IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS INC.
Petitioner,

v.

3M COMPANY
Patent Owner.

U.S. Patent No. 6,743,413 to Schultz *et al.*
Issue Date: June 1, 2004
Title: Suspension Aerosol Formulations

_____

Inter Partes Review No.: IPR2015-_____

Petition for *Inter Partes* Review of U.S. Patent No. 6,743,413
Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

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1001	U.S. Patent No. 6,743,413
1002	U.S. Patent Application Ser. No. 07/809,791
1003	U.S. Patent Application Ser. No. 07/810,401
1004	December 8, 1998 Request that an Interference Be Declared
1005	July 30, 2002 Amendment
1006	Declaration of Hugh Smyth
1007	International Patent Application Publication No. WO 1991/004011
1008	RESERVED
1009	U.S. Patent No. 4,866,051
1010	Weir, D.C., et al. "Corticosteroid trials in non-asthmatic chronic airflow obstruction: a comparison of oral prednisolone and inhaled beclomethasone dipropionate." 45 Thorax 112 (1990)
1011	International Patent Application Publication No. WO 1990/007333
1012	Curriculum Vitae of Hugh Smyth
1013	RESERVED
1014	Joseph P. Remington, Remington's Pharmaceutical Sciences 308-17 (Alfonso R. Gennaro ed., 17 ed. 1985)
1015	G. S. Banker and C. T. Rhodes, Eds., Modern Pharmaceutics, Second Edition 341 (Marcel Dekker, Inc., New York 1990)

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") petitions for *Inter Partes* Review ("IPR") seeking cancellation of claims 1-24 ("challenged claims") of U.S. Patent No. 6,743,413 to Schultz *et al.* ("the '413 patent") (EX1001), which is owned by 3M Company ("3M" or "Patent Owner").

II. OVERVIEW

A. The '413 Patent

The '413 patent issued June 1, 2004, from U.S. Appl. No. 08/455,280. The original priority application was filed in 1991, but the '413 patent will not expire until 2021, giving the patentee an almost thirty-year (30) monopoly. The '413 patent, however, never should have issued as its claims are anticipated and/or rendered obvious by the prior art. Petitioner files this IPR asking to end Patent Owner's wrongful monopoly.

The '413 patent's independent, challenged claims are directed to nothing more than pharmaceutical suspension formulations or apparatuses suitable for aerosol administration of such formulations. The base limitations of every claim involve aerosol formulations that contain a: (1) particulate drug; (2) 1,1,1,2-tetrafluoroethane (HFC-134a) as propellant; and (3) either being surfactant-free or "substantially surfactant free."

B. The Priority Date of the '413 Patent

1. The Earliest Effective Date for the Claims of the '413 Patent is May 4, 1992

The '413 patent issued from U.S. Application Serial Number 08/455,280 ("the '280 application"), filed May 31, 1995, which was a divisional application of U.S. Application Serial Number 07/878,039 ("the '039 application") filed May 4, 1992, now abandoned, which was a continuation-in-part application of commonly assigned, co-pending applications: U.S. Application Serial Number 07/809,791 ("the '791 application") and U.S. Application Serial Number 07/810,401 ("the '401 application"), both filed December 18, 1991 and both abandoned. (EX1001, "Related U.S. Application Data"). However, as explained below, the earliest effective priority date that the '413 patent should be afforded is May 4, 1992.

a) The '791 Application Does Not Provide Adequate Support for the Claims of the '413 Patent

The '791 application (EX1002), filed December 18, 1991, is directed to compositions containing albuterol sulfate and 1,1,1,2,3,3,3-heptafluoropropane (HFC-227) as the propellant. The '791 application states, "[t]his invention provides suspension aerosol formulations comprising a therapeutically effective amount of micronized albuterol sulfate and 1,1,1,2,3,3,3-heptafluoropropane *as substantially the only propellant*." (EX1002, p. 2) (emphasis added). Only three formulations are described in the '791 application, all of which include 1,1,1,2,3,3,3-

heptafluoropropane as the propellant and albuterol sulfate. (EX1002, pp. 5-6 (Examples 1-3)). Because the '791 application does not disclose any composition containing 1,1,1,2-tetrafluoroethane, it does not provide adequate support for the claimed subject matter of the '413 patent. *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306 (Fed. Cir. 2008).

b) The '401 Application Does Not Provide Adequate Support for Claims of the '413 Patent

The '401 application (EX1003), filed December 18, 1991, is directed to compositions containing pirbuterol acetate and 1,1,1,2,3,3,3-heptafluoropropane (HFC-227) as the propellant. The formulation of the '401 application "is further characterized in that it is substantially free of perfluorinated surfactant." (EX1003, p. 2). All five of the formulations set forth in the '401 application include pirbuterol acetate and 1,1,1,2,3,3,3-heptafluoropropane (HFC-227) as the propellant. (EX1003, pp. 5-8 (Examples 1-5)).

The '401 application states that "[t]he propellant comprises 1,1,1,2,3,3,3-heptafluoropropane, preferably as substantially the only propellant. However, one or more other propellants such as propellant 142b (1-chloro-1,1-difluoroethane), HFC-134a, and the like can be used, preferably in formulations of the invention containing ethanol." (EX1003, p. 9). This disclosure should be interpreted as encompassing formulations containing HFC-134a *in addition to* 1,1,1,2,3,3,3-heptafluoropropane as opposed to in place of 1,1,1,2,3,3,3-heptafluoropropane.

Thus, the ’401 application fails to provide adequate support for the claimed subject matter of the ’413 patent, which recites compositions and apparatuses for administering compositions “consisting essentially of” HFC-134a as the sole propellant.

c) Applicant Admitted that the Effective Priority Date of the ’413 Patent is May 4, 1992

The ’280 application, from which the ’413 patent issued, was a divisional of the ’039 application, which in turn was a continuation-in-part (“CIP”) application of the ’791 and ’401 applications. Claims in a CIP application are entitled only to the benefit of priority of an earlier application that has adequate written description support for the claims at issue. *Augustine Med., Inc. v. Gaymar Indus.*, 181 F.3d 1291, 1302-03 (Fed. Cir. 1999).

On December 8, 1998, during prosecution of the ’280 application, the Applicant filed a Request that an Interference be Declared. In that document, Applicant stated, “[a]s demonstrated above claims 105[1]-115 are fully supported by the disclosure in the parent application, U.S. Application No. 07/878,039, which was filed May 4, 1992, and the instant application. *Accordingly, the effective priority date of the present application is May 4, 1992*.” (EX1004, Request for Interference

[1] Claim 105, submitted by Applicants in their Response dated December 8, 1998, is *identical* to issued claim 1 of the ’413 patent. (EX1004, p. 1).

at p. 22) (emphasis added). Thus, by Applicants' admission, the '413 patent claims are entitled only to an effective filing date of May 4, 1992.

III. STANDING (37 C.F.R. § 42.104(A)); PROCEDURAL STATEMENTS

Petitioner certifies that: (1) the '413 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '413 patent on the grounds identified herein. This Petition is filed in accordance with 37 CFR § 42.106(a). Concurrently filed herewith are a Power of Attorney and an Exhibit List pursuant to § 42.10(b) and § 42.63(e), respectively. The required fee is paid when filing the Petition and the Office is authorized to charge any fee deficiencies and credit overpayments to Deposit Acct. No. 160605 (Customer ID No. 00826).

IV. MANDATORY NOTICES (37 C.F.R. § 42.8(A)(1))

A. Each Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real parties in interest are Mylan Pharmaceuticals, Inc., Mylan, Inc., Mylan N.V.,[2] and Mylan Pharma U.K. Limited.

[2] Petitioner identifies Mylan N.V. ("MNV") as a real party-in-interest ("RPI") out of an abundance of caution, due to a pending issue in IPR2015-01069 (an unrelated proceeding), wherein the petitioner in that proceeding has opposed an allegation that MNV should have been identified as an RPI. (Paper 12). Petitioner's identification

B. Notice of Related Matters (37 C.F.R. § 42.8(b)(2))

1. Judicial Matters Involving the '413 patent

To Petitioner's knowledge, there are no judicial matters to report.

2. Administrative Matters

The Public Patent Application Information Retrieval ("Public PAIR") system indicates that U.S. Patent No. 7,101,534, which issued September 5, 2006, and U.S. Patent No. 7,105,152, which issued September 12, 2006, both claim priority to the '413 patent's parent application, the '039 application. Public PAIR further indicates that all other corresponding U.S. patent applications have been abandoned.

C. Designation of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

Lead Counsel	Back-Up Counsel
Jitendra Malik, Ph.D. Reg. No. 55823 ALSTON & BIRD LLP 4721 Emperor Blvd., Suite 400 Durham, NC 27703-8580 jitty.malik@alston.com	Robert Caison Reg. No. 72939 ALSTON & BIRD LLP 101 South Tyron Street, Suite 400. Charlotte, NC 28280-4000 robert.caison@alston.com

of MNV as an RPI in the instant proceeding in no way constitutes an admission that MNV is or was an RPI in any other IPR proceeding.

D. Notice of Service Information (37 C.F.R. § 42.8(b)(4))

Please direct all correspondence to lead counsel at the above address. Petitioner consents to email service at: jitty.malik@alston.com and robert.caison@alston.com.

V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR (37 C.F.R. § 42.22(A))

Petitioner requests IPR and cancellation of claims 1-24 of the '413 patent. A detailed statement of the reasons for the relief requested is set forth below.

VI. THE '413 PATENT AND CLAIM CONSTRUCTION

The challenged claims must be given their broadest reasonable interpretation in light of the specification of the '413 patent. *See* 37 C.F.R. § 42.100(b). Under this standard, no terms or phrases require specific construction.[3]

[3] The term "substantially free of surfactant"—as found, for example, in claim 5—is no exception. In a July 30, 2002 amendment, the applicant stated that the term "substantially free of surfactant" was to be used in a manner consistent with the specification (EX1005, 7/30/02 amendment, p. 8). The specification includes no further explanation as to its meaning. As such, "substantially free of surfactant" should be accorded the definition it would have had to a person of ordinary skill in the art at the time.

