anticipates all of the asserted claims. Defendants are correct that anticipation merely 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.

The Court is persuaded by Dr. Barnes' testimony that a person of ordinary skill in the art, reading the article as a whole, would understand that it discloses once-daily dosing of nebulized budesonide. Tr. 2378 (Barnes). The Court has no reason to believe that his assessment is the result of impermissible hindsight. Further, the Court did not find Dr. Chipps' opinion convincing. He did not address Dr. Barnes' contention that, reading the article as a whole, a person of ordinary skill in the art would understand it to teach once-daily nebulized budesonide. Instead, Dr. Chipps appeared to read the relevant sentences separately from one another, rather than in the context of the larger article. Further, Dr. Chipps conceded that the section discussing once-a-day dosing was not limited to any particular type of delivery device. Tr. 40677-18 (Chipps).

Further, the plain language of the article supports Dr. Barnes' interpretation. While AstraZeneca is correct that the sentence regarding nebulization does not specify once-a-day dosing, neither does it limit its scope to twice-a-day dosing. Moreover, while the Ilangovan article discusses twice-daily dosing, this is not apparent from the title of the article as

recited in the footnote. As for the "one dose per day may suffice" language, Dr. Barnes testified that this refers to budesonide, which is the subject of the footnote to that sentence. Tr. 2310 (Barnes).

The Court notes that the organization and layout of the article also support Dr. Barnes' opinion. It is divided into eight sections, which are easily identified, because each heading is in bold print with capital letters; i.e., "**CLINICAL EFFICACY**" and "**FREQUENCY OF ADMINISTRATION**". Some of these sections include subsections, which are also easy to identify, because their headings are in bold print with only the first letter of each word capitalized, such as "**Studies in Adults**" and "**Studies in Children**", which are two subsections within the "**CLINICAL EFFICACY**" section. The distinction between sections and subsections is therefore immediately apparent. The Barnes article discloses the use of nebulized budesonide in young children in the "**Studies in Children**" subsection within the "**CLINICAL EFFICACY**" section. Common sense suggests that the fact that "**FREQUENCY OF ADMINISTRATION**" has its own section separate from the others signals to the reader that it sets forth general information relevant to all the other sections. Conversely, if the frequency of administration language were instead located within one of the subsections, i.e., the

"**Studies in Children**" or "**Studies in Adults**" subsection, a reader would reasonably infer the dosing information to be limited to that particular subsection and the population described therein. Thus, the layout of the article further supports Dr. Barnes' opinion that the once-a-day dosing language encompasses nebulized budesonide.

As for the dependent claims (claims 2, 3, 7, 8, 12-17, and 24-28), Dr. Barnes testified that the Barnes article, when read as a whole, also disclosed these additional limitations. Tr. 2212:19-2213:2.[38]

Claim 2 limits the dosing to "once and only once per day". Dr. Barnes stated that this additional limitation is disclosed in the "one dose per day may suffice" language. Tr. 2213 (citing Barnes at 870). The Court found this persuasive.

Claims 3, 8, 13, 15, 17, 25, 27, and 28 specify that budesonide is the only active ingredient in the composition. Dr. Barnes testified that the article discloses the benefits of budesonide, independent of any other drug, in treating asthma. Tr. 2213. He pointed out that the article references certain preparations, where budesonide is the only active ingredient,

[38] Dr. Barnes testified as to dependent claims 6, 11, 18, and 21-23, which are no longer asserted. The Court therefore need not address these claims.

such as the nebulized budesonide used in the Ilangovan study and the Pulmicort Turbuhaler used in the Jones study. Tr. 2213-14. Further, he noted that at the time, steroids such as budesonide were given on their own without any other drugs, because such "combination treatments" were not yet available. Tr. 2213. The Court was persuaded by this testimony.

Claim 7 limits the invention to the treatment of asthma specifically. As Dr. Barnes testified, this article clearly discloses this limitation; in fact, its title is apt: "Inhaled Glucocorticoids for Asthma." Tr. 2214-15 (Barnes). The Court agrees.

Claims 12, 14, and 16 set forth age limitations (one day to 15 years; one month to 8 years; and 6 months to 5 years, respectively). Dr. Barnes testified that the sub-section entitled "Studies in Children" discloses these age limitations, because it states that "[i]nhaled glucocorticoids are equally effective in children" and cites to studies showing the effectiveness of inhaled budesonide in children between the ages of 7 and 17, and under the age of 3. Tr. 2215 (citing Barnes at 869 and discussing H.J. Waalkens, et al., Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration, 148 Am. Rev. Respir. Dis. 1252-7 (1993) and Ilangovan reference). He suggests that a

person of ordinary skill in the art would extrapolate from this data that once-daily nebulized budesonide would be effective in children up to age 15 (as required to satisfy the dependent claims), in light of the language about nebulized budesonide and once-daily dosing. This is consistent with his testimony regarding the Boutin & Boulet reference, discussed supra, where he stated that the term "children" would be understood to cover the range from birth to age 16. Tr. 2317. This is also consistent with Dr. Wolf's testimony, discussed supra, that the term "children" as used in the IPPL would be understood to mean patients under the age of 16. Tr. 1327:10-16, 1349:20-24. While the question is close, the Court finds that Defendants have established the invalidity of these claims as well. The Court notes that Dr. Barnes was well-qualified and credible in his testimony.

Claim 24 specifies that the budesonide composition "contains 0.25 mg to 1.0 mg budesonide." The Barnes article does not identify these exact quantities, but Dr. Barnes testified that the article disclosed this limitation because it states that "[e]xtensive studies . . . have demonstrated that inhaled glucocorticoids, irrespective of the preparation, have minimal systemic effects . . . at doses of up to 400 mcg per day for children and up to 800 mcg per day for adults. Tr. 2216;

Barnes at 873. Dr. Barnes explained that one milligram contains one thousand micrograms, so 400 mcg would equal 0.4 mg, and thus the amount lies in the appropriate range.

The Court also finds that the Barnes article discloses the additional limitation of claim 26, that the budesonide composition is a suspension. Dr. Barnes testified that the Ilangovan reference cited in the "Studies in Children" subsection discloses nebulized budesonide suspensions, and the Court agrees. In fact, the title of the Ilangovan article explicitly mentions such suspensions.

Accordingly, the Court finds as a matter of law that the Barnes reference anticipates all of the asserted claims of the '603 Patent.

ii. Boutin & Boulet

Since the Court has already found the asserted claims invalid, it only briefly addresses the Defendants' anticipation argument with respect to the Boutin & Boulet reference.[39] The Boutin & Boulet book was written for patients with asthma and published in 1995. Tr. 2203 (Barnes). It is undisputedly prior art pursuant to 35 U.S.C. § 102(b). The central dispute over

[39] See Helene Boutin & Louis-Philippe Boulet, UNDERSTAND AND CONTROL YOUR ASTHMA (McGill-Queen's Univ. Press 1995) (DTX 1048A) ("Boutin & Boulet").

this reference concerns whether it discloses once-daily dosing of nebulized budesonide as arranged in claim 1. Defs.' FF 89 & AZ's Resp. [Dkt. Ent. 675]. The relevant section of Boutin & Boulet is entitled "STEROIDS (CORTICOSTERIODS, CORTISONE, DERIVATIVES)". Boutin & Boulet, supra, Ex. DTX 1048A at 47. It begins with a brief description of inhaled steroids, followed by two tables listing "low-concentration inhaled steroids" and "high-concentration inhaled steroids". Id. at 48. The DPI formulation of budesonide (Pulmicort) is listed in both tables, but the nebulized formulation is not. Id. Following these tables is a sub-section entitled "Side Effects", followed by another sub-section entitled "How do I take them?". Accompanying the text are two figures – "Figure 19" is entitled "LOW-CONCENTRATION INHALED STEROIDS" and is situated on the first page of the section. Id. at 47. "Figure 20" is titled "HIGH-CONCENTRATION INHALED STEROIDS" and is located on the same page with the "Side Effects" and "How do I take them?" sections. Id. at 49. Figure 20 displays two inhaler devices; one is a product using beclomethasone dipropionate (another inhaled steroid) and the other is the Pulmicort Turbuhaler (a DPI). The only reference to nebulized budesonide is at the bottom of Figure 20, which reads: "Note: Pulmicort® is now available in a nebulizing solution (see the description of a nebulizer on

p.00), at 250 and 500 mg/ml." Id. at 49. The only reference to once-daily dosing is in the sub-section entitled "How do I take them?", which provides:

> Inhaled steroids are given at a dosage appropriate to the symptoms . . . . It has been suggested recently that once a day (in the late afternoon or evening) may be sufficient for some patients whose asthma is stable, particularly if they are taking a low dose."

