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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COMPLEX INNOVATIONS, LLC,

Petitioner,

v.

ASTRAZENECA AB,

Patent Owner

Case IPR2017-TBA

U.S. Patent 7,759,328

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,759,328

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EXHIBIT LIST

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Ex. 1002 The file history of the '328 Patent

Ex. 1003 U.S. Patent No. 6,123,924 ("Mistry")

Ex. 1004 World Intellectual Property Organization, Intl. Publication No. WO 02/03958 ("Rogueda")

Ex. 1005 U.S. Pat. No. 5,674,860 ("Carling")

Ex. 1006 World Intellectual Property Organization, International Publication No. WO 99/64014 ("Ekström")

Ex. 1007 U.S. Pat. App. Publ. No. 2003/0018019 ("Meade")

Ex. 1008 U.S. Pat. No. 8,142,763 ("Lewis")

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Ex. 1015 PATHOLOGIC BASIS OF DISEASE (Robbins, 5th Ed. 1994).

Ex. 1016 Declaration of Sharad K. Bijanki, Esq.

I. Introduction

Petitioner submits this Petition to address AstraZeneca's improper attempt to extend patent protection for its blockbuster drug Symbicort®. Symbicort® utilizes the active pharmaceutical ingredients ("APIs") of formoterol and budesonide for use in treating respiratory disorders and other diseases. Both improve airway flow—formoterol is a bronchodilator that acts by relaxing smooth muscles in the airway, and budesonide is a corticosteroid that reduces and prevents inflammation of the airway. AstraZeneca has owned base patents covering Symbicort® since at least 1997. (*See* U.S. Patent No. 5,674,860, filed October, 3, 1994 (the "Carling" patent, submitted herein as Ex. 1005)).

AstraZeneca has filed numerous subsequent patents seeking to extend patent protection for the billion dollar Symbicort® market. AstraZeneca is doing this through a process called "evergreening" – simply reformulating a drug through techniques well known to pharmaceutical scientists. The challenged patent here, U.S. Patent No. 7,759,328 ("the '328 Patent," submitted herein as Ex. 1001), is one such patent. It purports to cover an inhalation formulation of the same APIs claimed in Carling but reformulated using the excipients polyvinylpyrrolidone ("PVP") and polyethylene glycol ("PEG"). However, the use of PVP and PEG in formulations, including to enhance the stability of inhalation formulations, was well known prior to the time of the purported invention. The '328 Patent adds

nothing innovative and should never have issued. For this reason, as detailed further below, Petitioner respectfully submits that this Petition should be granted.

A. The Petitioner – Complex Innovations LLC

Complex Innovations LLC (referred to as "Petitioner" or "Complex Innovations", www.comlexinnovations.com), is an advocate for a patent system that benefits all. All participants – the inventor, the patent office, and the public – deserve a system where the outcome encourages true innovation while at the same time protecting the public. Petitioner thinks that too often pharmaceutical companies improperly seek extensions of the patent protection through "evergreening" – simply reformulating a drug through techniques well known to pharmaceutical scientists. This is to the detriment of the consumer in the form of higher prices and diminished alternatives, and is an abuse of the system. Petitioner challenges these patents, seeking to have the patents released to the public domain such that others can manufacture the drugs, thereby lowering costs to the consumer.

Here, AstraZeneca's original patents covering Symbicort®, a product with over $1 billion in annual sales in the United States, have expired or are expiring. In advance of expiration, AstraZeneca began a campaign of "evergreening." The '328 patent is a result of this "evergreening" campaign. The means by which AstraZeneca obtained the alleged improvement in stability was well known in the

prior art. The ’328 Patent never should have issued. It adds nothing novel to the art because, as is shown below in Grounds I-IV, each and every claimed element had already been anticipated or rendered obvious by the 35 U.S.C. § 102(b) references, including Mistry (Ex. 1003), Rogueda (Ex. 1004) and other prior art.

Thus, Petitioner files this Petition to stop the ’328 patent from improperly extending AstraZeneca’s Symbicort® patent protection, and by extension, its ill gained profits.

B. Anticipatory Prior Art

The most important patent covering Symbicort® is Carling. Carling claims the use of formoterol (a beta-agonist bronchodilator) and budesonide (an anti-inflammatory steroid) for administration by inhalation for the treatment of inflammatory respiratory disorders such as asthma. (Ex. 1005, Abstract). The inhalation system disclosed in Carling utilizes chlorofluorocarbons (“CFCs”). (*Id.*, 4:4-5).

As discussed in the expert declaration of Martin Beasley, Ph.D., a pharmaceutical scientist with over twenty-five years of industry experience in pharmaceutical drug development including inhalation formulations, policymakers in the late 1980s came to understand that CFCs released into the atmosphere had a detrimental effect on the earth’s ozone layer. (Ex. 1012, ¶¶ 19, 21). Consequently, the pharmaceutical industry sought to quickly reformulate inhaled drugs with non-

CFC ingredients. (*Id.*, ¶¶ 19, 21-23). Put another way, the regulatory environment created a strong motivation to combine known APIs with alternative propellants and other excipients.

One location of this reformulation work was in Leicestershire England, the location of several pharmaceutical reformulation inventors. (Ex. 1012, ¶ 19). Two sets of these inventors, different than those of the ’328 patent, actually discovered and published non-CFC reformulations, including formoterol and budesonide as APIs, before the effective filing date of the ’328 patent. (*Id.*). These publications render the ’328 patent invalid based on anticipation. (*Id.*; *see also* Grounds I and II).