VII. PERSON OF ORDINARY SKILL IN THE ART ("POSA") & STATE OF THE ART

A POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 420 (2007). A POSA in the field of the '413 patent would have had education and/or experience in particulate drug formulations and drug delivery via inhalation and knowledge of the scientific literature in the field.[4] Although the education and experience levels may vary, a POSA would have had at least a bachelor's degree in pharmacy or chemistry and work experience in the field of aerosol formulations and aerosol delivery systems for medications, including working with propellant based systems. A POSA would also have had experience in the research and/or development of inhalers to administer various medications, including inhalers directed to the treatment of asthma and chronic obstructive pulmonary disease ("COPD"). A person holding only a Bachelor's degree would be required to have had five to ten years of relevant work experience to qualify as a POSA, but a person with a more advanced degree, such as a master's of science, could qualify as a POSA with fewer years of

[4] Regardless of which priority date applies, the knowledge of the scientific literature, common sense, and skill of the POSA would remain the same. (EX1006, Declaration of Hugh Smyth, ¶ 17).

experience. A POSA is not necessarily limited to his or her own skills but also may work as part of a team and utilize specialized skills of other team members in order to solve a particular problem.

VIII. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(B))

IPR of claims 1-24 of the '413 patent is respectfully requested on the grounds of unpatentability listed below. Per 37 C.F.R. § 42.6(d), copies of the references are filed herewith. In support of the proposed grounds for unpatentability, this Petition includes the declaration of a technical expert, Dr. Hugh Smyth (EX1006), explaining what the art would have conveyed to a POSA as of the priority date. Dr. Smyth has offered a declaration from the perspective of a person of ordinary skill.

Reference(s)	Basis	Claims Challenged
WO 91/04011 (EX1007)	§ 102	1-2, 4, 6-7, 10, 12, 14-20, 22-24
WO 90/07333 (EX1011)	§ 102	1-5, 14, 20-22
WO 91/04011 (EX1007)	§ 103	1-14, 17, 20-22
WO 90/07333 (EX1011)	§ 103	1-14, 17, 20-22
WO 91/04011 (EX1007) in view of U.S. Patent No. 4,866,051 (EX1009)	§ 103	15, 18, 23
WO 90/07333 (EX1011) in view of U.S. Patent No. 4,866,051 (EX1009)	§ 103	15, 18, 23
WO 91/04011 (EX1007) in view of Weir, D.C., *et al*. (EX1010)	§ 103	16, 19, 24
WO 90/07333 (EX1011) in view of Weir, D.C., *et al*. (EX1010)	§ 103	16, 19, 24

Prior art references, in addition to the primary references listed above, provide further background in the art, further motivation to combine the teachings of these

references, and/or further support for why a POSA would have a reasonable expectation of success in combining the teachings of the primary references to arrive at the formulations and apparatuses suitable for aerosol administrations of such formulations recited in the challenged claims.

IX. INVALIDITY ANALYSIS

A. The ’011 Publication Anticipates Claims 1-2, 4, 6-7, 10, 12, 14-20, and 22-24

Anticipation under 35 U.S.C. § 102 requires that each and every element of the claimed invention be disclosed expressly or inherently in a single prior art reference. *See, e.g., In re Paulson*, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994). International Patent Application Publication No. WO 1991/004011 (“the ’011 publication”) (EX1007) anticipates Claims 1-2, 4, 6-7, 10, 12, 14-20, and 22-24 of the ’413 patent. The ’011 publication, entitled “Medicinal Aerosol Formulations” published April 4, 1991. Accordingly, the ’011 publication qualifies as a prior art reference with respect to the ’413 patent under 35 U.S.C. § 102(b), as the earliest priority date for the ’413 patent is May 4, 1992.[5] The ’011 publication discloses

[5] Even if the ’413 patent is entitled to a filing date of the ’791 or ’401 applications, the ’011 publication still qualifies as prior art under 35 U.S.C. § 102(a).

medicinal aerosol formulations suitable for pulmonary, nasal, buccal, or topical administration. (EX1007, p. 1, ll. 1-6).[6]

1. Independent Claim 1

Claim 1 recites "[a] pharmaceutical suspension formulation suitable for aerosol administration consisting essentially of: (i) particulate drug; and (ii) 1,1,1,2-tetrafluoroethane as propellant, wherein the formulation is further characterized in that it contains no surfactant." The phrase "consisting essentially of" signals that a claim includes the components recited therein and is only open to additional unlisted ingredients that do not "materially affect the basic and novel properties of the invention." *Ecolab, Inc. v. FMC Corp*., 569 F.3d 1335, 1343 (Fed. Cir. 2009).

The preamble of the '413 patent states: "[t]he term 'suspension aerosol formulation' as used herein refers to a formulation in which the drug is in particulate

[6] The '011 publication was disclosed to the PTO during prosecution of the '280 application but it was not cited in an Office Action or referred to during prosecution. Although courts have stated that overcoming the presumption of validity of an issued patent is more difficult where the PTO has considered the reference, the standard of proof remains the same. *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371 at 1378, 1381 (Fed. Cir. 2007); *see also IPXL Holdings, L.L.C. v. Amazon.com, Inc.*, 430 F.3d 1377, 1381-83 (Fed. Cir. 2005).

form and is substantially insoluble in the propellant." (EX1001, 3:27-29). Similarly, the '011 publication states that "[d]esirably the finely divided solid materials should be substantially insoluble in both the liquefied propellant and the surface-active agent." (EX1007, p. 10, ll. 3-5). Moreover, the formulations described in Example 1 of the '011 publication are "suitable for aerosol administration," as the '011 publication clearly describes adding the drug to aluminum aerosol cans and then equipping the cans with an aerosol valve before adding the propellant, HFC-134a. (EX1007 at p. 12, ll. 18-23). The '011 publication further states that "[t]his invention relates to medicinal aerosol formulations and in particular to formulations suitable for pulmonary, nasal, buccal or topical administration . . . ." (EX1007 at p. 1, ll. 2-5). Thus, the '011 publication clearly teaches formulations suitable for aerosol administration containing particulate (*i.e.*, substantially insoluble) drugs. (EX1006, ¶ 35).

Example 1 of the '011 publication describes the production of seven separate "control" pharmaceutical aerosol suspension formulations containing 1,1,1,2-tetrafluoroethane (Propellant 134a)[7] and one of several drugs, *without the*

[7] EX1007 at p. 2, ll. 6-11 ("It is disclosed that 1,1,1,2-tetrafluoroethane, hereinafter referred to as Propellant 134a...").

use of any surfactant. Relevant portions of Example 1 of the ’011 publication are reproduced below:

> **Example 1**
>
> The surfactant coated drug was prepared as described above from micronised drug in dehumidified conditions. *The control comprising the same formulation but omitting the surfactant was subjected to the same procedure.*
>
> *69 mg of the coated drug (or control)* was added to each of several 10 ml capacity aluminium aerosol cans. Polyethylene terephthalate (PET) aerosol containers may be substituted where appropriate. *An aerosol valve was crimped into place before addition of Propellant 134a* (7.9g). Once crimping had been effected cans could be removed from the dehumidified environment.

(EX1007, pp. 12-13) (emphasis added).

Example 1 includes a results table that lists a “Drug Deposition Potential” parameter. To generate this parameter, the Applicants of the ’011 publication had to make at least seven corresponding control formulations that “omitt[ed] the surfactant” using the various drugs and containers reported in the table. (EX1006, ¶ 40). As such, Example 1 of the ’011 publication discloses at least seven formulations designated as “controls” which consist essentially of a particulate drug (*e.g.*, beclomethasone dipropionate, betamethasone, ergotamine tartrate, salbutamol

B.P., sodium cromoglycate B.P., salbutamol sulphate, or salbutamol sulphate B.P.) and 1,1,1,2-tetrafluoroethane (*i.e.,* Propellant 134a) without any surfactant. *Id.*

For the purpose of anticipation, it is immaterial that the Petitioner relies on the reported "control" formulations. "A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. Thus, the question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis." *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.,* 150 F.3d 1354, 1361 (Fed. Cir. 1998); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.,* 246 F. 3d 1368, 1378 (Fed. Cir. 2001).

In fact, the '011 publication reports that the Drug Deposition Potentials of Salbutamol B.P. and Salbutamol Sulphate B.P. are 0.92 and 0.85, respectively. (EX1007, p. 14). As these values are likely not statistically different, the inclusion of the surfactant in these formulations resulted in minor, if any, changes between the control formulations and the surfactant formulations. (EX1006, ¶¶ 41-42). In other words, the Salbutamol B.P. and Salbutamol Sulphate B.P. "control" formulations were almost as successful, if not as successful, as the surfactant-containing formulations. *Id.* Thus, because each "control" formulation disclosed in Example 1 of the '011 publication consists essentially of 1,1,1,2-tetrafluoroethane and a particulate drug without a surfactant, the '011 publication teaches each and every element of claim 1. (EX1006, ¶ 45).

2. Independent Claim 4

The limitations of claim 4 are similar to those set forth in claim 1 in that they recite a "pharmaceutical formulation" consisting essentially of (i) one or more particulate drugs, and (ii) 1,1,1,2-tetrafluoroethane as propellant, which formulation is "free of surfactant." For the reasons provided in the analysis of claim 1, the '011 publication discloses these limitations.