Id. at 49 (emphasis added).

Defendants argue that while the discussion of "once a day" dosing does not expressly include nebulized budesonide, this is understood because Figure 20 is on the same page and identifies two high concentration steroids, only one of which (budesonide) could be effectively administered once per day. Defs.' FF 90 (citing Tr. 2374-75).

Notably, however, Dr. Barnes did not testify that a person of ordinary skill in the art would draw such an inference. He merely testified that budesonide was the only high concentration steroid listed on the page that could be effectively administered once a day. Tr. 2374-75. He gave the Court no reason to believe that a person skilled in the art would understand the "once a day" language to be limited to the "high-concentration" steroids listed in Figure 20. In fact, the plain language of this paragraph suggests otherwise – it refers to "inhaled steroids" generally and does not limit its discussion

to high or low concentration steroids at all. Since Dr. Barnes indicated that a person of ordinary skill in the art would have known that beclomethasone diproprionate could not be given effectively once-a-day, then a person of ordinary skill in the art would have understood that the section discussing once-a-day administration was not referring to "inhaled steroids" generally but only to some, unspecified inhaled steroids. Dr. Chipps confirmed this, testifying that the paragraph discussing once-daily dosing does not disclose anything about the administration of nebulized budesonide. Tr. 3971.

While Dr. Barnes testified that it would be "implicit" to a person of ordinary skill in the art after reading all of the sections in this reference that it teaches the once-daily administration of nebulized budesonide, Tr. 2378, he did not support this statement with any explanation as to why such a skilled person would understand the once-daily language to apply to nebulized budesonide specifically. Such conclusory testimony does not persuade the Court.

Moreover, "[t]he question is not whether a prior art reference 'suggests' the claimed subject matter. . . . Rather, 'the 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, 633 F.3d at 1055 (quoting In re Baxter Travenol Labs., 952 F.2d 388, 390 (Fed. Cir. 1991)).

The Court concludes that Defendants have not established by clear and convincing evidence that Boutin & Boulet discloses every element of claim 1. Because claim 1 is not anticipated, its dependent claims are not anticipated. Corning Glass Works v. Sumitomo, 868 F.2d 1251, 1256 n.4 (Fed. Cir. 1989) ("Because we conclude that claim 1 is not anticipated, claim 2, which is dependent on claim 1, need not be separately discussed."); RCA Corp. v. Applied Digital Data Sys., Inc., 730 F.2d 1440 (Fed. Cir. 1984) ("Since claim 3 of the Cole patent is dependent upon claim 2, which is not anticipated, claim 3 cannot be anticipated.").

iii. The '528 Patent[40] and Foreign Labels[41]

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[40] U.S. Patent No. 5,192,528 to Radhakrishnan et al., DTX 821 ("Radhakrishnan Patent" or "'528 Patent").

[41] The "foreign labels" Defendants refer to are the Thorax Ad and the German prior art label for PULMICORT RESULES®, Ex. DTX 527A. Though AstraZeneca presented its own translation of the German label (PTX 1653), the parties' experts agree that there is no material difference in the translation of the relevant titration down language. Tr. 2245:9-2247:12 (Barnes); Tr. 4080:22-4082:4 (Chipps).

Since the Court has already determined that the asserted claims are both invalid as obvious and anticipated, it need not reach Defendants' remaining anticipation arguments.

c. Enablement

Likewise, the Court need not reach Defendants' final invalidity argument that the full scope of the '603 patent is not enabled.

d. Dependent Claims

Defendants also argue that certain dependent claims of the '603 patent are improper. Since the Court finds these dependent claims invalid as obvious and anticipated, it need not address this argument.

B. The '834 Patent

The '834 Patent is entitled "STERILE POWDERS, FORMULATIONS, AND METHODS FOR PRODUCING THE SAME".[42] AstraZeneca asserts that prior to the '834 Patent, no one had sterilized an inhaled

[42] It names Ann-Kristin Karlsson, Cheryl Larrivee-Elkins, and Ove Molin as the inventors on the face of the patent and issued on April 28, 2009. The '834 Patent was filed as U.S. patent application Serial No. 09/993,669 on November 27, 2001, as a continuation of U.S. patent application Serial No. 09/230,781 (the "'781 application"), which was filed as application No. PCT/SE98/02039. The '781 application issued as U.S. Patent No. 6,392,036 ("the '036 Patent") and claims priority to Swedish patent application No. 9704186, which was filed on November 14, 1997. Stipulated Facts ¶¶ 28-29 [Dkt. Ent. 700-1, Tab 1].

suspension. Faced with the FDA's request to make PULMICORT RESPULES® sterile,[43] AstraZeneca initially attempted to show that it could not be done. Despite shared skepticism with the FDA, AstraZeneca succeeded in sterilizing an inhaled suspension. This resulted in the '834 Patent, which is directed to pharmaceutically acceptable budesonide powders and suspensions that meet sterility requirements.[44] According to AstraZeneca, the '834 Patent relates to (1) a process for sterilization of a powdered form of a glucocortico-steroid, (2) sterile glucocorticosteroids, (3) sterile formulations containing glucocorticosteroids and (4) use thereof in the treatment of an allergic and/or inflammatory condition of the nose or lungs. AZ's Resp. Markman Br. 32-33. AstraZeneca argues that the only claims at issue here are directed to the sterile budesonide powder and formulation.

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[43] See e.g., PTX 611 at 017835. ("When AstraZeneca proposed to market this unsterilized oral inhalation suspension product in the U.S., AstraZeneca was informed by FDA that FDA was moving toward requiring that this particular type of product, i.e., aqueous-based drug products for oral inhalation, be manufactured sterile").

[44] Another patent issued as well directed to the inventive heat sterilization process, which is not at issue here, See U.S. Patent No. 6,392,036.

AstraZeneca asserts that Defendants Apotex and Sandoz infringe claims 50 and 51 literally and under the doctrine of equivalents and that Breath/Watson infringes claims 1, 2, 50 and 51 under the doctrine of equivalents.

As an initial matter, the Court notes that the opinions of the Defendants' experts would not change if they applied AstraZeneca's expert's definition of a person of ordinary skill in the art. AZFF ¶ 145; Tr. 1890:20-1891:16 (Dr. Mike Zaccheo, Breath/Watson expert). Accordingly, the Court adopts AstraZeneca's definition: a person of ordinary skill in the art pertinent to the '834 patent would have had either a Ph.D. in pharmaceutics, microbiology, chemical engineering or a related field, and 3-5 years of practical experience in one or more aspects of the pertinent art, or a Bachelor's or Master's degree in pharmaceutics, microbiology, chemical engineering or a related field, and 5-7 years of practical experience in one or more aspects of the pertinent art. Tr. 815:7-819:3, 3784:15-23 (Dr. Robert O. Williams, AstraZeneca's expert).