Specifically, Mistry, which issued in 2000 (and was based on research from as early as 1991), anticipates Claims 1 and 4-15 of the ’328 Patent by providing a detailed description of a stable HFA medicament formulation comprising budesonide and formoterol with all of the same limitations as the ’328 Patent. (*See* Ground I Analysis). And the Rogueda reference—filed by AstraZeneca and published January 17, 2002, days before the ’328 Patent was filed in Sweden, and over a year before its PCT filing date—actually refers to “Symbicort™

(budesonide and formterol)". (Ex. 1004, p. 3, lines 4-5).[1] In fact, the Rogueda reference's experimental and control samples have a distinctive resemblance to the claims of the '328 Patent listed for Symbicort. (*See* Ground II Analysis). The Rogueda reference anticipates Claims 1 and 4-15 of the '328 Patent. (*See id.*)

C. Obviousness of the '328 Patent Claims

Furthermore, Mistry in view of Rogueda and Carling renders Claims 1 and 4-15 of the '328 patent obvious, and Mistry in view of Rogueda, Meade and Lewis renders obvious claims 2 and 3 of the '328 patent. (*See* Grounds III, IV Analysis).

As discussed in Dr. Beasley's declaration, at best, any development of formulations having the stability attributes described in the '328 Patent was the result of mere routine formulation work that was based on known and expected properties of commonly used formulation additives. (*See, e.g.*, Ex. 1012, ¶¶ 40-48, 57, 79; *see also* Ground III Analysis).

The PTAB frequently has instituted decisions based on obviousness where the formulation development stemmed from mere routine experimentation. For instance, the PTAB recently issued a final written decision arising from a petition filed by "Coalition for Affordable Drugs II LLC" which found claims unpatentable

[1] The trademark Symbicort was filed as early as 1994 (*see* Trademark Reg. No. 1885787), or perhaps even 1992 (*see* Trademark Serial No. 74285663).

because they were based on such routine formulation and experimentation. (*See, e.g.*, *Conopco, Inc. DBA Unilever v. Procter & Gamble Co.*, IPR2013-00505, 2014 WL 1253037 at *6-7 (Patent Tr. & App. Bd. Feb. 12, 2014); *Endo Pharm., Inc., v. Depomed, Inc.*, IPR2014-00652, 2014 WL 4925712, at *10 (Patent Tr. & App. Bd. Sept. 29, 2014); *Coalition for Affordable Drugs II LLC v. NPS Pharm., Inc.*, IPR2015-00990, Decision to Institute, Paper 28 at 19 (Patent Tr. & App. Bd., Oct. 23, 2015); *Coalition for Affordable Drugs II LLC v. NPS Pharm., Inc.*, IPR2015-00990, Final Written Decision, Paper 68 at 26, 29 (Patent Tr. & App. Bd., Oct. 21, 2016) ("The preponderance of evidence of record shows that the identification of the optimal sugar and amino acid to add to a formulation for stability purposes was nothing more than routine experimentation." and "We, thus, determine that Petitioner has established that the claimed GLP-2 formulations, methods, and kits are a combination of known ingredients for a predictable result of stability achieved by routine testing.") (emphasis added)).

The Court of Appeals for the Federal Circuit likewise has stated that routine formulation and optimization ordinarily results in formulations that are obvious:

> We find this case analogous to the optimization of a range or other variable within the claims that flows from the "normal desire of scientists or artisans to improve upon what is already generally known." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (determining

> where in a disclosed set of percentage ranges the optimum combination of percentages lies is prima facie obvious). In *In re Aller*, 42 C.C.P.A. 824, 220 F.2d 454, 456 (1955), our predecessor court set forth the rule that the discovery of an optimum value of a variable in a known process is usually obvious. *See also In re Boesch*, 617 F.2d 272, 276 (C.C.P.A.1980) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.").

See Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1368 (Fed. Cir. 2007).

II. Mandatory Notices (37 C.F.R. § 42.8(a)(1))

A. Notice of related matters (37 C.F.R. § 42.8(b)(2))

Petitioner is aware from the public Patent Application Information Retrieval system that United States Patent Application Number 15/186,665, filed on June 20, 2016, is listed as "Pending" and apparently claims the benefit of United States Patent Application Number 10/502,685, the same application to which the '328 Patent claims priority. Petitioner was unable to access the file history of the U.S. Appl. No. 15/186,665. Petitioner is not aware of any other judicial or administrative matter that would affect, or be affected by, a decision in the proceeding.

B. Real party-in-interest (37 C.F.R. § 42.8(b)(1))

The real party in interest is: Complex Innovations LLC.

C. Notice of Counsel and Service Information (37 C.F.R. § 42.8(b)(3-4))

Lead Counsel: Sharad K. Bijanki (Reg. No. 73,400)

Backup Counsel: Vivek Ganti (Reg. No. 71,368)

Address: HILL, KERTSCHER & WHARTON, LLP, 3350 Riverwood Parkway SE, Suite 800, Atlanta, GA 30339. Tel. 770.953.0995. Fax. 770.953.1358.

Petitioner consents to electronic service of papers by email at: sb@hkw-law.com, and vg@hkw-law.com. Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney by Petitioner appointing each of the above designated counsel is concurrently filed.

III. Grounds for Standing and Fees

Petitioner certifies that the ’328 Patent is eligible for *inter partes* review and that the Petitioner is not estopped or barred from requesting *inter partes* review challenging the claims identified in the Petition.

The undersigned provides an online USPTO deposit account to pay the required fees ($9,000 request fee and $14,000 post-institution fee), as set forth in 37 C.F.R. § 42.15(a) for this Petition. The undersigned further authorizes payment for any additional fees (or fee deficiency) that might be due in connection with this Petition to be charged to the Deposit Account 506541 (Customer ID No. 87296).