Claim 4 further recites that "the particulate drug or drugs being present in a therapeutically effective amount *less than* 1.6% w/w relative to the total weight of the formulation *and* wherein 90% or more of the particles have a diameter of less than 10 microns." (emphasis added). Example 1 of the '011 publication describes surfactant-free "control" formulations containing "69 mg of the coated drug (or control)" and "7.9 g" of 1,1,1,2-tetrafluoroethane (Propellant 134a). (EX1007, p. 12, ll. 18-24). Accordingly, the '011 publication describes formulations in which the particulate drug is present at 0.87% w/w [69 mg drug/(69 mg drug + 7.9 g propellant 134a)] relative to the total weight of the formulation. (EX1006, ¶ 47). 0.87% is less than 1.6% as required by claim 4. Thus, this "therapeutically effective amount" of less than 1.6% w/w element of claim 4 is disclosed in the '011 publication. *Id.*

Claim 4 requires that "90% or more of the particles have a diameter of less than 10 microns." But Example 1 of the '011 publication explicitly states "[t]he surfactant coated drug was prepared as described above from *micronised* drug in

dehumidified conditions. The control comprising the same formulation but omitting the surfactant was subjected to the same procedure." (EX1007, p. 12, ll. 13-17) (emphasis added). The '011 publication "define[s]" micronized drug powder as "comprising particles having a size distribution of 95% of particles below 10 um and a mean size in the range of 1 to 5 um." (EX1007, p. 11, ll. 6-9). Example 1 of the '011 publication discloses "90% or more of the particles hav[ing] a diameter of less than 10 microns." (EX1006, ¶ 49). Thus, claim 4 is anticipated by the '011 publication. (EX1006, ¶ 51).

3. Independent Claim 6

Claim 6 is similar to claim 1:

6. A pharmaceutical suspension formulation suitable for aerosol administration, consisting essentially of:	*See* claim 1 analysis; EX1007, p. 10, ll. 3-5, p. 12, ll. 18-23, and p. 1, ll. 2-4.
a *therapeutically effective amount* of particulate drug;	*See* claim 1 analysis; EX1007, p. 10, ll. 3-5, p. 12, ll. 18-23, and p. 14, Table. The requirement for "therapeutically effective amount" is discussed below.
and propellant HFC 134a,	*See* claim 1 analysis; EX1007, p. 2, ll. 6-11, p. 3, ll. 29-31, and p. 12, ll. 21-23.
wherein the formulation is substantially and readily redispersible,	Discussed below.
and upon redispersion does not flocculate so quickly as to prevent reproducible dosing of the drug and	Discussed below.
wherein the formulation is free of a surfactant.	*See* claim 1 analysis; EX1007, p. 12, ll. 13-17 and p. 14, Table.

Claim 6 also requires that the particulate drug be present in a "therapeutically effective amount." Example 1 of '011 publication discloses that 69 mg of the particulate drug were used, constituting 0.87% w/w relative to the total weight of the formulation. (EX1007, p. 12, ll. 18-19; EX1006, ¶ 53). The '011 publication further states that amounts ranging from 20% to 0.001% would be therapeutically effective, depending on the "specific activity" of the drug. (*See* EX1007, p. 10, ll. 20-28; EX1006, ¶ 53).

Claim 6 further recites that the formulation be "substantially and readily redispersible. . . ." Steps (c) and (d) of Example 1 of the '011 publication describe an ultrasonic energy procedure to ensure homogenization. (EX1007, pp. 12-13). After homogenization (step (c)), the aerosol cans were placed on a rolling apparatus to "promote drug deposition." (EX1007, p. 12, ll. 29-35; EX1006, ¶ 57; *see generally*, Step (d)). Following this procedure, the '011 publication discloses that dispersion of the particulate required no more than inverting the can. (EX1007, p. 13, ll. 1-3).[8] Thus, the formulations of Example 1 of the '011 publication were "substantially and readily redispersible." (EX1006, ¶ 56).

[8] For at least two formulations, salbutamol B.P. and salbutamol sulphate B.P., the addition of the surfactant resulted in very little improvement, if any, as compared to the non-surfactant formulations. (EX1007, p. 14, Table; EX1006, ¶ 57).

Claim 6 requires that "upon redispersion [the formulation] does not flocculate so quickly as to prevent reproducible dosing of the drug." Example 1 of the '011 publication uses a "micronised drug" and defines "micronised drug powder" as "comprising particles having a size distribution of 95% of particles below 10 um and a mean size in the range of 1 to 5 um." (EX1007, p. 11, ll. 6-9; EX1006, ¶ 58). As the '011 publication explains, the "particle size of the powder for inhalation therapy should preferably be in the range of 2 to 10 microns," because larger particle sizes (*i.e.*, greater than 100 microns) "may tend to agglomerate [or] separate from the suspension . . . . " (EX1007, p. 9, ll. 31-33 and p. 11, ll. 24-25; EX1006, ¶ 58).

The applicants of the '011 publication specifically selected a "micronised drug" with its particular particle size distribution so that the formulation would not agglomerate or separate from suspension such as occurs during rapid flocculation. (EX1006, ¶ 58). Therefore, the '011 publication discloses each and every limitation of claim 6 of the '413 patent. (EX1006, ¶ 60).

4. Independent Claim 12

Claim 12 recites that "the formulation is substantially free of surfactant." The '011 publication discloses formulations that a POSA would consider to be "substantially free of surfactant." (EX1006, ¶ 64). As set forth in the table on page 14 of the '011 publication, Formulation 1 contains the particulate drug "beclomethasone dipropionate" coated using a 0.001% w/v of surfactant. (EX1007,

p. 14; EX1006, ¶ 66; *see also* EX1007, p. 11, ll. 1-3, disclosing concentrations between 0.001 to 5% (w/v)). Moreover, Formulation 1 would *have less than* 0.001% (w/v) of surfactant as not all of the surfactant comes out of solution and deposits on the particulate drug. (EX1006, ¶ 66). Therefore, a POSA would consider this formulation "substantially free of surfactant." (*Id.*).

Claim 12 also requires a "plurality of therapeutically effective doses." Formulation 1 of the '011 publication contains 69 mg of the particulate drug beclomethasone dipropionate. As with claim 6, 69 mg constitutes 0.87% w/w relative to the total weight of the formulation (or a therapeutically effective amount), which would be sufficient to provide a plurality of therapeutically effective doses.[9] (EX1006, ¶¶ 62-63; *see* EX1007, pp. 12-14).

As for the remaining limitations of claim 12, Formulation 1 contains HFC-134a as the propellant. (*See* EX1007, pp. 12-14). As with claim 6, Formulation 1 was subjected to steps (c) and (d) of Example 1 and would be substantially and readily redispersible because it would require no more than simply inverting the can. (EX1006, ¶ 56). Furthermore, because the drug was "micronised," it would not flocculate for the same reasons as with claim 6. (EX1006, ¶ 58). Moreover, the

[9] The volume of the propellant in the canister is at least 7.9g. (EX1007, p. 12, ll. 21-23). 7.9g is sufficient to dispense multiple doses. (EX1006, ¶ 63).

Drug Deposition Potential of Formulation 1 (0.64) indicates that Formulation 1 performed well when tested. (EX1006, ¶ 67). Thus, Formulation 1 of the '011 publication anticipates claim 12. The chart below provides additional details:

12. An aerosol canister containing a formulation suitable for aerosol administration, consisting essentially of:	*See* claim 1 analysis; EX1007, p. 10, ll. 3-5, p. 12, ll. 18-23, and p. 1, ll. 2-6; *see* Example 1 disclosing "69 mg of the coated drug (or control) was added to each of several 10 ml capacity *aluminium aerosol cans*." (EX1007, p. 12, ll. 18-19.)
particulate drug in an amount sufficient to provide a plurality of therapeutically effective doses of drug;	Formulation 1 containing beclomethasone dipropionate. (EX1007, p. 14). Formulation 1 contains 69 mg of the particulate drug which, as with claim 6, constitutes 0.87% w/w relative to the total weight of the formulation or a therapeutically effective dose. (*See* EX1007, pp. 12-14). *See* EX1007 at p. 10, ll. 3-5, 20-26.
and propellant HFC 134a,	*See* claim 1 analysis; EX1007, p. 2, ll. 6-11, p. 3, ll. 29-31, and p. 12, ll. 21-23; Example 1 disclosing "propellant [HFC] 134a." (EX1007, p. 12, l. 22).
wherein the formulation is substantially and readily redispersible,	After employing steps (c) and (d), the drug is redispersed by simple inversion. *See* discussion in connection with claim 6 for further explanation; EX1007, p. 11, ll. 16-19, p. 12, ll. 29-35, p. 13, ll. 1-3, and p. 14, Table.
and upon redispersion does not flocculate so quickly as to prevent reproducible dosing of the drug and	The beclomethasone dipropionate used in Formulation 1 was "micronised." (EX1007, p. 12, ll. 8-9). As with claim 6, a micronized drug was used to prevent agglomeration or separation from rapid flocculation. *See* claim 6 analysis; EX1007, p. 11, ll. 6-9, p. 9, ll. 31-33, and p. 11, ll. 24-25.
wherein the formulation is substantially free of surfactant.	Formulation 1 of Example 1 containing beclomethasone dipropionate used 0.001 % w/v of surfactant. (EX1007, p. 14). This would make the formulation "substantially free of surfactant."

5. Independent Claim 14

Independent claim 14 is similar to claim 12 in that it also recites a formulation "consisting essentially of" a formulation that is "substantially free of surfactant." For the reasons stated above with respect to claim 12, and as shown in the chart below, the Formulation 1 of the '011 publication, which contains the particulate drug "beclomethasone dipropionate" with less than 0.001% (w/v) of surfactant, anticipates claim 14:

14. A method of treating a mammal having a condition capable of treatment by inhalation, comprising the step of: administering by inhalation a formulation suitable for aerosol administration, wherein the formulation consists essentially of:	*See* claim 12 analysis (explaining how Example 1 discloses this element); *see also* claim 1 analysis; EX1007, p. 10, ll. 3-5, p. 12, ll. 18-23, and p. 1, ll. 2-10 ("This invention relates to medicinal aerosol formulations and in particular to formulations suitable for pulmonary, nasal, buccal or topical administration . . . .Since the metered dose pressurized inhaler was introduced in the mid 1950's, inhalation has become the most widely used route for delivering bronchodilator drugs and steroids to the airways of asthmatic patients.")
(i) particulate drug; and	Formulation 1 of Example 1 contains beclomethasone dipropionate. (EX1007 at p. 10, ll. 3-5; p. 14, Table).
(ii) 1,1,1,2-tetrafluoroethane as propellant,	*See* claim 1 analysis; EX1007, p. 2, ll. 6-11, p. 3, ll. 29-31, and p. 12, ll. 21-23; Example 1 disclosing "propellant [HFC] 134a." (*Id*. at p. 12, l. 22.)
wherein the formulation is substantially free of surfactant.	As with claim 12, Formulation 1 containing beclomethasone dipropionate with less than 0.001 % w/v of surfactant. (*Id*. at p. 14.) This would make the formulation "substantially free of surfactant."