The Court now turns to the disputed claims. The only asserted independent claims, claims 1 and 50, teach a powder and suspension, respectively, comprising a "micronized powder composition." 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.

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. 55-60.

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.

As discussed above, the first step of an infringement analysis requires the Court to construe the claims to determine their scope and meaning. Wolverine World Wide, Inc. v. Nike, Inc., 38 F.3d 1192, 1196 (Fed. Cir. 1994) ("Determining whether a patent claim is infringed requires a two-step inquiry: 'First, the claim must be properly construed to determine its scope and meaning. Second, the claim as properly construed must be compared to the accused device.'") (internal citation omitted).

Claim construction is purely a matter of law. Markman v. Westview Instruments, Inc., 517 U.S. 370, 372 (1996).

In construing a claim, the Court must first look to the intrinsic evidence, including the claim language, specification, and prosecution history.[45] Phillips v. AWH Corp., 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc). Within the intrinsic evidence, the claim construction inquiry begins with the plain and ordinary meaning of the claim, which defines the scope of the right to exclude. See Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996). "[T]here is a heavy presumption that the language in the claim carries its ordinary and customary meaning amongst artisans of ordinary skill in the relevant art at the time of the invention." Housey Pharms., Inc. v. AstraZeneca UK Ltd., 366 F.3d 1348, 1352 (Fed. Cir. 2004) (citations and quotations omitted); see also Phillips, 415 F.3d at 1312-13. A patentee may, however, assign a claim term a meaning "other than its ordinary and accustomed meaning . . . if the patentee has chosen to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term."

[45] The prosecution history "consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent." Phillips, 415 F.3d at 1317.

Johnson Worldwide Assocs., Inc. v. Zebco Corp., 175 F.3d 985, 990 (Fed. Cir. 1999); see also Markman, 52 F.3d at 979-80; Schering Corp. v. Amgen Inc., 222 F.3d 1347, 1353 (Fed. Cir. 2000). Additionally, "the claims themselves provide substantial guidance as to the meaning of particular claim terms." Phillips, 415 F.3d at 1314. The context of the surrounding words of the claim can be highly instructive. Id.

"Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification" and prosecution history. Phillips, 415 F.3d at 1313. Further, the court should consult the specification to determine whether the patentee has disavowed or relinquished claim scope. See SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337, 1341 (Fed. Cir. 2001) ("Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims . . . might be considered broad enough to encompass the feature in question."). The Federal Circuit has repeatedly stressed that "the specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the

single best guide to the meaning of a disputed term.'" Phillips, 415 F.3d at 1315 (quoting Vitrionics, 90 F.3d at 1582.

The court should further consult the patent's prosecution history so it can exclude any interpretation that was disclaimed during prosecution. Phillips, 415, F.3d at 1317; Hockerson-Halberstadt, Inc. v. Avia Group Int'l, Inc., 222 F.3d 951, 957 (Fed. Cir. 2000) (holding that the public is entitled to rely on the patentee's representations in the prosecution history concerning the scope and meaning of the claims). "Where an applicant argues that a claim possesses a feature that the prior art does not possess in order to overcome a prior art rejection, the argument may serve to narrow the scope of otherwise broad claim language." Seachange Int'l, Inc. v. C-COR Inc., 413 F.3d 1361, 1372-73 (Fed. Cir. 2005) (citing Rheox, Inc. v. Entact, Inc., 276 F.3d 1319, 1325 (Fed. Cir. 2002)). Stated another way, a patentee cannot recapture in litigation a claim scope surrendered during the prosecution of the patent, either by amendment or argument. See Pharmacia & Upjohn Co. v. Mylan Pharms., Inc., 170 F.3d 1373, 1376-77 (Fed. Cir. 1999); see also Southwall Techs., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1576 (Fed. Cir. 1995) ("Claims may not be construed one way in order to obtain their allowance and in a different way against accused infringers.").

1. Claim Construction of "Micronized Powder Composition"

The parties dispute the meaning of the term "micronized powder composition", which is included in claims 1 and 50 of the '834 Patent. The critical issue is whether this term includes a limitation pertaining to heat sterilization, which would effectively exclude Defendants' products from the claimed invention and render them non-infringing. After holding a five-day Markman hearing, the Court construed the term to mean "heat sterilized finely divided dry particles". [Dkt. Ent. 372.] The Court now sets forth the basis for this construction.

Additionally, the Court notes that the parties have disputed whether the term "heat sterilized" imputes a process limitation into the claims. The Court finds that it does. The term "heat sterilized", for purposes of the Court's claim construction, refers to particles that have been sterilized through a process, consistent with heat sterilization, that allows them to essentially maintain the same pharmacological activity, physico-chemical properties, chemical purity, and physical form as the starting material. This definition captures the critical, distinctive element of the claimed particles and comports with the description of them in the specification. See '834 Patent, col. 4, ll. 58-63 ("The glucocorticosteroid according to the invention will essentially

maintain the same pharmacological activity and physico-chemical properties/its chemical purity and physical form as the starting material from which it is prepared, i.e. the degradation, and especially the chemical degradation, caused by the present sterilization process will be limited.").[46]

The parties agree that the term "micronized powder composition" is directed to the novel glucocorticosteroid particles claimed in the Patent. '834 Patent, col. 4, ll. 39-43 ("According to the invention there is further provided a sterile glucocorticosteroid (e.g. budesonide), suitably dry and preferably in the form of finely divided particles . . . ."). They also agree that the Patent specifically defines this term, although they dispute what that definition is. AstraZeneca proposed: "a powder composition in which the particle size has been mechanically reduced to form particles having a mass median

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[46] At the Markman hearing, Defendants' expert, Dr. David A. Porter, testified that a person skilled in the art would understand that the Patent teaches that the "only way" to achieve particles with the above-listed properties is to use the dry heat method embodied in the Patent. Markman Tr. 731. Defendants' other expert, Dr. Michael J. Miller, agreed, testifying that a person of ordinary skill in the art would have understood the above passage to mean that the claimed product must have been heat sterilized, because it touts the beneficial features associated with this process. Markman Tr. 831, 845. The Court found Dr. Porter and Dr. Miller's views consistent with the language of the Patent.

diameter (MMD) of approximately 20µm or less." AZ's Resp. Markman Br. 31. Defendants asserted slight variations on the definition ultimately adopted by the Court: "heat sterilized finely divided dry particles." Defs. Opening Markman Briefs.

Turning first to the term "micronized", the Court notes that the specification specifically defines this word to mean "finely divided." See '834 Patent, col. 1, ll. 65-67 ("finely divided, e.g. micronized, glucocorticosteroids"), col. 3, ll. 39-40 ("The glucocorticosteroid is preferably used in the form of a finely divided, e.g. micronized, powder . . . ."), col. 3, ll. 44-46 ("The finely divided particles may be produced by conventional techniques known per se. e.g. by micronization . . . ."), col. 5, ll. 13-17 ("According to the invention . . . the glucocorticosteroid is preferably a sterile finely divided glucocorticosteroid, such as budesonide."); see also Markman Tr. 65 (Williams) ("micronized is an example of a finely divided powder").