IV. Statement of Relief Requested and Overview of the Challenge

Petitioner requests *inter partes* review and cancellation of claims 1-15 of the '328 Patent based on the statements presented below.

A. Prior Art Patents and Printed Publications

The'328 Patent's foreign filing date is Feb. 1, 2002 in Sweden. Its PCT filing date is January 29, 2003. And its date under § 371 (c)(1), (2), and (4) is July 27, 2004. Accordingly, Petitioner identifies the following prior art references relied upon in its invalidity grounds.

1. Mistry

U.S. Patent No. 6,123,924 ("Mistry," submitted herein as Ex. 1003), issued September 26, 2000, is prior art as an issued patent under 35 U.S.C. § 102(b). Mistry teaches a stable formulation of budesonide and formoterol with the same three additional ingredients as claimed by the '328 Patent, *i.e.*, an HFA 227 propellant, polyvinylpyrrolidone ("PVP"), and polyethylene glycol ("PEG"). (*See, e.g.*, Ex. 1012, ¶¶ 58-81). Mistry was developed, as noted above, in response to policymaking pressures effectively banning CFCs that previously had been used in Symbicort formulations. (Ex. 1012, ¶¶ 28-30).

Mistry's formulation relates to the development of a stable HFA 227 formulation through the addition of PVP, within a preferred range of K-values, and at certain concentrations. (Ex. 1012, ¶ 30). While the anticipatory ranges of K-values and concentrations are wider than those claimed by the '328 Patent, there is

nothing suggesting or indicating that these ranges are not of critical importance to Mistry for stability. This is evident at least from the claims of Mistry. (Ex. 1012, ¶¶ 70-74). There simply is nothing inventive regarding the narrower ranges claimed in the ’328 Patent.

2. Rogueda

World Intellectual Property Organization, International Publication No. WO 02/03958 (“Rogueda,” submitted herein as Ex. 1004), was filed on July 10, 2001, and claims priority to a Great Britain application filed on July 11, 2000. Rogueda describes the same active and inactive ingredients as claimed by the ’328 Patent, and at the same concentrations too. (*See* Ground II and III below).

Rogueda published on January 17, 2002, over one year prior to the ’328 Patent’s filing date under either the PCT, or its filing date under § 371 (c)(1), (2), or (4). Therefore, Rogueda is prior art under pre-AIA 35 U.S.C. § 102(b). (*See* pre-AIA 35 U.S.C. §§ 104, 119 (stating: “but no patent shall be granted on any application for patent for an invention which had been patented or described in a printed publication in any country more than one year before the date of the actual filing of the application in this country.”)). Because Rogueda has a different inventive entity it is also a 102(a) reference.

Given the distinctive similarities between Rogueda and the claims of the ’328 Patent, and by analyzing the inventors’ residences, Dr. Beasley suggests that

the research for both the ’328 Patent and Rogueda came from the same laboratory in England that AstraZeneca purchased from a former competitor (Fisons, PLC), and from which Mistry originated too. (Ex. 1012, ¶¶ 28, 34). It is possible that Rogueda reflects the testing data later claimed by the ’328 Patent. Regardless, however, it is 102(b) prior art. Even if the ’328 patent can claim priority to its Swedish application, its priority claim cannot overcome publications more than a year prior to its actual filing date in the United States. (*See* pre-AIA 35 U.S.C. §§ 102(b), 104, 119).[2]

3. Carling

U.S. Pat. No. 5,674,860 (“Carling,” submitted herein as Ex. 1005), published on October 7, 1997, and is prior art under 102(b). Carling was one of the original patents to teach the combination of the active ingredients of Symbicort, *i.e.*, budesonide and formoterol, for the treatment of various respiratory conditions. (Ex. 1012, ¶ 25). As an important, early Symbicort patent, Carling has been the

[2] It is possible that AstraZeneca waited as long as possible before filing the PCT application that led to the ’328 patent, and in doing so effectively caused the Rogueda research to become a 102(b) reference against itself. Practitioners Millauer and White describe such a scenario as the “102(b) foreign filing catch”. (*See* Ex. 1014 pp. 1-3).

subject of other AstraZeneca attempts to improperly extend its monopoly on Symbicort. After about eight years, between 2006 and 2014, and two requests for reconsideration, AstraZeneca failed in trying to extend the monopoly granted by Carling past its natural termination date, based on alleged FDA delays under 35 U.S.C. § 156. (*See* Ex. 1013 at pp. 1-2 (explaining procedural background)). The USPTO, on advice of the FDA, denied AstraZeneca's petition, and denied its requests for reconsideration by, *inter alia*, applying longstanding law and policy that the combination of two prior art active ingredients did not create a "new drug" under 35 U.S.C. § 156. (*Id.* at p. 4). Following the USPTO's rejections of AstraZeneca's filings, the Carling Symbicort patent expired pursuant to its regular term.

4. Ekström, Meade, and Lewis

World Intellectual Property Organization, International Publication No. WO 99/64014 ("Ekström", submitted herein as Ex. 1006), published on December 16, 1999 and is prior art under § 102(b). Ekström teaches a broad range of ratios of formoterol to budesonide for an inhalable pharmaceutical formulation. (Ex. 1012, ¶¶ 27, 97).

U.S. Pat. App. Publ. No. 2003/0018019 ("Meade", submitted herein as Ex. 1007), published on January 23, 2003. Its filing date was on June 17, 2002, and it claims priority to a provisional application filed on July 10, 2001. Therefore,

Meade is 102(e) and 102(a) prior art. Meade teaches a formulation with a formoterol fumarate dihydrate R, R-enantiomer that can increase stability. (*See, e.g.*, Ex. 1007, pp. 1-2, ¶ 0010, 0012 ; p. 14, ¶ 0097; *see also* Ground III).