6. Independent Claim 17

Claim 17 includes a formulation requiring "no surfactant or less than a stabilizing amount of a surfactant." Since this limitation includes a disjunctive element (*i.e.*, "or"), a formulation that contains no surfactant would invalidate this claim. *See SkinMedica, Inc. v. Histogen, Inc.*, 727 F.3d 1187, 1199 (Fed. Cir. 2013). As shown in the claim chart below, the "control" formulations (described above in connection with claims 1 and 6) anticipate claim 17:

17. A method of treating a mammal having a condition capable of treatment by inhalation, comprising the step of: administering by inhalation a formulation suitable for aerosol administration, consisting essentially of:	*See* claim 12 analysis (explaining how Example 1 discloses this element); *see also* claim 1 analysis; EX1007, p. 10, ll. 3-5, p. 12, ll. 18-23, and p. 1, ll. 2-10 ("This invention relates to medicinal aerosol formulations and in particular to formulations suitable for pulmonary, nasal, buccal or topical administration . . . . Since the metered dose pressurized inhaler was introduced in the mid 1950's, inhalation has become the most widely used route for delivering bronchodilator drugs and steroids to the airways of asthmatic patients.")
a therapeutically effective amount of particulate drug; and	*See* analysis of claims 1 and 6, explaining that the 69 mg of the particulate drug used in the "control" formulation would constitute "a therapeutically effective amount of particulate drug." (EX1007, p. 10, ll. 3-5 and 20-28, p. 12, ll.18-24, and p. 14, Table).

propellant HFC 134a,	*See* claim 1 analysis; EX1007, p. 2, ll. 6-11, p. 3, ll. 29-31, and p. 12, ll. 21-23; Example 1 disclosing "propellant [HFC] 134a." (*Id*. at p. 12, l. 22.)
wherein the formulation is substantially and readily redispersible,	*See* claim 6 analysis, explaining that the procedure used in Example 1 would result in a formulation that would be substantially and readily redispersed; that is, after employing steps (c) and (d), the drug is redispersed by simple inversion; EX1007, pp. 12-13, p. 14, Table.
and upon redispersion does not flocculate so quickly as to prevent reproducible dosing of the drug to the mammal and	The drugs used in Example 1 were "micronised." (EX1007, p. 12, ll. 8-9). As with claim 6, a micronized drug was used to prevent agglomeration or separation from rapid flocculation. *See* claim 6 analysis; EX1007, p. 11, ll. 6-9, p. 9, ll. 31-33, and p. 11, ll. 24-25.
wherein the formulation contains no surfactant or less than a stabilizing amount of a surfactant.	*See* analysis of claims 1 and 6, explaining that "control" formulations contained no surfactant; EX1007, p. 12, ll. 13-17 and p. 14, Table.

7. Independent Claims 20 and 22

Claims 20 and 22 also include the disjunctive limitation "no surfactant or less than a stabilizing amount of a surfactant." As shown in the chart below, claims 20 and 22 are anticipated by the "control" formulations described in Petitioner's analysis of claim 1 and claim 6:

20. An aerosol canister containing a formulation suitable for aerosol administration, wherein said formulation consists essentially of:	*See* claim 1 analysis; EX1007, p. 10, ll. 3-5, p. 12, ll. 18-23, and p. 1, ll. 2-6; *see also* Example 1 disclosing "69 mg of the coated drug (or control) was added to each of several 10 ml capacity *aluminium aerosol cans*." (EX1007, p. 12, ll. 18-19) (emphasis added).

particulate drug in an amount sufficient to provide a plurality of therapeutically effective doses of drug;	*See* analyses of claim 1 and claim 6, explaining that the 69 mg of the particulate drug used in the control formulation would constitute "a therapeutically effective amount of particulate drug." (EX1007, p. 10, ll. 3-5, p. 10, ll. 20-28 and p. 12, ll. 18-24).
and propellant HFC 134a,	*See* claim 1 analysis; EX1007, p. 2, ll. 6-11, p. 3, ll. 29-31, and p. 12, ll. 21-23; Example 1 disclosing "propellant [HFC] 134a." (*Id*. at p. 12, l. 22.)
wherein the formulation is free of surfactant or contains less than a stabilizing amount of surfactant.	*See* claim 1 and claim 6 analyses explaining that "control" formulations contained no surfactant; EX1007, p. 12, ll. 13-17 and p. 14, Table.

22. A method of treating a mammal having a condition capable of treatment by inhalation, comprising: administering by inhalation a formulation consisting essentially of	*See* claim 12 analysis (explaining how Example 1 discloses this element); *see also* claim 1 analysis; EX1007, p. 10, ll. 3-5, p. 12, ll. 18-23, and p. 1, ll. 2-10 ("This invention relates to medicinal aerosol formulations and in particular to formulations suitable for pulmonary, nasal, buccal or topical administration . . . . Since the metered dose pressurized inhaler was introduced in the mid 1950's, inhalation has become the most widely used route for delivering bronchodilator drugs and steroids to the airways of asthmatic patients.")
particulate drug in an amount sufficient to provide a plurality of therapeutically effective doses of drug;	*See* analyses of claim 1 and claim 6 explaining that the 69 mg of the particulate drug used in the "control" formulation would constitute "a therapeutically effective amount of particulate drug." (EX1007, p. 10, ll. 3-5, p. 10, ll. 20-28 and p. 12, ll. 18-24).
and propellant HFC 134a,	*See* claim 1 analysis; EX1007, p. 2, ll. 6-11, p. 3, ll. 29-31, and p. 12, ll. 21-23; Example 1 disclosing "propellant [HFC] 134a." (*Id*. at p. 12, l. 22.)

wherein the formulation is free of surfactant or contains less than a stabilizing amount of surfactant	*See* claim 1 and claim 6 analysis explaining that "control" formulations contained no surfactant; EX1007, p. 12, ll. 13-17 and p. 14.

8. Dependent Claim 2

Claim 2 depends from claim 1 and further requires that "the particulate drug is micronized." Example 1 of the '011 publication explicitly states that "[t]he surfactant coated drug was prepared as described above from *micronised* drug . . . . The control comprising the same formulation but omitting the surfactant was subjected to the same procedure." (EX1007, p. 12, ll. 13-17) (emphasis added). Thus, claim 2 is anticipated by the "control" formulations described in the '011 publication. (EX1006, ¶ 72).

9. Dependent Claim 7

Claim 7 depends from claim 6 and further recites the disjunctive limitation "wherein the formulation exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period." As with claim 6, Example 1 of the '011 publication used a "micronised drug," which was chosen to prevent particle agglomeration. (EX1007, p. 9, ll. 24-33; p. 11, ll. 6-9). Thus, the "control" formulations of Example 1 would exhibit substantially no growth in particle size. (EX1006, ¶¶ 73-74). Moreover, the lack of growth in particle size of the formulations of the '011 publication is an inherent property and the '413 patent's description of this inherent property does not defeat a finding of anticipation. *See*

King Pharms., Inc. v. Eon Labs, Inc., 616 F.3d 1267, 1275 (Fed. Cir. 2010) ("It is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable."). Thus, claim 7 is anticipated by the '011 publication. (EX1006, ¶¶ 73-74).[10]

10. Dependent Claim 10

Claim 10 depends from claim 6 and further recites "wherein the drug concentration is greater than about 0.5 percent." As explained above, Example 1 of the '011 publication describes "control" surfactant-free formulations containing "69 mg of the coated drug (or control)" and "7.9 g" of 1,1,1,2-tetrafluoroethane (Propellant 134a). (EX1007, p. 12, ll. 18-23). The particulate drug is present at 0.87% w/w relative to the total weight of the formulation, which meets the "greater than about 0.5 percent" limitation of claim 10. (EX1006, ¶ 75). Thus, claim 10 is anticipated by the '011 publication. (EX1006, ¶ 75).

[10] To the extent that "over a prolonged period" is a limitation that modifies "substantially no growth in particle size," use of the "micronised drug" would prevent agglomeration over a prolonged period of time thereby exhibiting no growth in particle size. (EX1006, ¶ 74 fn. 5.)

11. Dependent Claims 15, 16, 18, 19, 23, and 24

Claims 15 and 16 depend from claim 14, which recites formulations that are "substantially free of surfactant." Claim 15 recites that "the condition capable of treatment by inhalation is asthma," while claim 16 recites that the "condition capable of treatment by inhalation is chronic obstructive pulmonary disease." As stated above, claim 14 is anticipated by the '011 publication's disclosure of Formulation 1, which contains the particulate drug beclomethasone dipropionate. (EX1007, p. 14). Beclomethasone dipropionate is used in the treatment of asthma and COPD. (EX1009 at 1:23-27; EX1010 at 116; EX1006, ¶ 78). Thus, claims 15 and 16 are anticipated by the '011 publication. (EX1006, ¶ 78).

Claims 18, 19, 23, and 24 depend from claims that recite surfactant-less formulations. Claims 18 and 23 recite that "the condition capable of treatment by inhalation is asthma." Claims 19 and 24 recite that the "condition capable of treatment by inhalation is chronic obstructive pulmonary disease [or COPD]." As discussed above, the table set forth on page 14 of the '011 publication discloses preparing aerosol canisters containing a beclomethasone dipropionate "control" formulation. (*See* EX1007, p. 14, Table). Beclomethasone dipropionate, in aerosol form, is used for the treatment of both asthma and COPD. (EX1006, ¶ 79-80). Thus, claims 18, 19, 23, and 24 are anticipated by the '011 publication. (EX1006, ¶ 80).

B. The Challenged Claims Would Have Been Obvious Given the '011 Publication Alone or in Combination

1. The Scope and Content of the Prior Art

The related content of the '011 publication and other references have been described above in the anticipation section.