The specification also makes clear, consistent with the ordinary and customary meaning of the term "powder", that the "micronized powder composition" is dry. '834 Patent, col. 4, ll. 39-41 ("According to the invention there is further provided a sterile glucocorticosteroid (e.g. budesonide), suitably dry and preferably in the form of finely divided particles . . . .").

Indeed, the use of the word “powder” in the claim language indicates that the composition is dry. See Markman Tr. 80 (Williams) (a micronized powder is “dry”).

The Court now turns to the third and most contentious element of its claim construction, the “heat sterilized” limitation.

AstraZeneca argues that this element improperly imposes a process limitation into its product claims. See Cendis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352, 1357 (Fed. Cir. 2003), cert. den'd, 540 U.S. 1213 (2004) (“[W]e decline to superimpose a process limitation in the product claims at issue.”); Vanguard Prods. Corp. v. Parker Hannifin Corp., 234 F.3d 1370, 1372-73 (Fed. Cir. 2000) (holding scope of claim for electromagnetic shielding gasket not limited to method of manufacture set forth in specification); Astra Aktie bolag v. Andrx Pharms., Inc., 222 F. Supp. 2d 423, 469 (S.D.N.Y. 2002), aff'd, 84 F. App'x 76 (Fed. Cir. 2003) (“It is improper to limit product claims to a particular process. A novel product that meets the criteria for patentability is not limited by the process by which it is made. . . .”).

Defendants respond that AstraZeneca consciously decided to describe and claim only a particular composition that had been heat sterilized, and to distinguish, criticize, and disavow all

other compositions resulting from any other type of sterilization process. Breath/Watson's Resp. Markman Br. 17 [Dkt. Ent. 170].

Against this backdrop, the Court begins its analysis with the specification and claim language of the Patent.

a. The Patent

The Patent begins with a section entitled "FIELD OF THE INVENTION", which reads:

> This invention relates to a process for sterilization of a powderdered [sic] form of a glucocortico-steroid, sterile glucocorticosteroids, sterile formulations containing glucocorticosteroids and use thereof in the treatment of an allergic and/or inflammatory condition of the nose or lungs.

'834 Patent, col. 1, ll. 17-21 (emphasis added).

In the "BACKGROUND OF THE INVENTION" section, the Patent identifies the problem: finding a method suitable for producing "therapeutically acceptable glucocorticosteroids and formulations thereof." '834 Patent, col. 1, ll. 40-41. It then identifies the conventionally used methods for sterilization, i.e., ethylene oxide, high dry heat, ß- or *y*-irradiation, moist heat, and filtration. Col. 1, l. 25 – col. 2, l. 39. It discusses and ultimately rejects each of these methods because

they fail to produce an acceptable product.[47] '834 Patent, col. 1, ll. 25-41 (finding cold sterilization with ethylene oxide "unsuitable"); col. 1, ll. 42-53 (moist heat sterilization at 100-130° C "is not suitable"); col. 1, ll. 51-54 (dry heat sterilization (140-180° C for 0.5 to 4.0 hours) causes "significant degradation"); col. 1, ll. 62-67 (ß- or *y*-irradiation causes significant degradation); col. 2, ll. 31-39 (suspension of glucocorticosteroids "cannot normally be sterilized by sterile filtration as most of the particles of glucocorticosteroid will be retained on the filter"); col. 2, ll. 36-39 ("We have also shown that moist heat sterilization . . . leads to an unacceptable change in particle size.").

After setting forth why all of the other conventional forms of sterilization do not work, the specification states: "Accordingly a new process for the sterilization of glucocorticosteroids (and formulations containing them) is required." '834 Patent, col. 2, ll. 45-48 (emphasis added). It then identifies the solution, which is the asserted invention:

> Surprisingly we have now found that effective sterilization of dry glucocorticosteroids can be

[47] Defendants' expert, Dr. Porter, explained that the methods identified and rejected in the Patent constitute all the conventionally known methods of sterilization at the relevant time. Markman Tr. 738:22-739:2.

> carried out at a significantly lower temperature than that considered necessary for the heat sterilization of other substances. Such sterile glucocorticosteroids can be used in the preparation of sterile formulations containing them.

'834 Patent, col. 2, ll. 45-53.

Significantly, AstraZeneca's expert, Dr. Robert O. Williams, III, explained that a person skilled in the art would understand the '834 Patent to be teaching that each of the conventional sterilization methods outlined in the "BACKGROUND OF THE INVENTION" section produces a "pharmaceutically unacceptable" product. Markman Tr. 165 ("The '834 patent goes through those methods and then says that there is either degradation or some effect on particle size or something that would deem the product not pharmaceutically acceptable."). He then testified that a person skilled in the art would read the '834 Patent to "rule out" those sterilization methods that did not produce "pharmaceutically acceptable" glucocorticosteroids.[48]

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[48] Dr. Williams testified in relevant part as follows:

> Q: Let's take a look at . . . the declaration of . . . one of the inventor[s] of the '834 patent provided to the U.S. Patent Office. . . [I]t says . . "By 1997 it was understood in the pharmaceutical arts that a budesonide powder composition that had been exposed to ethylene oxide gas in efforts to sterilize it would not be considered 'pharmaceutically acceptable' because the possibility of

residual ethylene gas molecules remain in the product.' . . . So the person of ordinary skill in the art reading this would just rule out cold sterilization as a method to make the claimed glucocorticosteroids of the '834 patent, correct?

A: Probably so, yes.

* * *

Q: Alright, let's go back to . . . the '834 Patent. . . . Now, do you see, just after that, the inventors conclude "this [moist heat] method is not suitable for suspensions of fine particles of glucocorticosteroids which are intended for inhalation because the water and the heating and cooling involve[d] produce unfavorable changes in the size of the particles." Do you see that?

A: Yes.

Q: So that tells you that this method is also pharmaceutically unacceptable, correct?

A: Yes.

* * *

Q: And do you see what it says in the last sentence in Column 1 [of the '834 Patent], it says, however, when such irradiation is used to sterilize certain finely divided, e.g. micronized glucocorticosteroids, they are significant[ly] degraded, do you see that?

A: Yes.

Q: And so this method also yielded a pharmaceutically unacceptable product, correct?

A: Yes.

Q: And a person of ordinary skill in the art reading this is going to deem this method unsuitable and pharmaceutically unacceptable for producing the composition of the '834 patent, correct?

A: Yes.

Markman Tr. 168-71 (Williams) (emphasis added).

Later in his testimony, Dr. Williams reiterated this point by stating that the only sterilization process deemed "pharmaceutically acceptable" in the Patent is the low dry heat method. Markman Tr. 222:4-7.

Defendants' expert, Dr. Porter, concurred with Dr. Williams. He first explained that a person skilled in the art would understand "pharmaceutically acceptable" to refer to a sterile product whose physico-chemical properties and purity are left essentially unchanged during the sterilization process. Markman Tr. 729, 778; see also Markman Tr. 90 (Williams) ("If the particle size is changing, it would not be pharmaceutically acceptable."). He then testified, "the inventors are telling us" that since the conventional processes are unsuitable, "it's required that you have this new process." Markman Tr. 730.

The Court found Dr. Williams and Dr. Porter's testimony persuasive and consistent with the language of the Patent. Importantly, claims 1 and 50 explicitly require the micronized powder composition and formulation to be "pharmaceutically acceptable." Col. 11, l. 48 ("A pharmaceutically acceptable, micronized powder composition . . . ."); col. 13, ll. 55 ("A pharmaceutically acceptable suspension consisting of a micronized powder composition . . . .") (emphasis added). The

Patent therefore teaches that the claimed particles may not be produced using the conventional sterilization techniques.