U.S. Pat. No. 8,142,763 ("Lewis", submitted herein as Ex. 1008), published on March 27, 2012. Lewis claims priority to at least Nov. 23, 1999, and is 102(e) prior art. Lewis teaches a budesonide 22R-epimer in a stable formulation with less interaction with the walls of an inhaler canister. (*See, e.g.*, Ex. 1008, 3:6-11; 3:27-67; 4:5-15; 5:13-17; 6:16-20; 6:43-47; *see also* Ground IV).

B. Overview of Grounds for Unpatentability

Petitioner challenges claims 1-15 of the '328 Patent, which is all of the claims, as unpatentable under pre-AIA 35 U.S.C. §§ 102 and 103.

This Petition is supported by the Declaration of Dr. Martin Beasley (submitted herein as Ex. 1012), who has more than 25 years of experience in the pharmaceutical development field. (Ex. 1012, ¶ 7; Ex. 1011). Pertinent to this Petition, Dr. Beasley obtained his Ph.D. in Pharmaceutical Sciences in 1985. (*Id.*). He worked as a Senior Scientist for Schering-Plough from 1985 to 1988, during which time he worked on formulation development including nasal sprays. (Ex. 1012, ¶ 8). From 1991 to 1997, Dr. Beasley served as a Senior Manager, Formulations Development Laboratory for the pharmaceutical company AAI. (Ex. 1012, ¶ 9, Ex. 1011). Dr. Beasley coordinated and directed product

development for AAI, working with up to eighteen (18) formulation scientists and working on formulations that included an anti-asthma formulation. (*Id.*). And from 2001 to 2011 Dr. Beasley worked as Director and Senior Director in Pharmaceutical Development for King Pharmaceuticals Research and Development, Inc., which work included due diligence regarding pressurized dose inhalers for treatment of asthma and chronic obstructive pulmonary disorder. (Ex. 1012, ¶ 10, Ex. 1011).[3]

Dr. Beasley is at least a person of ordinary skill in the art (POSITA) with respect to the invalidity analysis of the '328 Patent and its Claims 1-15. (Ex. 1012, ¶¶ 7-12). The prior art read in light of Dr. Beasley's Declaration demonstrates a reasonable likelihood that Petitioner should prevail with respect to the challenged claims. The Grounds proposed are:

Ground I: Mistry anticipates Claims 1 and 4-15.

Ground II: Rogueda anticipates Claims 1 and 4-15.

Ground III: Mistry in view of Rogueda and Carling renders obvious Claims 1 and 4-15.

[3] Petitioner notes that Dr. Beasley's Declaration (Ex. 1012) may cite the native page numbers for some references, including Ex. 1004 "Rogueda," as opposed to the page numbers provided by Petitioner (to which the Petition cites).

Ground IV: Mistry in view of Rogueda, Meade, and Lewis renders obvious Claims 2 and 3.

V. Overview of the '328 Patent

A. The Research Described in the '328 Patent

The '328 Patent admits, as it must, that the combination of formoterol and budesonide, sold under the name Symbicort®, was known in the art. (Ex. 1001, 1:25-27). Carling confirms this point. The '328 Patent then goes on to state: "It has now been found that certain HFA formulations comprising formoterol and budesonide together with polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) exhibit excellent physical suspension stability." (*Id.*, 1:32-35). But HFA was a well-known alternative to CFCs; PVP was a well-known stabilizer; PEG was a well-known valve lubricant; and all three had been taught in the prior art together in budesonide and formoterol formulations. (*See* Ex. 1012, ¶¶ 29-30, 32-33, 37-38, 40, 45, 47). The APIs in these formulations, budesonide and formoterol, are used to treat a variety of conditions and disorders by acting to increase air flow via anti-inflammation and bronchodilation.

1. HFA 227

Hydrofluroalkanes or HFAs were one of the primary propellants that pharmaceutical scientists looked toward to replace CFCs. (Ex. 1012, ¶¶ 21, 26, 30). The '328 Patent uses HFA 227. (*Id.*, ¶ 36; Ex. 1001, 8:18-19). By the critical prior art date of the '328 Patent, *i.e.*, January 29, 2002, over one year before the PCT

filing date, HFA 227 had been tested, used, and was preferred in the prior art, even among other hydrofluoroalkanes. (*See* Ground I, Limitation 1(a) Analysis; *see also* Ex. 1012, ¶¶ 27, 60, 92; Ex. 1006 at p. 8, lines 26-30; Ex. 1003, 2:64-65). This is a critical backdrop that the applicants of the '328 Patent failed to bring to the attention of the examiner.

2. Polyvinylpyrrolidone ("PVP")

Proper stability is important in many drug formulations including formulations relating to inhalant delivery systems. (Ex. 1012, ¶ 40). The particles of the API must be suspended, neither falling out of suspension and accumulating on the bottom of the vessel, nor rising to the top of the vessel. (*Id.*). This goal is reached by making sure that the viscosity of the formulation is correct. (*Id.*). Viscosity is the thickness or stickiness of a fluid or semi-fluid substance under sheer. (*Id.*)

The use of PVP as a stabilizer was well known in the art prior to the priority date of the '328 patent. (Ex. 1003, 1:65-67, 2:4-11, 12:1-9; Ex. 1007, ¶ 0050; Ex. 1008, 3:57; Ex. 1012, ¶¶ 38, 40, 45). In fact, PVP is widely known to pharmaceutical scientists as a common pharmaceutical additive affecting viscosity, and also as a suspending and stabilizing agent. (Ex. 1012, ¶ 40; *see* Ex. 1002, pp. 275-76, 288-94 (citing 3rd edition of the Handbook of Pharmaceutical Excipients, published in 2000 and submitted by applicants in prosecution of the '328 Patent)).