2. Differences Between the Claims and the Prior Art

a) Claims 1, 2, and 4 Would Have Been Obvious

The "control" formulations of Example 1 of the '011 publication anticipate claims 1, 2, and 4. But these "control" formulations not only anticipate the claims, they also render them obvious. *See In re Kalm*, 378 F.2d 959 (C.C.P.A. 1967). Moreover, the '011 publication would have provided a POSA with explicit motivation to produce aerosol formulations that were either surfactant-free or "substantially surfactant free:" "[f]or best results, the concentration of the surface-active agent[11] is kept at a minimum as it may tend to increase the droplet size particles and particle agglomeration." (EX1007 at p. 7; EX1006, ¶ 117).

With respect to the aerosol canisters containing micronized salbutamol B.P. and salbutamol sulphate B.P., the '011 publication discloses that formulations containing surfactant showed little improvement, if any statistical difference, over

[11] As defined in the '011 publication, surface-active agents are surfactants. (EX1007 at pp. 6-7).

the surfactant-less formulations (Drug Deposition Potential: 0.92 and 0.85, with a value of 1.0 indicating no change in performance with the surfactant over the control). (EX1007, p. 13, ll. 22-24, p. 14; EX1006, ¶ 118). The marginal change, if any, in performance of the surfactant-less formulation would not be found to teach away from the use of such a formulation in an obviousness analysis. (EX1006, ¶ 119); *see, e.g.*, *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) (stating that "just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes"); *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004) (holding that mere disclosure of alternative designs does not teach away).

Moreover, in light of the high values of the Drug Deposition Potential of the salbutamol B.P. and salbutamol sulphate B.P. formulations (0.92 and 0.85, respectively), a POSA would have had a reasonable expectation of success. (EX1006, ¶ 120). Claims 1, 2, and 4, therefore, would have been obvious in view of the '011 publication. *Id.*

b) Claim 3 Would Have Been Obvious

Even if the aerosol canisters disclosed in Example 1 do not expressly include a "metering valve" or an "amount sufficient to provide a plurality of therapeutically effective doses of the drug," these further limitations of claim 3 would have been obvious in light of the '011 publication.

Example 1 of the ’011 publication discloses “aluminum aerosol cans” equipped with “aerosol valve[s].” (EX1007, p.12, ll. 19, 21). The ’011 publication further states: “Since the metered dose pressurised inhaler was introduced in the mid 1950’s, inhalation has become the most widely used route for delivering bronchodilator drugs and steroids to the airways of asthmatic patients . . . .” (EX1007, p.1, ll. 8-10). Moreover, the ’413 patent refers to metered dose valves as “conventional valves.” (EX1001 at 6:21-22). Utilization of an aerosol canister equipped with a “conventional valve” such as a metering valve to provide a plurality of therapeutically effective doses of the drug would simply have been a matter of design choice, falling well within the scope of routine experimentation carried out by one of ordinary skill. (EX1006, ¶ 124). A POSA would have been motivated to select a metering valve, given that it is the “most widely used” choice. *Id.*; *KSR*, 550 U.S. at 417 (a claim is likely obvious if it is no “more than the predictable use of prior art elements according to their established functions”).

Finally, the 0.87% w/w of the particulate drug used in Example 1 of the ’011 publication is a “therapeutically effective” amount and/or such a limitation would have been obvious in light of the disclosure of the ’011 publication. (EX1006, ¶ 125). The ’011 publication discloses that a therapeutically effective amount depends on the nature of the particulate drug itself. (EX1007, p. 10, ll. 20-28) (disclosing amounts ranging from 20% to 0.001% and stating that “[t]he minimum concentration

of the solid material is governed by its *specific activity*") (emphasis added). Claim 3's requirement of an "amount sufficient to provide a plurality of therapeutically effective doses of the drug" would have been obvious in light of the disclosure of the '011 publication, as a POSA would have been motivated to provide a therapeutically effective amount of the drug and would have had a reasonable expectation of success in altering the amount of the effective doses "to discover the optimum or workable ranges by routine experimentation." (EX1006, ¶ 128); *In re Aller*, 220 F.2d 454, 456-57 (C.C.P.A. 1955); *Metrics, Inc. v. Senju Pharmaceutical Co., Ltd.*, IPR2014-01041 [Paper 19, p. 17].

c) Claims 5 and 14 Would Have Been Obvious

Independent claim 5 recites that "the formulation is substantially free of surfactant." As discussed above, the '011 publication discloses Formulation 1 which contains the particulate drug "beclomethasone dipropionate" with less than 0.001% (w/v) of surfactant. (EX1007, p. 14; EX1006, ¶ 66). A POSA would consider this formulation "substantially free of surfactant." (EX1006, ¶¶ 66, 131).

While Formulation 1 of the '011 publication is "substantially free" of surfactant, claim 5 would still have been obvious to a POSA, who would have had the requisite skill to manipulate the concentration of surfactant "to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456-57 (C.C.P.A. 1955) (holding that "where the general conditions of a claim are

disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation"). This is particularly the case because the '011 publication discloses working control formulations that include no surfactant, providing a POSA with a reasonable expectation of success. (EX1006, ¶¶ 40-41, 131-32). Moreover, the '011 publication would have provided a POSA with explicit motivation to produce aerosol formulations that were "substantially surfactant free" because it states "[f]or best results, the concentration of the surface-active agent[12] is kept at a minimum as it may tend to increase the droplet size particles and particle agglomeration." (EX1007 at p. 7).

Claim 5 also recites that the administering apparatus is a "metered dose inhaler." The '011 publication renders a claim directed to "metered dose inhalers" obvious for the same reasons set forth with respect to claim 3, and a POSA would have had a reasonable expectation of success in arriving at the claimed inhaler. (EX1006, ¶ 133).

Claim 14 is similar to claim 5, with the primary difference being that claim 14 is directed to "treating a mammal," whereas claim 5 is directed to a "metered dose inhaler." The '011 publication, which focuses on the treatment of mammals, renders

[12] As defined in the '011 publication, surface-active agents are surfactants. (EX1007 at pp. 6-7).

claim 14 obvious for the reasons stated above with regard to claim 5. (EX1006, ¶ 134).

d) Claim 6 Would Have Been Obvious

Independent claim 6 is similar to claim 1. Example 1 of the '011 publication discloses a "therapeutically effective amount" and/or such a limitation would have been obvious in light of the '011 publication. (EX1006, ¶ 135; *see* discussion of therapeutically effective amount in the claim 3 analysis). Moreover, the formulations of Example 1 were dispersed by simply inverting the canister. (EX1006, ¶ 136; EX1007, p.13, ll. 1-4).

Further, the '011 publication discloses the limitation that "upon redispersion [the formulation] does not flocculate so quickly as to prevent reproducible dosing of the drug and wherein the formulation is free of a surfactant" (hereinafter "the flocculation element") and/or such a limitation would have been obvious. (EX1006, ¶ 137). It is important to note that the applicants of the '011 publication did not disclose any issues with flocculation. (*Id.* at ¶ 138). But, even if they experienced flocculation, the '011 publication explains that agglomeration (or flocculation) can be prevented so long as particle size does not exceed 100 microns in diameter (and most preferably, is in the range from 2 to 10 microns), "since larger particles may tend to agglomerate, separate from the suspension," and "clog the valve or orifice of the container." (*Id.*; EX1007, p. 9, ll. 22-33, p. 10, ll. 15-19 (explaining that

agglomeration can make the suspension undesirably unstable)). Moreover, the claimed composition's tendency to not flocculate upon redispersion is an unpatentable, inherent property of the formulation. *See Santarus v. Par Pharm*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (explaining that the testing and claiming of an inherent property cannot make an obvious formulation nonobvious).

Thus, a POSA reviewing the '011 publication would have found it obvious to make a formulation that did not flocculate so quickly as to prevent redispersion and would have been motivated to do so. (EX1006, ¶ 141). Furthermore, a POSA would have had a reasonable expectation of success of preventing flocculation because the '011 publication would inform the POSA that it is just a matter of selecting the correct particle size. (*Id.*; EX1007, p. 9, ll. 22-33). Claim 6 would have been obvious as the remaining elements are disclosed for the same reasons as with claim 1. (EX1006, ¶ 142).

e) Claim 7 Would Have Been Obvious

Claim 7 requires that the formulation of claim 6 "exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period." As with claim 6, the '011 publication provides clear instructions on how to prevent particle agglomeration, *i.e.*, "growth in particle size." (EX1007, p. 9, ll. 22-33; EX1006, ¶ 143). Such an endeavor would have been a matter of routine skill. (EX1006, ¶ 144; EX1007, p. 9, ll. 22-33); *In re Aller*, 220 F.2d at 256-57; *Santarus*,

694 F.3d at 1354. Thus, a POSA would have been motivated to prevent particle agglomeration, and would have had a reasonable expectation of success in doing so. (EX1006, ¶ 145). Therefore, claim 7 would have been obvious. (*Id.*)[13]

f) Claims 8-11 Would Have Been Obvious

Claims 8-11, all dependent on claim 6, recite various drug concentrations: "less than about 0.1 percent" (claim 8); "greater than about 0.1 percent and less than about 0.5 percent" (claim 9); "greater than about 0.5 percent" (claim 10); and "a concentration of less than about 0.1 percent is therapeutically effective" (claim 11). The '011 publication discloses all of these amount limitations. (EX1007, p. 10, ll. 20-28; EX1006, ¶¶ 147-48). As such, claims 8-11 would have been rendered obvious by the '011 publication. (*Id.* at ¶ 149). Moreover, given the '011 publication's disclosure that the drug amount is dependent on "its specific activity," a POSA would have been motivated to determine the optimal drug concentration for the individual drug and would have had a reasonable expectation of success in doing so. (*Id.* at ¶ 150). Such endeavors would fall well within the scope of routine experimentation. *In re Aller,* 220 F.2d at 456.