Following the "BACKGROUND" section is the "DESCRIPTION OF THE INVENTION". This section describes the patented glucocorticosteroid as follows:

> The glucocorticosteroid according to the invention will essentially maintain the same pharmacological activity and physico-chemical properties/its chemical purity and physical form as the starting material from which it is prepared, i.e. the degradation, and especially the chemical degradation, caused by the present sterilization process will be limited.[49]

'834 Patent, col. 4, ll. 58-63 (emphasis added). While not determinative, this statement's location in the "DESCRIPTION OF THE INVENTION" section signals the likelihood that it limits the definition of "micronized powder composition". C.R. Bard, Inc. v. U.S. Surgical Corp., 388 F.3d 858, 864 (Fed. Cir. 2004). Moreover, by prefacing the above statement with "according to the invention," the specification is asserting what the invention is limited to rather than what it can preferably be. See id. ("Statements that describe the invention as a whole, rather than statements that describe only preferred embodiments,

[49] Dr. Williams testified that this paragraph would indicate to a person of ordinary skill in the art "that you want to make sure that the starting . . . material, budesonide, is not changed, chemically or physically, from the final suspension product or whatever the final product is." Tr. 1083.

are more likely to support a limiting definition of a claim term.") (citation omitted); Sigma-Adrich, Inc. v. Open Biosystems, Inc., 521 F. Supp. 2d 975, 985 (E.D. Mo. 2007) ("according to the invention" language evidenced a claim limitation). At the Markman hearing, Defendants' expert, Dr. Porter, testified that a person skilled in the art would understand this passage to "emphasize" that "it's necessary to retain the physico-chemical properties of your starting material in your ending product." Markman Tr. 731. He explained, as discussed above, that since the Patent teaches that the dry heat method is the "only way" to do this, a skilled person would have understood this passage to mean that the claimed product must be heat sterilized. Id. Dr. Miller agreed. Markman Tr. 831, 845.

Following the "DESCRIPTION OF THE INVENTION" section, the specification includes eight examples, seven of which exemplify the low dry heat sterilization method. The final, comparative example disparages the use of ß- and *y*-irradiation. See Markman Tr. 173 (Williams). Dr. Porter testified that these examples teach that the low, dry heat method "is suitable for use in creation of a pharmaceutically acceptable product." Markman Tr. 742. He explained that this is "in part because [low, dry heat] destroys microorganisms, that's the sterilization part and it preserves physico-chemical purity properties." Id. He

explained that the patent teaches away from the use of any other sterilization method. Id.

In the "DESCRIPTION OF THE INVENTION" section and, again, in one of the examples, the Patent repeatedly states that sterile filtration can be used to sterilize the other components of the suspension but cannot be used to sterilize the budesonide. Col. 6, ll. 44-45 ("All components, other than the glucocorticosteroid, can be produced by sterile filtration of their aqueous solutions."); col. 9, ll. 32-35 ("All the components, other than the budesonide, can be produced by sterile filtration."). This is consistent with the inventors' rejection of sterile filtration in the "BACKGROUND OF THE INVENTION" section. Importantly, however, the rest of the specification gives no indication that the inventors' position on sterile filtration differs from their position on any of the other conventional forms of sterilization that were previously rejected. Compare col. 2, ll. 34-37 ("Such suspensions cannot normally be sterilized by sterile filtration as most of the particles . . . will be retained on the filter.") with col. 1, ll. 39-40 (rejecting ethylene oxide as unsuitable since it is "toxic" and has been found to leave "residual amounts" that contravene pharmaceutical guidelines) and col. 2, ll. 37-39 ("We have also shown that moist heat sterilization . . . leads to an

unacceptable change in particle size.”). Rather, the context suggests that the inventors call out the filtration method specifically because it is a method used to sterilize suspensions and thus relevant to the budesonide suspension here. Markman Tr. 840-41 (explaining that “sterile filtration is a process . . . use[d] to physically remove microorganisms normally from an aqueous sample.”) (Miller). This fact further supports Defendants’ contention that the ‘834 Patent expressly excludes sterilization methods other than dry heat.

At the Markman hearing, AstraZeneca’s experts made much of the following passage from the specification:

> The invention further provides a method for treatment of an inflammatory condition of the nose or lungs by administering to a mammal . . . a sterile glucocorticosteroid or a sterile formulation containing a glucocorticosteroid, preferably a sterile formulation containing a sterile glucocorticosteroid produced according to the present invention.

‘834 Patent, col. 6, ll. 52-59. The sentence following this one repeats the same language but speaks specifically to the treatment of certain diseases and conditions. Col. 6, ll. 59-67. This language does not trouble the Court. The position of the term “preferably”, directly following the language about the types of formulations, suggests that it modifies the type of formulation used (i.e., a sterile formulation containing a sterile glucocorticosteroid), not the method of sterilizing the

glucocorticosteroid. Dr. Porter testified that the use of the term "preferably" here would not cause a skilled artisan to believe that the product could be made in a way other than using heat. Markman Tr. 743-44.

AstraZeneca also asserts a claim differentiation argument, pointing to claim 38, which recites:

> A pharmaceutically acceptable, sterilized powder composition at least 98.5% by weight of which is pure budesonide or an ester, acetal or salt thereof, wherein the sterilized powder composition was produced by sterilization of viable-microorganism-containing particles of budesonide or an ester, acetal or salt thereof.

'834 Patent, col. 13, ll. 25-30 (emphasis added). Claim 42 is dependent upon claim 38 with the additional limitation that "the sterilization was accomplished by a method comprising heat sterilization." Col. 13, ll. 38-39 (emphasis added). Claims 43-47 include additional limitations concerning the conditions of the heat sterilization.[50] "[C]laim differentiation takes on relevance in the context of a claim construction that would render additional, or different, language in another independent claim superfluous." AllVoice Computing PLC v. Nuance Commc'ns, Inc., 504 F.3d 1236, 1247-48 (Fed. Cir. 2007) (citations and

[50] For example, claim 43 further requires that "the heat sterilization was carried out in air." Col. 13, ll. 40-41. Claims 45 to 47 specify precise temperatures.

quotations omitted). Here, the express language of claim 38 differentiates it from claims 1 and 50, which do not discuss a "sterilized powder composition" or "sterilization of viable-microorganism-containing particles". Further, as set forth above, "heat sterilized" for purposes of the Court's claim construction encompasses particles that have been sterilized through a process, consistent with heat sterilization, that permits them to essentially maintain the same pharmacological activity, physico-chemical properties, chemical purity, and physical form as the starting material. See supra.

b. Prosecution History

Throughout this Patent's 936-page prosecution history, AstraZeneca repeatedly characterized its invention as "heat sterilized". See, e.g., Ex. PTX 611 at 017293 ("Applicants have discovered a pharmaceutically inhalation [sic] acceptable powder . . . in the form of finely divided particles . . . [such] particles are heat sterilized."); BB 017311-12 (same); BB 017313; BB 017338 ("Applicants have discovered a pharmaceutically acceptable inhalation powder is [sic] in the form of dry, finely divided, heat sterilized particles . . . ."); BB 017361 (same); BB 017379-81 (same). AstraZeneca also repeatedly distinguished its unique budesonide product from the prior art based on the dry heat method used to obtain it. See,

e.g. Ex. PTX 611 at BB 017998 ("Steam sterilization would not produce the same product as dry heat sterilization."); BB 017482 (sterilization with ethylene oxide "unsuitable"); BB 017296 ("Heat sterilization gave superior results to irradiation."); BB 017536 (arguing that "one of ordinary skill in the art . . . would be dissuaded from trying filtration as a means to sterilize a pharmaceutical powder") (emphasis in original); BB 017338 ("Nothing in Jakupovic teaches or suggests an inhalation powder in the form of dry, finely divided heat sterilized particles.") (emphasis in original); BB 017537 (noting that "the filter-sterilized composition is necessarily different from the heat-sterilized composition").[51]

For example, AstraZeneca distinguished its product from that produced through steam sterilization as follows:

> All of claims 84-93 98-100 and 146 specify that the claimed composition or suspension be "pharmaceutically acceptable". The method of steam-sterilizing

[51] At trial, after the Court had issued its claim construction ruling, Dr. Williams testified for AstraZeneca that these statements in the prosecution history did not constitute a "disclaimer" of pharmaceutically acceptable products resulting from the alternative processes discussed. Tr. 899. This distinction is immaterial. AstraZeneca cannot now, with the benefit of hindsight, change the language in the Patent, which rejected the alternative methods. The specification and prosecution history make clear that the inventors viewed the novel process as critical to achieving the sterile drug particles.