The K-value of PVP, determined by the Fikentscher equation, relates to the viscosity of the PVP, and therefore, PVPs at different K-values and concentrations can yield different viscosities in the formulation. (Ex. 1012, ¶¶ 40, 43, 71). In the '328 Patent, the only PVP tested was at a K-value of 25 (Ex. 1001, 1:46-48), although PVPs at other K-values also were known as formulation stabilizers. (Ex. 1012, ¶¶ 38, 40, 43 (explaining that K-values correspond to PVP molecular weight), 45, 56; Ex. 1002 at pp. 288-94; Ex. 1003 1:65-2:11).

The '328 Patent stresses that the concentration of PVP K-25 at 0.001% w/w "has been found to give consistently stable formulations over the required dose range, incorporating a wide range of concentrations of the active components. . . ." (Ex. 1001, 2:17-20). Critical here, the '328 Patent never states or otherwise contends that this finding was unexpected or novel or unanticipated. Moreover, the applicants made a false statement regarding PVPs. While the '328 Patent states that a PVP at 0.001% w/w is "at a much lower concentration than indicated in the prior art" (*id.*, 2:19-20)— Dr. Beasley shows how this is false, based no less on the Mistry prior art. (Ex. 1012, ¶ 41 (explaining that Mistry teaches a PVP concentration lower by a factor of 100 compared to the '328 Patent); *see also id.* ¶ 42 (citing to Ex. 1002, p. 317)).

3. Polyethylene Glycol ("PEG")

PEG is a relatively simple repeating hydrocarbon chain and therefore comes in a variety of molecular weights; it is also a very common additive to pharmaceutical formulations. (Ex. 1012, ¶ 47; Ex. 1002, pp. 275-76, 281 (stating, from Handbook of Pharmaceutical Excipients, (3rd Ed. 2000), that "[p]olyethylene gylcols are widely used in a variety of pharmaceutical formulations" including oral preparations)).

Return force is related to the force of the propellant and medicament when it leaves the inhaler upon actuation. Including a lubricant in the formulation allows for a higher return force, and a sufficient return force is of "critical importance for administration of prescription medicament to a patient or consumer." (Ex. 1012 at ¶ 57). The routine formulation in the '328 Patent indicated that PEG, a common valve lubricant, in certain concentrations allowed for a formulation with a slightly higher return force over 120 actuations of an inhaler, although in the range of 20-40 actuations it had a slightly lower return force. (*See, e.g.*, Ex. 1001, Fig. 7, p. 8; Ex. 1012, ¶ 48).

The '328 Patent only tested and used PEG at an average molecular weight of 1000, and apparently, the PEG 1000 used in the '328 Patent was stable at all tested concentrations except for the lowest, 0.005% by weight. (*See, e.g.*, Ex. 1001, Fig. 8, p. 9; Ex. 1012, ¶ 48). As shown in Grounds I-III below, using PEG as an inhaler

lubricant at the claimed concentration and molecular weight was anticipated and obvious in light of the prior art.

B. Level of Skill in the Art

A person of ordinary skill in the art (POSITA) with respect to the '328 Patent possesses a Bachelor of Science degree, or an equivalent, in chemistry, pharmacy, or a related field with at least two years of relevant experience in respiratory drug delivery and development, including formulation work and stability studies. (Ex. 1012, ¶ 12). As stated above, Dr. Beasley is at least a POSITA with respect to the invalidity analysis of the '328 Patent and its Claims 1-15. (*Id.*, ¶¶ 7-12).

C. Representative Claimed Embodiment of the '328 Patent

Exemplary claim 1 of the '328 Patent, from which Claims 2-11 ultimately depend, and which encompasses Claims 12-15, contemplates a pharmaceutical formulation with active ingredients budesonide and formoterol, and with inactive ingredients PVP, PEG, and HFA227 (*see* Ex. 1012, ¶¶ 50, 58):

> A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, 1,1,1,2,3,3,3-heptafluoropropane (HFA227), PVP K25 (polyvinyl pyrrolidone with a nominal K-value of 25), and PEG-1000 (polyethylene glycol with an average molecular weight of 1,000), wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

(Ex. 1001, p. 21, 8:17-26 (emphasis added)).

VI. Claim Construction

A. Applicable Principles of Claim Construction

The Board should construe the claims using the broadest reasonable interpretation ("BRI")—a claim in an unexpired patent that will not expire before a final written decision is issued shall be given its broadest reasonable construction in light of the specification of the patent in which it appears. *See* 37 C.F.R. § 42.100(b). Petitioners propose BRI-based constructions of terms herein solely for purposes of the *inter partes* review ("IPR") proceeding as provided by 37 C.F.R. §§ 42.100(b) and 42.104(b)(3). A BRI of a claim term may be the same as or broader than the construction under the *Phillips* standard, but not narrower. *See, e.g.*, *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142, 195 L. Ed. 2d 423 (2016) (holding that USPTO's statutory authority allows it to give claims a broader meaning than the standard under *Phillips*); *Facebook, Inc. v. Pragmatus AV, LLC*, 582 Fed. App'x 864, 869 (Fed. Cir. 2014), *reh'g denied* (Oct. 30, 2014).

Here, pursuant to 37 CFR 42.104(b)(3), Petitioners submit that the plain and ordinary meaning should apply to all claims. There is no need for the Board to provide an express claim construction to resolve the dispute over invalidity.

VII. The Grounds for Unpatentability

As required by 37 C.F.R. § 42.104(b)(4)-(5), this section details how the teachings of the prior art anticipate or render obvious the challenged claims.