[13] *See supra* fn.10 for additional discussion related to the "prolonged period" recitation.

g) Claim 12 Would Have Been Obvious

Independent claim 12 recites that the formulation is "substantially free of surfactant." A POSA would consider Formulation 1, with less than 0.001% of surfactant, as being substantially free of surfactant. (*See* analysis of claim 5, *supra*; EX1006, ¶ 151). Claim 12 also recites a "plurality of therapeutically effective doses." Formulation 1 of Example 1 contains 7.9g of propellant, which is enough to administer a plurality of doses. (EX1007, p.12, ll. 21-23; EX1006, ¶ 152). Example 1 discloses "therapeutically effective doses" and/or such a limitation would have been obvious in light of the '011 publication. (*Id.*).

The formulations of Example 1, including Formulation 1, were "dispersed" by simply inverting the canister. (EX1007, p. 13, ll. 1-4). Claim 12 also includes the "flocculation element," which would have been obvious since the '011 publication provides clear instructions on how to address flocculation by controlling particle size and it was well known in the art that particle concentration could also control flocculation kinetics. (EX1007, p. 9, ll. 22-33, p. 10, ll. 15-19; EX1006, ¶ 154). Moreover, the claimed composition's tendency to not flocculate upon redispersion is an unpatentable, inherent property of the formulation. *See Santarus*, 694 F.3d at 1354. Given that the remaining elements of claim 12 are disclosed for the reasons stated for claim 1, claim 12 would have been obvious, and a POSA would

have had a reasonable expectation of success in arriving at the claim. (EX1006, ¶ 156).

h) Claim 13 Would Have Been Obvious

Claim 13 is similar to claim 12, except that claim 13 is directed to a metered dose aerosol canister, whereas claim 12 is directed to an aerosol canister. As with claim 3, use of a metering valve, which the '413 patent admits is "conventional," would have been obvious in light of the '011 publication. (EX1006, ¶ 159). Moreover, Example 1 discloses a "therapeutically effective amount" and/or such a limitation would have been obvious in light of the '011 publication. (*See* related discussion *supra* regarding claims 3, 4, 6, and 11). The formulations were "dispersed" by simply inverting the canister. Claim 13 also includes the "flocculation element," which would have been obvious because the '011 publication provides clear instructions on how to deal with flocculation and it was well known in the art that particle concentration could also control flocculation kinetics. (EX1006, ¶¶ 154, 160).

Moreover, the claimed composition's tendency to not flocculate upon redispersion is an unpatentable, inherent property of the formulation. *See Santarus*, 694 F.3d at 1354. Given that the remaining elements of claim 13 are disclosed for the reasons stated in the analysis for claim 12, claim 13 would have been obvious, and a POSA would have had a reasonable expectation of success. (EX1006, ¶ 160).

i) Claim 17 Would Have Been Obvious

Claim 17 is similar to claim 1. Example 1 discloses a "therapeutically effective amount" and/or such a limitation would have been obvious in light of the '011 publication. Moreover, as noted above, the formulations were "dispersed" by simply inverting the canister. (EX1006, ¶ 161). Claim 17 also includes the "flocculation element," which would have been obvious because the '011 publication provides clear instructions on how to deal with flocculation. (EX1006, ¶¶ 154, 162). Further, the claimed composition's tendency to not flocculate upon redispersion is an unpatentable, inherent property of the formulation. *See Santarus*, 694 F.3d at 1354. Given that the remaining elements of claim 17 are disclosed for the reasons stated in the analysis for claim 1, claim 17 would have been obvious, and a POSA would have had a reasonable expectation of success. (EX1006, ¶ 164).

j) Claim 20 Would Have Been Obvious

Independent claim 20, which is similar to claim 1, is directed to an aerosol canister and recites an "amount sufficient to provide a plurality of therapeutically effective doses of the drug." The "control" formulations of Example 1 each contain 7.9g of propellant, which is enough to administer a plurality of doses. (EX1007, p.12, ll. 21-23; EX1006, ¶ 165). If there is any question that Example 1 discloses "therapeutically effective doses," as shown in the analysis of claims 3, 4, and 6-11, such a limitation would have been obvious in light of the '011 publication and a

POSA would have had a reasonable expectation of success. (EX1006, ¶ 165). Given that the remaining elements of claim 20 are disclosed for the reasons stated in the analysis for claim 1, claim 20 would have been obvious. (EX1006, ¶ 166).

k) Claims 21 and 22 Would Have Been Obvious

Claim 21 is similar to claim 1, except that claim 21 is directed to a "metered dose aerosol canister." As with claim 3, use of a conventional valve such as a metered dose valve would have been obvious in light of the express disclosure of the '011 publication. (EX1006, ¶ 167; EX1007 at p.1, ll. 8-20). Claim 22 is also similar to claim 1, and claims 21 and 22 require a "therapeutically effective amount." Example 1 discloses a "therapeutically effective amount" and/or such a limitation would have been obvious in light of the '011 publication. (EX1006, ¶¶ 152, 168). Given that the remaining elements of claims 21 and 22 were previously disclosed for the same reasons as claim 1, these claims would have also been obvious. (EX1006, ¶ 168).

l) Dependent Claims 15, 16, 18, 19, 23, and 24 Would Have Been Obvious

Claims 15 and 16 each depend from claim 14, which recites formulations that are "substantially free of surfactant." Claim 15 is directed to the treatment of asthma, while claim 16 is directed to the treatment of COPD. Claim 14 is anticipated by Formulation 1 of the '011 publication, which contains beclomethasone dipropionate. (*Supra*; EX1007, p. 14; EX1006, ¶ 45). Beclomethasone dipropionate is used in the

treatment of asthma (*see* U.S. Patent No. 4,866,051, "the '051 patent," EX1009[14] at Abstract) and COPD (*see* Weir, D.C., *et al.* "Corticosteroid trials in non-asthmatic chronic airflow obstruction: a comparison of oral prednisolone and inhaled beclomethasone dipropionate." 45 Thorax 112, 112-17 (1990), "the Weir reference," EX1010[15] at Abstract, p. 112). While claims 15 and 16 are anticipated in light of the known medical uses of the drug disclosed in the '011 publication, the claims would have also been obvious to a POSA, who would have had a reasonable expectation of success in light of the state of the art. (EX1006, ¶ 181). That is, claim 15 would have been obvious to a POSA in view of the '011 publication, alone or in combination with the '051 patent. (*Id.* at ¶ 174). Further, claim 16 would have been obvious to a POSA in view of the '011 publication, alone or in view of the Weir reference. (*Id.* at ¶ 180).

Claims 18, 19, 23, and 24 also depend from claims that recite surfactant-free formulations. Claims 18 and 23 are directed to the treatment of asthma, while claims

[14] The '051 patent issued on September 12, 1989 and antedates the '413 patent by more than one year. As such, it qualifies as prior art under 35 U.S.C. § 102(b).

[15] Weir was published in February of 1990 and antedates the priority date of the '413 patent by more than one year. It, therefore, qualifies as prior art under 35 U.S.C. § 102(b).

19 and 24 are directed to the treatment of COPD. The ’011 publication discloses aerosol beclomethasone dipropionate formulations (EX1007, p. 14, Table) and it was known at the time of the alleged invention that beclomethasone dipropionate in aerosol form was used to treat both asthma and COPD. (EX1009 at Abstract; EX1010 at Abstract, p. 112; EX1006, ¶¶ 173, 177-78). While claims 18, 19, 23, and 24 are anticipated in light of the known medical uses of the drug disclosed in the ’011 publication, the claims would have also been obvious to a POSA, who would have had a reasonable expectation of success in arriving at the alleged invention. (EX1006, ¶ 188). That is, claims 18 and 23 would have been obvious in view of the ’011 publication alone or in combination with the ’051 patent, and claims 19 and 23 would have been obvious in view of the ’011 publication alone or in combination with the Weir reference. (EX1006, ¶¶ 185-88).

C. The ’333 Publication Anticipates Claims 1-5, 14, and 20-22

International Patent Application Publication No. WO 1990/007333 (“the ’333 publication”) (EX1011), entitled “Fentanyl Containing Aerosol Compositions,” published July 12, 1990 and discloses analgesic formulations comprising fentanyl

suitable for administration by inhalation. (EX1011, p. 1). The '333 publication is prior art to the '413 patent under 35 U.S.C. § 102(b) regardless of the priority date.[16]

1. Independent Claim 1

The '333 publication discloses a formulation suitable for aerosol administration and containing a particulate drug. The '413 patent defines a suitable suspension aerosol formulation as "a formulation in which the drug is in particulate form and is substantially insoluble in the propellant." (EX1001 at 3:27-29). The '333 publication describes the use of "finely divided solid fentanyl or derivatives thereof" that can be mixed with a wide range of propellants, preferably Propellant 134a. (EX1011, p. 7, stating that "[p]ropellant 134a is preferred because of its ozone friendly properties").

The '333 publication states that "according to the present invention there is provided an *aerosol formulation comprising fentanyl* or a physiologically acceptable

[16] Although the '333 publication was disclosed to the PTO during prosecution of '280 application, the Examiner did not rely on it to reject any claim of the '413 patent, nor was it referenced during prosecution. The mere disclosure of the '333 publication during prosecution does not preclude its use in invalidating the claims of the '413 patent. *Liebel-Flarsheim,* 481 F.3d at 1378, 1381; *IPXL Holdings,* 430 F.3d at 1381-83.

derivative thereof *dispersed* or dissolved *in an aerosol propellant*." (EX1011, p. 2) (emphasis added). In particular, the '333 publication discloses:

> [t]he formulations used in the invention contain fentanyl or a derivative thereof either in solution or suspension in the aerosol propellant system, *optionally in the presence of a cosolvent*. . . . The compositions *may additionally* comprise one or more surface active agents, for example . . . fluorinated surfactants"

(EX1011, p. 2) (emphasis added).

The transitional phrase "consisting essentially of" does not save any of the '413 patent's claims from being anticipated by the '333 publication. The phrase "consisting essentially of" signals that an invention includes the ingredients recited in the claim and is only open to additional unlisted ingredients that do not "materially affect the basic and novel properties of the invention." *Ecolab*, 569 F.3d at 1343 (citation omitted). The cosolvent of the '333 publication is "optional[]," as is the surface active agent (*i.e.*, the surfactant). (EX1011, p. 2; EX1006, ¶ 84). Thus, the only materials that the formulation must contain are the fentanyl derivative and the propellant. (*Id*.) ("The formulations used in the invention contain fentanyl or a derivative thereof, either in solution or suspension in the aerosol propellant system .