> budesonide suspension . . . would produce changes in the budesonide suspension that would render it no longer pharmaceutically acceptable and so outside of these claims. . . . [S]team heat sterilization . . . leads to "unacceptable change in particle size." Since particle size is crucial to the effective administration of the inhaled suspension . . . any process that increases agglomeration and/or particle size significantly will render the product no longer pharmaceutically acceptable and thus outside the scope of the present claims.

Ex. PTX 611 at 017800 (emphasis added). This passage underscores the importance of the "pharmaceutically acceptable" limitation of claims 1 and 50.

AstraZeneca points out that at one point during prosecution, it removed the term "heat sterilized" and inserted the "meets the criteria of sterility" language in order to distinguish the prior art. The "heat sterilized" term was not required, since the new claim language included the phrase "pharmaceutically acceptable", which, as discussed above, essentially served the same purpose as the "heat sterilized" requirement, that is, it required the particles to become sterile through a process that left their physico-chemical properties and purity essentially unchanged. See Markman Tr. 729, 778 (Porter); see also Markman Tr. 90 (Williams).

This interpretation is supported by the fact that AstraZeneca continued to distinguish other methods of producing the sterile inhalation products asserted in the Patent, see

supra, and also did not alter its specification, which continued to describe the essential characteristics of the budesonide particles by stating that they maintain the same "pharmacological activity", "physico-chemical properties", "chemical purity" and "physical form" as the starting material. '834 Patent, col. 4, ll. 58-63.

c. Extrinsic Evidence

Extrinsic evidence "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." Phillips, 415 F.3d at 1317 (quoting Markman, 52 F.3d at 980). Although AstraZeneca has insisted that the asserted claims are directed only to the sterile product and not the method of production, the inventors of the '834 Patent indicated otherwise. Inventor Ove Molin testified at trial that the invention in this Patent is "the dry sterilizing method for budesonide." Tr. 3237 (emphasis added). Similarly, just prior to allowance of the '834 Patent, inventor Ann-Kristin Karlsson submitted an independent declaration advising the Patent Examiner that "the present application" disclosed the "novel method" she and her co-inventors discovered for sterilizing budesonide. Ex. PTX 611 at BB 017835 (emphasis added).

The expert testimony at the Markman hearing, discussed throughout, also supports a finding that the process and product here are intrinsically linked and that the Patent disclaims the conventional sterilization methods. Dr. Porter testified that during the prosecution history of the '834 Patent, the inventors "disavowed" the conventional techniques.[52] Even Dr. Williams,

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[52] During cross-examination, Dr. Porter testified:

> QUESTION: Now, in your opinion, during the prosecution history of the '834 patent, the inventors did not disavow all techniques other than dry heat sterilization, correct?
> ANSWER: They disavowed the techniques that, again, would have been in [Chapter] 1211 [of the U.S. Pharmacopeia] and would have been known as the conventional techniques.
> QUESTION: Okay. But it's your opinion that they didn't disavow all techniques?
> ANSWER: As a person of ordinary skill in the art, you would not be aware of other techniques.
> THE COURT: When you say disavow, what do you mean?
> THE WITNESS: Well, yes, that's a good point. The patent indicates that all of these other conventional techniques that would have been written in that USP chapter, well known at the time, it indicates that none of them are suitable. You need to have -- and it talks about this one line here about <u>you need to have this new process in order to create a pharmaceutically acceptable [p]article</u>. So I think what it teaches is that the conventional techniques, as known and as written in 1211, didn't work in terms of producing a pharmaceutically acceptable particle. That's why they needed this new process, which is what they describe in the patent.

AstraZeneca's own expert, testified, as set forth above, that a skilled artisan would view the Patent as "rul[ing] out" the sterilization methods that produce non-pharmaceutically acceptable product. Tr. 168-69.

d. Conclusion

The Court is mindful of the "exacting" standard for limiting claim scope. Thorner v. Sony Comp. Entm't Am. LLC, 669 F.3d 1362, 1366 (Fed. Cir. 2012). However, disavowal does not require "an expression of manifest exclusion or restriction in the form of 'my invention does not include ____.'" AstraZeneca v. Mutual Pharm. Co., 384 F.3d 1333, 1340 (Fed. Cir. 2004). Such rigid formalism is improper. Rather, "[w]here the general summary or description of the invention describes a feature of the invention . . . and criticizes other products . . . that lack that same feature, this operates as a clear disavowal of

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* * *

> The trick is, with sterilization methods, to do it in such a way that you leave the starting material essentially the same when you're done. And that's what they disclose, and that's why they keep talking about the physical chemical properties and purity and so forth, and they mention that -- they state that this process that they teach ensures that your end product is essentially unchanged relative to the starting product. The other methods didn't do so.

Tr. 796 (emphasis added).

these other products (and processes using these products)." Id. (citing SciMed Life Sys., Inc. v. Adv. Cardiovascular Sys., Inc., 242 F.3d 1337, 1340-45 (Fed. Cir. 2001)). In other words, where the specification makes clear that the invention must be produced using a particular process, that process is imputed into the claims of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass all products regardless of the method of production used. See Thorner, 669 F.3d at 1366 (quoting SciMed Life Sys., Inc. v. Adv. Cardiovascular Sys., Inc., 242 F.3d 1337, 1341 (Fed. Cir. 2001)); see, e.g., Anderson Corp. v. Fiber Composites, LLC, 474 F.3d 1361, 1372-75 (Fed. Cir. 2007) (product claim included "pelletization" process based on specification, which indicated that this process was required and prosecution history, in which patentee distinguished invention from prior art based on this process); Southwall Tech., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1576 (Fed. Cir. 1995) (a claim to a sputter-deposited dielectric layer had to be read as limited to a dielectric prepared by a particular process because the prosecution history demonstrated that the applicant had defined its invention restrictively, as limited to a dielectric layer prepared by a one-step process).

Here, as AstraZeneca's own expert testified, the Patent lists and then rules out all of the conventional sterilization methods because they produce pharmaceutically unacceptable results. Markman Tr. 168-70 (Williams). The claims explicitly require the patented glucocorticosteroid to be "pharmaceutically acceptable", and the specification identifies the novel dry heat method as the only means of achieving this. See supra. Further, the specification repeatedly states, in the context of making sterile suspension, that budesonide cannot be sterilized using filtration, and as discussed above, there is no reason to believe the inventors were more averse to filtration than any of the other conventional sterilization methods identified. The specification also discloses the claimed invention as particles that have "maintain[ed] the same pharmacological activity[,] physico-chemical properties[,] chemical purity and physical form as the starting material from which it is prepared." '834 Patent, col. 4, ll. 58-63. The experts agreed that this excludes all of the sterilization techniques previously rejected by the Patent and leaves only the novel, low, dry heat method.