Petitioner adopts Dr. Beasley's claim element formatting of the '328 Patent in the interest of clarity—Dr. Beasley combines into one claim element those elements that describe the same chemical entities twice in Claim 1. (Ex. 1012, ¶ 58). For example, budesonide is listed twice in Claim 1, before and after the "wherein" clause. (Ex. 1001, p. 21, 8:16-26). Therefore, Dr. Beasley combines both of the budesonide references into Claim element 1(c). (Ex. 1012, ¶ 58). As he notes, this is a "more logical format because following the claim consecutively as written would lead to repetitive analysis and about double the number of claim elements." (*Id.*).

Further, Dr. Beasley finds that Claims 12-15 only differ from Claim 1 in budesonide concentration. (Ex. 1012, ¶ 50). However, Claims 12-15 "specify single points of concentration for budesonide," but "all of the points are still within the range of Claim 1." (*Id.*). Therefore, given that the ranges of Claim 1 fully embody Claims 12-15, Dr. Beasley did not analyze Claims 12-15 separately. (Ex. 1012, ¶ 58). Instead, he analyzes them as part of Claim element 1(c) regarding the concentration of budesonide, which is the only limitation that changes in Claims 12-15. (*Id.*). Petitioner here adopts the same approach and agrees with Dr. Beasley's findings that Claims 12-15 are fully embodied within the ranges of Claim 1.

A. Ground I: Mistry Anticipates Claims 1 and 4-15 of the '328 Patent

1. Overview of Mistry (Ex. 1003)

As noted above, Mistry was the product of research by Fisons, PLC, a British competitor of the predecessor to AstraZeneca. (Ex. 1012, ¶ 28). Fisons, PLC, was a former leader of inhaler formulations research, and operated a facility in England through about 1994 or 1995 when it was acquired by a predecessor to AstraZeneca. (Ex. 1012, ¶¶ 28, 34). While Mistry has no recorded assignments, it is very likely to be owned by AstraZeneca and even appears listed in the Orange Book under the AstraZeneca owned Symbicort drug. (*Id.*).

2. Claim 1 and Claims 12-15 (Analyzed Under Limitation 1(c))

Limitation 1(a) – "A pharmaceutical composition comprising . . . 1,1,1,2,3,3,3-heptafluoropropane (HFA227)". (Ex. 1001, 8:17-19). To the extent the preamble is limiting, Mistry discloses a "[p]ressurized aerosol inhalation composition," and teaches an invention relating to "compositions of inhalation medicaments." (Ex. 1003, Abstract, 1:7-9). A POSITA would understand this to teach a pharmaceutical composition. (Ex. 1012, ¶ 59). Moreover, Mistry teaches three hydrofluoroalkane propellants of interest, and states that: "We particularly prefer compositions including propellant 227." (Ex. 1003, at 2:64-65; Ex. 1012, ¶ 60). Dr. Beasley in his declaration states that a POSITA would understand that "propellant 227" is the same as the claimed HFA 227. (Ex. 1001, 8:18-19;

Ex. 1012, ¶ 60). Accordingly, Mistry teaches each and every element of limitation 1(a). (*Id.*, ¶ 61).

Limitation 1(b) – "formoterol fumarate dihydrate . . . , wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml". (Ex. 1001, 8:17-23).

Mistry teaches that the formulation containing HFA 227 also would contain any medicaments that are "conventionally administered to the lung and/or nose by inhalation of a pressurised aerosol formulation. Such medicaments include drugs for use in the prophylactic or remedial treatment of reversible obstructive airways disease . . . ." (Ex. 1003, 3:27-33). As an example of one such medicament, Mistry lists "formoterol . . . and salts thereof". (*Id.*, 3:37-38). In the understanding of a POSITA the term "formoterol" as a "medicament" would include formoterol fumarate dihydrate, which would have been known to a POSITA at that time as a medicament. (Ex. 1012, ¶¶ 29, 37, 138).

The concentration limitation of formoterol fumarate dihydrate at 0.09 mg/ml is also satisfied by Mistry. Dr. Beasley explains that a POSITA would understand that the pressurized aerosol formulation taught by Mistry would be contained within a standard-size canister at that time, in particular between 10 ml and 19 ml. (Ex. 1012, ¶ 65). A POSITA also would understand that the total fill weights would range from 6 grams to 10 grams. (*Id.*). Therefore, a concentration of 0.09

mg/ml of formoterol fumarate dihydrate in a 10 ml canister with 6 grams of fill weight yields a weight percentage of formoterol fumarate dihydrate of 0.015%, and a concentration of 0.09 mg/ml of formoterol fumarate dihydrate in a 19 ml canister yields a weight percentage of formoterol fumarate dihydrate of 0.017%. (*Id.*). The Mistry specification teaches a stable formulation, and claims formoterol medicament, including formoterol fumarate dihydrate, upwards from 0.01% by weight concentration. (Ex. 1003, 3:27-33, 3:37, 3:62-67; Ex. 1012, ¶¶ 29, 62-66). Therefore, Mistry anticipates the '328 Patent claims of 0.09 mg/ml of formoterol fumarate dihydrate, which is the equivalent of 0.015% to 0.017% by weight in a canister. (*Id.*; *see also* Ex. 1001, 8:22-23).

Limitation 1(c) – "budesonide . . . , wherein . . . the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml." (Ex. 1001, 8:18-24).