. . .").[17] *See Upsher-Smith Labs.*, 412 F.3d at 1323 (reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component).[18]

Likewise, claim 1 of the '333 publication recites "[a]n aerosol formulation comprising fentanyl or a physiologically acceptable derivative thereof dispersed or dissolved in an aerosol propellant." (EX1011, p. 23). The language of the claim of the prior art reference, itself, indicates that there is no requirement for a solvent or a

[17] Claim 1 of the '413 patent does not require the inclusion of a surfactant or a cosolvent. Nonetheless, the '333 publication discloses, as an "*alternative system*," a composition containing "fentanyl or derivative thereof . . . coated with a dry coating or a perfluorinated surface-active dispersing agent and thereafter mixed with an aerosol propellant." (EX1011 at p. 4) (emphasis added). As such, even if claim 1 of the '413 patent is found to have a surfactant or cosolvent, the alternative system of the '333 publication had already disclosed that element.

[18] Although the working examples described in the '333 publication are specifically directed to formulations of fentanyl containing a surfactant as well as a propellant, the '333 publication is nevertheless relevant as prior art. *See Upsher-Smith Labs.*, 412 F.3d at 1323 (explaining that whether a reference "teaches away" from the claimed invention is irrelevant to an anticipation analysis).

surfactant.[19] (EX1006, ¶ 86). The '333 publication, therefore, anticipates claim 1 of the '413 patent as it discloses aerosol compositions "consisting essentially of" a particulate drug and a propellant, wherein the formulation does not contain any surfactant. (EX1006, ¶ 88).

2. Independent Claim 3

Independent claim 3 requires that the formulation of claim 1 be contained in an aerosol canister equipped with a metering valve to provide a plurality of therapeutically effective doses of the drug. The '333 publication discloses the metering valve limitation which would dispense multiple (*i.e.*, a plurality of) doses. (EX1011, p. 2) ("The invention also provides a pressurised aerosol inhaler comprising a container, containing an aerosol formulation as defined above, and a valve capable of dispensing metered *doses* of the formulation.") (emphasis added).

Furthermore, the '333 publication discloses using therapeutically effective weight amounts and explains that the "minimum concentration of the solid material is governed by its specific activity and in the case of a highly active material can be

[19] Furthermore, claim 1 of the '333 publication only requires the presence of fentanyl or a physiologically acceptable derivative and an aerosol propellant. "[S]olvents," "surface active agents," or "fluorinated surfactants" are not recited until dependent claims 4, 5, and 6 of the '333 publication. (EX1011, p. 23).

as low as 0.001% by weight of the total composition although a concentration of 0.01% is preferred." (EX1011, p. 7; *id.* (also disclosing other ranges as high as 20%); EX1006, ¶ 89). Thus, claim 3 is anticipated by the '333 publication. (EX1006, ¶ 90).

3. Independent Claim 4

Independent claim 4 is similar to claim 1 in that it requires one or more particulate drugs, 1,1,1,2-tetrafluoroethane as a propellant, and "is free of surfactant." As with claim 1, these elements are disclosed by the '333 publication. (EX1006, ¶ 91).

Claim 4 also requires that "the particulate drug or drugs be[] present in a therapeutically effective amount less than 1.6% w/w relative to the total weight of the formulation" and that "90% or more of the particles have a diameter of less than 10 microns." As with claim 3, the '333 publication discloses therapeutically effective doses of the drug. (EX1006, ¶¶ 90, 92). The '333 publication also states that "[t]he particle size of the powder for inhalation therapy should preferably be in the range 2 to 10 microns" (EX1011, p. 6) and, therefore, discloses the particle size limitation of claim 4. (EX1006, ¶ 94). The '333 publication anticipates claim 4 of the '413 patent. (*Id.*).

4. Independent Claims 5 and 14

Independent claims 5 and 14 require a particulate drug, 1,1,1,2-tetrafluoroethane, as propellant, and a formulation that is "substantially free of surfactant." The "alternative system" discussed above in connection with claim 1 provides for an inhaler containing "fentanyl or derivative thereof in the form of a finely divided solid . . . coated with a dry coating or a perfluorinated surface-active dispersing agent and thereafter mixed with an aerosol propellant." (EX1011, p. 4). "The preferred propellant for such a formulation is 1,1,1,2-tetrafluoroethane." (*Id.*).

The '333 publication also explains that perfluorinated surface-active dispersing agents are surfactants. (*Id*. at 4 ("The perfluorinated surface-active dispersing agents (hereinafter referred to as 'perfluorinated surfactants' or 'surfactants');" the "perfluorinated surface-active dispersing agent which constitutes at least 0.001%, normally 0.001 to 50%, preferably 0.001% to 20% by weight of the coated solid material."); EX1006, ¶ 96). Thus, the '333 publication discloses formulations that a POSA would consider "substantially free of surfactant" (*i.e*., 0.001%). (EX1006, ¶ 96).

Claims 5 and 14 differ in their preamble recitations and the '333 publication discloses both as shown in the table below:

Claim 5: "[a] metered dose inhaler containing a pharmaceutical suspension formulation	"The invention also provides a pressurized aerosol inhaler comprising a container, containing an aerosol formulation as defined

suitable for aerosol administration,"	above, and a valve capable of dispensing metered doses." (EX1011, p. 2).
Claim 14: "[a] method of treating a mammal having a condition capable of treatment by inhalation."	"Since the metered dose pressurized inhaler was introduced in the mid 1950's, inhalation has become the most widely used route for delivering bronchodilator drugs and steroids to the airways of asthmatic patients." (EX1011 at p. 1.) "The particle size of the powder for *inhalation therapy* should preferably be in the range 2 to 10 microns." (EX1011 at p. 6) (emphasis added). "Therefore according to the present invention there is provided an aerosol formulation comprising fentanyl or physiologically acceptable derivative thereof dispersed or dissolved in an aerosol propellant." (EX1011, p. 2).

Thus, claims 5 and 14 are anticipated by the '333 publication. (EX1006, ¶ 98).

5. Independent Claims 20, 21, and 22

Independent claims 20, 21, and 22 are similar to claim 1, requiring: (i) a particulate drug that is suitable for aerosol administration present in a therapeutically effective amount; (ii) 1,1,1,2-tetrafluoroethane as a propellant; and (iii) no surfactant.[20] As with claim 1, these elements are disclosed in the '333 publication.

[20] The claims recite "free of surfactant or contains less than a stabilizing amount of surfactant." Given that the claim is written in the disjunctive, a prior art reference

(EX1006, ¶ 88). Moreover, as with claim 4, the '333 publication discloses the "therapeutically effective amount" recitation. (EX1006, ¶ 94).

The differing preamble recitations of claims 20, 21, and 22 are disclosed in the '333 publication, as shown in the table below:

Claim 20: an "aerosol canister containing a formulation suitable for aerosol administration"	"[t]he invention also provides a pressurized aerosol inhaler comprising a container, containing an aerosol formulation as defined above, and a valve capable of dispensing metered doses." (EX1011, p. 2).
Claim 21: "metered dose aerosol canister containing a formulation suitable for aerosol administration."	"[t]he invention also provides a pressurized aerosol inhaler comprising a container, containing an aerosol formulation as defined above, and a valve capable of dispensing metered doses." (EX1011, p. 2).
Claim 22: "method of treating a mammal having a condition capable of treatment by inhalation."	"Therefore according to the present invention there is provided an aerosol formulation comprising fentanyl or physiologically acceptable derivative thereof dispersed or dissolved in an aerosol propellant." (EX1011, p. 2).

Therefore, the '333 publication discloses each of the limitations of claims 20, 21, and 22. (EX1006, ¶ 103).

6. Dependent Claim 2

Claim 2 depends from claim 1 and further requires that the particulate drug is micronized. In defining "micronized," the '413 patent states: "the drug is preferably micronized, *i.e.,* about 90 percent or more of the particles have a diameter of less

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disclosing a formulation that is free of a surfactant would invalidate the claim. *See SkinMedica*, 727 F.3d at 1199.

than about 10 microns . . . ." (EX1001, 3:57-59). The '333 publication teaches that "[t]he particle size of the powder for inhalation therapy should preferably be in the range 2 to 10 microns." (EX1011, p. 6). Thus, claim 2 is anticipated by the '333 publication. (EX1006, ¶ 104).

D. The '333 Publication Alone or in Combination Renders Obvious All of the Challenged Claims of the '413 Patent

Claims 1-5, 14, and 20-22 are anticipated by the '333 publication and also would have been obvious. *See Kalm*, 378 F.2d at 962 (a complete description of the invention in a prior art reference sufficient to anticipate a claim is the ultimate or epitome of obviousness).[21] Additionally, the '333 publication renders obvious the limitations set forth in claims 6-13, 15-19, 23, and 24. (EX1006, ¶¶ 196, 198, 209, 214, 222, 232-34).

1. The Base Limitations of Every Claim Would Have Been Obvious

The base limitations of every claim—*i.e.*, making an aerosol formulation using a particulate drug, using 1,1,1,2-tetrafluoroethane as a propellant, and having

[21] The level of skill of a POSA is described above. The scope and content of the '333 publication were discussed with regard to anticipation and all of the elements of the claims 1-5, 14, and 20-22 are explicitly disclosed in the '333 publication. Any differences between the challenged claims and the prior art is set forth below.

a surfactant-free or "substantially surfactant free" formulation—would have been obvious in light of the '333 publication. (EX1006, ¶ 190). The '333 publication would have provided the POSA explicit motivation to produce aerosol formulations that were either surfactant-free or "substantially surfactant free": "[f]or best results, the concentration of the perfluorinated surface-active agent[22] is kept at a minimum as it may tend to increase the droplet size of the aerosol particles." (*Id.* at 6; EX1006, ¶ 194).