The prosecution history and extrinsic evidence also support this conclusion. As set forth above, AstraZeneca repeatedly distinguished its product based on the method used and disparaged all other sterilization techniques. Even the

inventors themselves characterized this Patent as the "novel method" for sterilizing budesonide and the "dry sterilizing method for budesonide". Ex. PTX 611 at BB 017835; Tr. 3237.

In sum, the evidence makes clear that the claimed particles must be "heat sterilized". This is not a preferred embodiment but a critical step to achieving the "pharmaceutically acceptable, micronized powder composition" claimed. Thus, it is part of the claim itself. See Anderson Corp., 474 F.3d at 1368 (process steps are part of product claim if they are "an essential part of the claimed invention"). Indeed, this theme pervades throughout the Patent, and to omit such a process limitation would require the Court to ignore the express teachings of the specification, claim language, and prosecution history and do a manifest injustice to the record.

2. Non-Infringement

Having construed "micronized powder composition" in claims 1 and 50 to mean "heat sterilized finely divided dry particles", the Court turns next to the second step of the infringement analysis: a comparison of the properly construed claim to the accused products. To prove infringement, AstraZeneca must show that each Defendant's product contains each and every element of the asserted claims, either literally or under the doctrine of

equivalents. Allen Engineering Corp. v. Bartell Industries, Inc., 299 F.3d 1336, 1345 (Fed. Cir. 2002).

The Court first considers AstraZeneca's claims of literal infringement against Sandoz and Apotex and then AstraZeneca's claims of infringement under the doctrine of equivalents as to all Defendants. Before doing so, however, the Court describes each Defendant's sterilization process.

a. Defendants' Sterilization Processes

[redacted]

[redacted]

b. Literal Infringement

As mentioned, AstraZeneca brings claims for literal infringement against Sandoz and Apotex only, contending that their budesonide inhalation suspensions infringe claims 50 and 51 of the '834 Patent.[53] Claim 50 is directed to a suspension consisting of a "micronized powder composition" suspended in an aqueous solution. Defendants Sandoz and Apotex contend that they do not literally infringe because their budesonide suspension products do not include "heat sterilized finely divided dry particles" as required by the Court's construction of "micronized powder composition". [redacted]

[53] AstraZeneca does not claim literal infringement against Breath/Watson as it is undisputed that Breath/Watson does not use any form of heat sterilization, but [redacted].

[redacted]

The Court agrees. [redacted]

[redacted]

AstraZeneca attempts to circumvent this problem by injecting a temporal element into "heat sterilized finely divided dry particles" to mean that the budesonide particles need not be dry and sterile at the same time. Tr. 852:2-12, 24-853:13 (Williams). Dr. Williams testified that the Court's construction does not "necessarily" have to be at once sterile and dry because "there is another understanding to those words as well": that the budesonide particles are dry and then heat sterilization occurs later. Tr. 853:9-13 (Williams).

AstraZeneca's interpretation is creative, but incorrect. "Heat sterilized," "finely divided," and "dry" are all adjectives modifying a common noun: "particles". [redacted]

[redacted]

[redacted] Likewise, "boiling water" describes water that is boiling. See HP Intellectual v. Sunbeam Prods., Inc., Civ. No. 95-7488, 1999 WL 311692, *5 (N.D. Ill. May 13, 1999) (patentee's argument that a "boiling liquid reservoir" requires a reservoir that holds liquid that will boil at some point in time and at some place was rejected as an "awkward and unnatural" interpretation). This is common sense. Any other reading subverts the plain meaning of these words.

[redacted]

[redacted]

For these reasons, the Court concludes that AstraZeneca has failed to prove literal infringement of claims 1 and 50.

c. Doctrine of Equivalents

AstraZeneca next argues that Defendants each infringe under the doctrine of equivalents because the budesonide particles in their products are insubstantially different from the dry heat sterilized particles in PULMICORT RESPULES®. Specifically, AstraZeneca argues that [redacted]

[redacted] each Defendant infringes claims 50 and 51, and Breath/Watson also infringes claims 1 and 2 under the doctrine of equivalents because the differences between the Defendants' budesonide particles and the claimed micronized powder composition are insubstantial at best. In other words, AstraZeneca argues that regardless of how the budesonide particles are sterilized, [redacted] the accused products are substantially the same as the claimed product.

Defendants counter with three arguments. First, they contend that AstraZeneca should be estopped from arguing the doctrine of equivalents because AstraZeneca disavowed and disparaged their sterilization processes. Second, they argue that even if AstraZeneca is not estopped, there are substantial differences between their processes and products and the asserted claims. Third, they argue that their products would not meet the 1995 USP "criteria for sterility" set forth in claims 1 and 50.

The doctrine of equivalents permits a patentee to lay claim to "those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." Festo Corp. v. Shoketsu Kinzoku Kogyo

Kabushiki Co., Ltd., 535 U.S. 722, 733 (2002). Thus, an accused product that does not literally infringe upon the express terms of a claim may nonetheless still infringe "if there is 'equivalence' between the elements of the accused product or process and the claimed elements of the patented invention." See Warner-Jenkinson Co. v. Hilton Davis Chem. Co., Inc., 520 U.S. 17, 21, 40 (1997) (citing Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 609 (1950)). Such "equivalence" exists where only "insubstantial differences" distinguish the claimed element and the corresponding element of the accused product. Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1297 (Fed. Cir. 2009); Abbott Labs. v. Novopharm Ltd., 323 F.3d 1324, 1329 (Fed. Cir. 2003). Importantly, this analysis "proceeds element-by-element; a generalized showing of equivalency between the claim as a whole and the allegedly infringing product or process is not sufficient to show infringement." Abbott Labs., 566 F.3d at 1296; see also Warner-Jenkinson, 520 U.S. at 29 ("Each element contained in a patent claim is deemed material to defining the scope of the patented invention, and thus the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole."). This rule derives from the principle that the doctrine of equivalents may

not enlarge a patent beyond the scope of its claims. Warner-Jenkinson, 520 U.S. at 29-30.

The doctrine of equivalents is limited by (1) the "all elements" rule and (2) the doctrine of prosecution history estoppel. Lockheed Martin Corp. v. Space Sys./Loral, Inc., 324 F.3d 1308, 1320-21 (Fed. Cir. 1998). Under the all elements rule, "there can be no infringement under the doctrine of equivalents if even one limitation of a claim or its equivalent is not present in the accused device." Id. at 1321 (citing Pennwalt Corp. v. Durand-Wayland, Inc., 833 F.2d 931, 935-36 (Fed. Cir. 1987) (en banc)). Thus, if the court must vitiate a particular claim limitation in order to reach a finding of infringement, then the accused product does not infringe under the doctrine of equivalents. Id. (citations omitted); Warner-Jenkinson, 520 U.S. at 29, 40 (demanding "special vigilance against allowing the concept of equivalence to eliminate completely any such [individual] elements"). The application of this rule "must be premised upon a proper claim construction." Lockheed Martin, 324 F.3d at 1321 (citation omitted).

As for prosecution history estoppel, this doctrine bars "an equivalents argument for subject matter relinquished when a patent claim is narrowed during prosecution." Conoco, Inc. v.