As an initial matter, Mistry teaches that a medicament in its formulation may specifically be budesonide. (Ex. 1003, 3:35; Ex. 1012, ¶¶ 62-63, 65). Using the same analysis from limitation 1(b), and the particular canister fill weights or net weights known by a POSITA, then budesonide at concentrations of 1 mg/ml to 8 mg/ml would yield percentages by weight of between 0.17% and 1.5%. (Ex. 1001, 8:23-24; Ex. 1012, ¶¶ 65, 68). Again, the Mistry patent teaches stability (*e.g.*, Ex. 1003, 1:24-36; 1:39-41; 2:3-11; Ex. 1012, ¶ 30), and so a POSITA would understand from the claimed ranges of medicament of 0.01% by weight, and up,

that there is no indication that any of the ranges are not of "critical importance" for the invention's stability. (*See, e.g.*, Ex. 1012, ¶ 69). Therefore, Mistry anticipates limitation 1(c). (*Id.*). And, because the budesonide limitation in Claim element 1(c) is anticipated, then the budesonide limitations in Claims 12-15, over the same range, are also anticipated. (Ex. 1012, ¶ 69; Ex. 1001 at 8:51-10:5 (claims 12 through 15)).

Limitations 1(b) and 1(c) in the same formulation – Moreover, Mistry specifically teaches to a POSITA that the medicaments formoterol fumarate dihydrate and budesonide may be combined in the formulation. Budesonide, Mistry teaches, is a type of "prophylactic or remedial treatment of reversible obstructive airways disease," and formoterol is an example of a "bronchodilator[]." (Ex. 1003, 3:31-37). Mistry states that the medicaments include "a combination of a prophylactic agent with a bronchodilator." (*Id.*, 3:40-42; Ex. 1012, ¶ 85).

Limitation 1(d) – "PVP K25 (polyvinyl pyrrolidone with a nominal K-value of 25) . . . , wherein . . . the PVP K25 is present at a concentration of 0.001% w/w." (Ex. 1001, 8:19-26).

Mistry teaches that PVP in a range of average molecular weights gives acceptable suspensions, and that PVP with K values are "more preferabl[e]" between 15 and 120. (Ex. 1003, 1:65-2:9; Ex. 1012, ¶ 71). Dr. Beasley explains that a POSITA would understand that PVP is a critical element in the formulation

teachings of Mistry, and that nothing in Mistry regarding the disclosed K-value ranges suggests that they are not all of critical importance for a "successfully stable" medicament formulation of PVP, PEG, and HFA. (Ex. 1012, ¶ 72). Regarding concentration of the PVP polymer in those range of K-values, Mistry teaches that it is "preferably at least 0.001% w/w," and "especially 0.001 to 1% w/w". (Ex. 1003, 3:10-13, 2:25-29; Ex. 1012, ¶ 73). As Dr. Beasley notes, it is significant that the claimed value of PVP concentration, 0.001% w/w, is taught by Mistry no less than twice. (Ex. 1012, ¶ 74). This is nothing in the Mistry reference that is evidence that the 0.001% w/w value is not a critical limitation of the invention, even within the broader range it teaches and claims. (*Id.*). Accordingly, Mistry satisfies limitation 1(d). (Ex. 1012, ¶ 75).

Limitation 1(e) – "PEG-1000 (polyethylene glycol with an average molecular weight of 1000), wherein . . . the PEG-1000 is present at a concentration of 0.3% w/w." (Ex. 1001, 8:20-26).

Mistry teaches that the medicament formulation includes other ingredients, "in particular excipients intended to improve valve lubrication and excipients to modify flavour." (Ex. 1003, 2:32-33). Regarding lubricants, Mistry "especially" notes polyethylene glycol, and states that "[w]e prefer polyethylene glycol having a mean molecular weight of from 200 to 300, preferably 400 to 2000, eg 1500." (Ex. 1003, 2:31-37; Ex. 1012, ¶ 77). Mistry also claims a range encompassing the

PEG 1000 limitation twice, and nothing in the reference indicates or suggests that the ranges of average PEG molecular weights are not "critical" for valve lubrication in an inhaler. (Ex. 1012, ¶ 78; *see also* Ex. 1003, 12:33-34, 12:41-42 (claiming excipient comprising PEG acting as a valve lubricant)). Moreover, Mistry also teaches PEG 1000 in its examples. (Ex. 1003, 11:40, 11:54, 11:59; Ex. 1012, ¶ 77). Therefore, Mistry teaches inclusion of PEG 1000 in an HFA 227 medicament formulation. (Ex. 1012, ¶¶ 77-78).

Mistry also teaches the PEG 1000 concentration limitation encompassing the claimed concentration of 0.3% w/w. (*See, e.g.*, Ex. 1001, 8:26; Ex. 1003, 2:31-47; 12:33-35 (dependent claim 8), 12:41-42 (dependent claim 11), 12:49-54 (dependent claims 14-15)). While the amount of PEG may depend on factors such as the nature of the valve and the other components of the formulation, Mistry teaches a preferred PEG concentration of 0.01% to 4% w/w, and a more preferred concentration of 0.1% to 2% w/w. (Ex. 1003, 2:31-37, 2:42-47; Ex. 1012, ¶ 79). Mistry claims ranges of PEG encompassing 0.3% w/w twice, indicating the importance of that range to a POSITA. (Ex. 1003, 12:49-54; Ex. 1012, ¶ 80).

Finally, Dr. Beasley explains that a POSITA would understand that Mistry teaches Claim 1 of the '328 Patent, *i.e.*, PEG and PVP and combined in an HFA formulation anticipating budesonide and formoterol fumarate dihydrate as the two active ingredients. (Ex. 1012, ¶ 81; Ex. 1003, 12:1-22, 12:29-34; 12:41-54).

Therefore, Mistry fully anticipates Claim 1 of the '328 Patent. (Ex. 1012, ¶ 81). Given that Claim 1 encompasses the limitations of Claims 12-15, Mistry also fully anticipates Claims 12-15. (Ex. 1001, 8:51-10:5; Ex. 1012, ¶¶ 58, 69, 81, 87).