Moreover, a POSA would have had a reasonable expectation of success in arriving at surfactant-free or "substantially surfactant free" formulations because the '333 publication discloses formulations in which the surfactant is optional. (*Id*. at 2 ("[T]he compositions *may additionally* comprise one or more surface active agents.") (emphasis added); EX1006, ¶ 195). The '333 publication also suggests that "best results" can be obtained if surfactants are kept at a minimum. (*Id*. at 6). Therefore, the base limitations of every claim would have been obvious in light of the '333 publication.[23] (EX1006, ¶ 196).

[22] As defined in the '333 publication, perfluorinated surface-active agents are surfactants. (EX1011, p. 4).

[23] This alone renders claims 1 and 14 obvious.

2. Equipping the Aerosol Canister with a Metering Valve Would Have Been Obvious

Claims 3, 5, 13, and 21 include a limitation requiring the use of a metering valve or making a metered dose inhaler. Dispensing the formulation through a metered dose inhaler would have been obvious to a POSA in light of the '333 publication, which states that "since the metered dose pressurized inhaler was introduced in the mid 1950's, inhalation has become the most widely used route for delivering [medication] . . . to the airways." (EX1011 at p. 1; EX1006, ¶ 197). The '333 publication further explains that pressurized inhalers were being used to dispense other medications not tied to the treatment of bronchial malady. (EX1001 at p. 1; EX1006, ¶ 197)

A POSA would have been motivated to use a metered dose pressurized inhaler because it is the "widely used route" for delivering medication via inhalers. Moreover, a POSA would have had a reasonable expectation of success in view of the fact that metered dose inhalers (i) have been in use since 1950, (ii) are "widely used," and (iii) were—in the words of the '413 patent—"conventional" (EX1001, 6:21-22; EX1006, ¶ 198).

3. Selecting Therapeutically Effective Amounts/Doses Would Have Been Obvious

Claims 3-4, 6-13, and 17-24 recite either the generic use of a therapeutically effective amount of a particulate drug or a specific percentage of the drug. *See*

claims 3, 6, 12-13, and 17-24 ("therapeutically effective"); claim 4 ("therapeutically effective amount less than 1.6% w/w relative to the total weight of the formulation"); claim 8 ("drug concentration is less than about 0.1 percent"); claim 9 ("drug concentration is greater than about 0.1 percent and less than about 0.5 percent"); claim 10 ("drug concentration is greater than about 0.5 percent"); claim 11 ("the drug has a potency such that a concentration of less than about 0.1 percent is therapeutically effective"). The '333 publication discloses all of these ranges and explains that the therapeutic amount of the drug is determined by "specific activity."

> The finely-divided solid material may constitute up to about 20% by weight of the total composition. Generally it will constitute up to 10%, normally up to 5% and preferably up to 3%, by weight of the total composition. The minimum concentration of the solid material is governed by its specific activity and in the case of highly active material can be as low as 0.001% by weight of the total composition although a concentration of 0.01% is preferred.

(EX1011, p. 7; EX1006, ¶ 200). Overlapping ranges establish a *prima facie* case of obviousness. *In re Peterson,* 315 F.3d 1325, 1329-30 (Fed. Cir. 2005); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990); *In re Malagari*, 499 F.2d 1297, 1303 (C.C.P.A. 1974). As for a reasonable expectation of success, determining the amount of drug to include in the formulation, including a therapeutically effective

amount, would fall well within the scope of routine experimentation as would have been carried out by a POSA. *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955); (EX1006, ¶ 201-03).

4. The Dispersibility/Flocculation Element Would Have Been Obvious

Claims 6-13 and 17-19 include the dispersibility/flocculation element. The '333 publication stresses that an effective aerosol formulation needs to remain in solution, not agglomerate, and explains that control of particle size can prevent such agglomeration. (EX1011, p. 6). The redispersibility limitation would have been obvious to a POSA because he or she would have had to make formulations that were "substantially and readily redispersible." This would have been a common problem and a POSA would have been able to resolve any redispersibility issues using routine experimentation such as controlling the particle size of the drug and—if that did not resolve the problem—a POSA could also have used routine techniques such as controlling particle distribution, controlling the particle concentration, changing the morphology of the particles, or testing different salt forms of the drug. (EX1006, ¶¶ 206-09).

As to the flocculation limitation, it would have been obvious to a POSA at the time as he or she would have been able to resolve any flocculation issues using routine experimentation because it is a common issue. (EX1006, ¶¶ 210-11). If controlling the particle size of the particulate drug did not resolve a flocculation

problem, a POSA could also use routine techniques such as controlling particle distribution, controlling the particle concentration, changing the morphology of the particles, or changing the salt form of the drug. (EX1006, ¶¶ 211-14).

Therefore, a POSA would have been motivated to prevent agglomeration and create a solution that is redispersible. And a POSA would have had a reasonable expectation of success in preventing these undesirable outcomes by following the particle size instructions set forth in the '333 publication. (EX1011, p. 6) ("since larger particles may tend to agglomerate, separate from the suspension").

Moreover, these claim limitations are unpatentable, inherent properties of the formulation. *See Santarus*, 694 F.3d at 1354. The dispersibility/flocculation element of claims 6-13 and 17-19 would have been obvious. (EX1006, ¶¶ 205-14).

5. Selecting a Micronized Drug Particulate, or a Particulate Drug wherein 90% or More of the Particles Have a Diameter of Less than 10 microns, Would Have Been Obvious

Claim 2 requires that the "particulate drug is micronized" and claim 4 recites that "90% or more of the [drug] particles have a diameter of less than 10 microns." As to "micronized," the '413 patent states that "the drug is preferably micronized, *i.e.*, about 90 percent or more of the particles have a diameter of less than about 10 microns . . . ." (EX1001, 3:57-59). The selection of either of these criteria would have been obvious from the disclosure of the '333 publication.

The ’333 publication states that “the particle size of the powder for inhalation therapy should preferably be in the range of 2 to 10 microns” in order to reduce the tendency for particles to agglomerate, separate from suspension, or clog the valve or orifice of the aerosol container. (EX1011, p. 6). The ’333 publication encourages a POSA to use particles with a size range of 2 to 10 microns to address these problems. (EX1006, ¶ 217). Therefore, the selection of micronized particles (claim 2) or a formulation where “90% or more of the [drug] particles have a diameter of less than 10 microns” (claim 6) would have been obvious from the disclosure of the ’333 publication, and a POSA would have had a reasonable expectation of success. (*Id.*).

6. Selecting a Formulation that Exhibits Substantially No Growth in Particle Size Would Have Been Obvious

Claim 7 recites the disjunctive limitation that the “formulation exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period.” The ’333 publication repeatedly stresses the need to prevent growth in the particle size and discloses how such growth can be prevented. For example, the ’333 publication states that using smaller particle sizes reduces the tendency to agglomerate. (EX1011 at p. 6) (“The particle size of the powder should desirably be no greater than 100μm diameter, since larger particles may tend to agglomerate, separate from the suspension and may clog the valve or orifice of the container.”). Accordingly, selecting a formulation that “exhibits substantially no growth in particle size” would have been obvious from the disclosure of the ’333

publication and a POSA would have had a reasonable expectation of success of limiting particle growth by, *inter alia*, implementing the solutions provided therein. (EX1006, ¶ 222).

7. Using Surfactant-Less or Substantially Surfactant-Free Formulations for the Treatment of Asthma or COPD Would Have Been Obvious

Dependent claims 15, 18, and 23 are directed to using the surfactant-less or substantially surfactant-free formulations for the treatment of asthma while claims 16, 19, and 24 are directed to the treatment of COPD. The '333 publication renders such uses obvious.

The '333 publication explains that inhalers, including metered dose inhalers, are the "most widely used route" for the treatment of "asthmatic patients" or other "bronchial malady." (EX1011, p. 1; EX1006, ¶ 224). This disclosure would also have motivated a POSA to use another drug in place of fentanyl derivatives to treat other bronchial diseases, including asthma or COPD. (EX1006, ¶ 224). Moreover, the successful use of inhalers in treating bronchial disease was well-known in the art, and a POSA would have had a reasonable expectation of success of treating maladies such as asthma and COPD by combining the surfactant-less (or substantially surfactant-free) formulations disclosed in the '333 publication with a particulate drug known to be effective in treating bronchial disease. For example, the drug beclomethasone dipropionate can be administered via inhalation for the

treatment of COPD and asthma. (EX1009, 1:15-27 (disclosing use of beclomethasone dipropionate for asthma); EX1010, p. 112 (disclosing use of beclomethasone dipropionate for COPD); EX1006, ¶¶ 226-30). Therefore, claims 15, 16, 18, 19, 23, and 24 would have been obvious to a POSA in view of the '333 publication, alone, or in combination with the '051 patent or the Weir reference. (EX1006, ¶ 231).

E. Objective Indicia of Non-Obviousness

As the challenged claims are anticipated, objective indicia have no relevance since they are only relevant to the obviousness inquiry. *Bristol-Myers Squibb Co. v. Ben Venue Labs.*, 246 F.3d 1368, 1380 (Fed. Cir. 2001). Although objective indicia of non-obviousness must be taken into account in the obviousness calculus, they do not necessarily control the obviousness conclusion. *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988).

A strong case of obviousness, such as the instant one, cannot be overcome by objective evidence of non-obviousness. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2008); *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1334 (Fed. Cir. 2014). To the extent 3M does in fact assert any objective indicia in this proceeding, detailed consideration of 3M's evidence should not be undertaken until Petitioner has had an opportunity to respond to 3M's position. *Amneal*

Pharmaceuticals, LLC v. Supernus Pharmaceuticals, Inc., IPR2013-00368 [Paper 8, pp. 12-13].

X. CONCLUSION

Petitioner has demonstrated by a preponderance of the evidence that claims 1-24 of the ’413 patent are unpatentable as anticipated and/or obvious over the prior art cited herein and respectfully requests that the Board so find.

RESPECTFULLY SUBMITTED,

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CERTIFICATION OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e), 42.8(b)(4) and 42.105, the undersigned certifies that on the 29th day of September, 2015, a complete copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 6,743,413, Power of Attorney, Exhibit List, and all supporting exhibits were served via UPS® to the Patent Owner by serving the correspondence address of record for the '413 patent:

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Respectfully submitted,

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