Energy & Envtl. Int'l, L.C., 460 F.3d 1349, 1363 (Fed. Cir. 2006).

i. All Elements Rule

AstraZeneca argues that the difference in sterilization processes has no impact on the equivalents analysis because the budesonide particles in the Defendants' products are insubstantially different from those sterilized using dry heat. AZFF ¶ 171 (citing Tr. 1506:8-23, 1512:4-11 (Agalloco)). AstraZeneca relies on the testimony of its expert, Dr. Agalloco, who testified that based on his technical comparison of the attributes of each Defendants' products to PULMICORT RESPULES®, each Defendant infringed the '834 Patent because the products were insubstantially different. Dr. Agalloco testified that he compared the data for Apotex's ANDA test results with the PULMICORT RESPULES® test results. Specifically, he compared "the appearance of the suspensions themselves, the identification of the budesonide itself, the budesonide assay, in milligrams per milliliter, the impurities and degradation products which meet the specification and the sterility tests." Tr. 1505. From this comparison, Dr. Agalloco concluded that there were no substantial differences between the two products.

Dr. Agalloco next compared the results of testing performed by Sandoz with the PULMICORT RESPULES® test results. Dr.

Agalloco likewise concluded that there were insubstantial differences between Sandoz's product and PULMICORT RESPULES®. Tr. 1506-09.

Dr. Agalloco also compared Breath/Watson's ANDA product with PULMICORT RESPULES®. He specifically looked at the particles before they were put into suspension. Tr. 1509-10. He concluded that any differences between Breath/Watson's [redacted] budesonide particles and AstraZeneca's budesonide particles were insubstantial. Tr. 1512, 1514.

The Court finds that Dr. Agalloco's testimony is insufficient to establish infringement under the doctrine of equivalents. As an initial matter, it bears noting that "bioequivalency and equivalent infringement are different inquiries." Abbott Labs., 566 F.3d at 1298. Otherwise, "if bioequivalency meant per se infringement, no alternative to a patented medicine could ever be offered to the public during the life of a patent." Id. As set forth above, "[t]estimony as to the doctrine of equivalents must focus on an element by element basis and the 'role played by each element in the context of the specific patent claim.'" Acorda Therapeutics Inc. v. Apotex, Inc., Civ. No. 07-4937, 2011 WL 4074116, *9 (D.N.J. Sept. 6, 2011) (citing Warner-Jenkinson Co., 520 U.S. at 40)). "[G]eneralized testimony as to the overall similarity between

the claims and the infringer's product . . . does not suffice." Id. (quoting American Calcar, Inc.v. Am. Honda Motor Co., Inc., 651 F.3d 1318, 1339 (Fed. Cir. 2011)).

Dr. Agalloco's testimony here was "generalized". He testified only about the overall similarities between the Defendants' and AstraZeneca's final products and never identified the elements in the Defendants' manufacturing processes that equate to the heat-sterilized element in the claimed "micronized powder composition" pursuant to the Court's claim construction. As explained by AstraZeneca's own witness, Dr. Williams, the heat sterilized particles according to the Patent must not change, either chemically or physically, from the starting material to the final product. Tr. 1083 (Williams); '834 Patent, col. 4, ll. 58-63; see also Tr. 928:4-8 ("Q: And so this ['834 Patent, col. 4, ll. 58-63] is referring to maintaining the same pharmaceutical activity and physical properties and physical form from your starting material through your sterilization process all the way to your end product, correct? A: I believe that's true, yes."). Yet Dr. Agalloco did not perform a comparison of whether Defendants' products maintained the same chemical and physical properties from beginning to end. [redacted]

[redacted]

Finally, as to Breath/Watson's product, Dr. Agalloco testified that Breath/Watson's [redacted] sterilization process changes the particle size:

[redacted]

> Q: Now in the low dry heat sterilization process used for PULMICORT RESPULES® as described in '834 Patent, that does not change the particle size, correct?
>
> A: That's correct.

Tr. 1616:9-17. He also testified that it changes the particles' form:

[redacted]

Tr. 1615:8-22.

Thus, rather than establish infringement, Dr. Agalloco's testimony actually showed the greater likelihood of non-infringement; i.e., that the accused products do undergo various physical and chemical changes during the manufacturing process, in contrast to the claimed "heat sterilized" products. In fact, Dr. Agalloco admitted that he had "thrown out" the heat element.[54]

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[54] Dr. Agallaco testified:

> Q: Now, in the particle to particle analysis you were not at all looking at heat, correct?
>
> A: That's correct.
>
> Q: So this analysis, this comparison throws out heat and solely looks at the final product to product. Correct?
>
> A: I'm throwing out [redacted] as well. I'm only looking at the materials because that's all I can assess.

Tr. 1632.

[redacted] The doctrine of equivalents does not permit the patentee to "throw out" an element of the claim simply because the products look the same. See Warner-Jenkinson Co. v. Hilton Davis Chem. Co., Inc., 520 U.S. 17, 21, 40 (1997) (patentee cannot establish infringement under doctrine of equivalents without establishing the presence of each and every element of a claim or its equivalent in the accused device). If that were the case, the doctrine of equivalents would become the doctrine of appearances.

Finally, Dr. Agalloco never explained the contradiction between his testimony that there are no substantial differences between the parties' final products and AstraZeneca's representations to the Patent Office throughout prosecution that Defendants' sterilization processes create structurally different and pharmaceutically unacceptable products. See supra "Prosecution History". In fact, he testified that he had not reviewed the entire file history. Tr. 1602 ("Q. And therefore is it fair to say that you did not consider the entirety of the

file history of the '834 patent in rendering your opinions? A. That's correct.").

For these reasons, the Court finds that AstraZeneca has not carried its burden. Dr. Agalloco's testimony that the Defendants' products "look like" AstraZeneca's product fails to prove infringement under the doctrine of equivalents.[55]

ii. Prosecution History Estoppel

Even if AstraZeneca had satisfied the "all elements" rule, which it has not, Defendants also argue in the alternative that AstraZeneca should be estopped from relying on the doctrine of equivalents because during the prosecution of its patent, AstraZeneca repeatedly disclaimed budesonide formulations that were not heat sterilized. The Court agrees. [redacted]

AstraZeneca contends that it never disclaimed any product made by Defendants' sterilization methods, and thus, it should be permitted to argue the doctrine of equivalents. Here, the

[55] Thus, the Court need not address the parties' dispute regarding the "criteria of sterility" element.

distinction between disparaging the product versus the process is illusory. The record is replete with statements made by AstraZeneca during prosecution that disparaged and distinguished both the conventional sterilization methods and the resulting products. See supra "Prosecution History". [redacted]

Thus, AstraZeneca's theory of infringement under the doctrine of equivalents fails for this additional reason.

Since the Court finds that Defendants have not infringed independent claims 1 and 50, it also finds that Defendants have not infringed dependent claims 2 and 51. Wahpeton Canvas Co. v. Frontier, Inc., 870 F.2d 1546, 1552 n.9 (Fed. Cir. 1989) ("One who does not infringe an independent claim cannot infringe a claim dependent on . . . that claim.") (citation omitted). Accordingly, the Court need not address Defendants' invalidity arguments as to the '834 Patent.

IV. CONCLUSION

For the foregoing reasons, the Court finds that the Defendants will induce infringement of the '603 Patent, but the Court also finds that Patent invalid. The Court additionally finds that Defendants do not infringe the '834 Patent. Accordingly, the Court enters judgment in favor of Defendants and against AstraZeneca. AstraZeneca's preliminary injunction motion and the parties' oral motions for partial findings pursuant to Federal Rule of Civil Procedure 52(c) are DISMISSED as MOOT. Additionally, the Court notes that this Opinion shall be filed temporarily under seal. To the extent the parties wish to request redactions of this Opinion, they shall do so on or before April 2, 2013. An appropriate Order will issue herewith.

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

Date: April 1, 2013