3. Claims 4-7

These claims are analyzed together given their similar substance.

Claim 4 – "The method of treating symptoms of a respiratory disorder, comprising administering to a patient the pharmaceutical composition according to claim 1, wherein the respiratory disorder is asthma, rhinitis, or chronic obstructive pulmonary disease (COPD)." (Ex. 1001, 8:32-36). **Claim 5** – "The method of claim 4, wherein the respiratory disorder is asthma." (*Id.*, 8:37-38). **Claim 6 –** "The method of claim 4, wherein the respiratory disorder is rhinitis." (*Id.*, 8:39-40). **Claim 7** – "The method of claim 4, wherein the respiratory disorder is COPD." (*Id.*, 8:41-42).

Mistry teaches that medicaments, including the combination of budesonide and formoterol fumarate dihydrate as described above, are drugs "for use in the prophylactic or remedial treatment of reversible obstructive airways disease." (Ex. 1003, 3:27-40; Ex. 1012, ¶ 85; *see also supra* analysis of limitations 1(b) and 1(c)). Moreover, a POSITA would understand that for remedial or prophylactic purposes, "reversible obstructive airways diseases would include asthma, rhinitis, or COPD." (Ex. 1012, ¶ 85).

Regarding Claim 7, relating to COPD, a POSITA would understand from PATHOLOGIC BASIS OF DISEASE (5th Ed., 1994), a reference medical textbook used throughout "four years of medical school and into . . . residencies" (Ex. 1015, p. 4) that COPD is an "umbrella" term that includes asthma, a "reversible airway" disease. (*See* Ex. 1015, p. 6, Table 15-3 (notation and highlighting was preexisting on copy of reference obtained Petitioner)). Therefore, a POSITA would understand that by treating at least asthma with the Mistry medicament, then he or she also would be treating forms of COPD. (*Id.*). Further, Rogueda indicates the state of knowledge of a POSITA at least by its publication date on January 17, 2002, and it teaches that Symbicort would be used for treatment of COPD. (*See, e.g.*, p. 11:29-32; p. 12:9-10; p. 45, lines 1-2 (claiming Symbicort for use in treatment of asthma, rhinitis or COPD)). Finally, as discussed previously, a POSITA also would understand that "formoterol" disclosed in Mistry would be understood as formoterol fumarate dihydrate, especially when used in an aerosol formulation, which a POSITA would understand to be the case in Mistry. (Ex. 1012, ¶¶ 29, 37, 85). Therefore, Mistry anticipates Claims 4-7.

4. Claims 8-11

These claims are analyzed together given their similar substance.

Claim 8 – "The method of claim 4, wherein the concentration of budesonide is 1 mg/ml." (Ex. 1001, 8:43-44). **Claim 9** – "The method of claim 4, wherein the

concentration of budesonide is 2 mg/ml." (*Id.*, 8:45-46). **Claim 10** – "The method of claim 4, wherein the concentration of budesonide is 4 mg/ml." (*Id.*, 8:47-48). **Claim 11** – "The method of claim 4, wherein the concentration of budesonide is 8 mg/ml." (*Id.*, 8:49-50).

These claims are anticipated by Mistry for the same reason that claim limitation 1(c) for budesonide is anticipated. (Ex. 1012, ¶ 86). The values 1 mg/ml through 8 mg/ml are all included in the ranges disclosed in the analysis of anticipation for limitation 1(c). (*Id.*; *see* Section VII.A.2 (analysis of Claim 1(c)).

In sum, Mistry fully anticipates Claims 1 and 4-15 of the '328 Patent.

B. Ground II: Rogueda Anticipates Claims 1 and 4-15 of the '328 Patent

1. Background of Rogueda

The Rogueda reference appears to be formulation research into budesonide and formoterol compositions following Mistry. Rogueda likely was developed by AstraZeneca at the same laboratory purchased from Fisons, PLC that also led to the Mistry invention and the '328 Patent. (Ex. 1012, ¶¶ 31, 35). In search of greater stability, Rogueda teaches that, among other things, a polar fluorinated molecule could also be added to a "budesonide, formoterol fumarate dihydrate, Symbicort™ (budesonide and formoterol)" HFA formulation, in addition to PVP K25 and PEG 1000, *i.e.*, the components that led to a stable formulation in Mistry. (Ex. 1004, p. 3:4-5; 3:13-16). Rogueda anticipates the budesonide and formoterol fumarate

dihydrate limitation under two different theories: (1) through Rogueda's examples, and (2) through its control samples. (*See, e.g.*, *id.*, pp. 22-27). Petitioner asserts both theories of anticipation without limitation.

Accordingly, by disclosing Symbicort HFA formulations with the exact same components and concentrations as the claimed formulation, Rogueda anticipates Claims 1, and 4-15 of the '328 Patent.

2. Claim 1 and Claims 12-15

Limitation 1(a) – "A pharmaceutical composition comprising . . . 1,1,1,2,3,3,3-heptafluoropropane (HFA227)". (Ex. 1001, 8:17-19). To the extent the preamble is limiting, this claim element is anticipated by Rogueda, which states that the invention it teaches "relates to a pharmaceutical aerosol formulation for the administration of a pharmaceutically active substance by inhalation." (Ex. 1004, p. 2:3-4; Ex. 1012, ¶ 91). Regarding HFA 227, Rogueda teaches this propellant in multiple formulations throughout the reference, referring to 1,1,1,2,3,3,3-heptafluoropropane as both P227 and as HFA 227. (*E.g.*, p. 3:13-15, p. 19:23-24, p. 54: Fig. 49; Ex. 1012, ¶ 92; *see also* Ex. 1012, ¶ 60).

Anticipation of Limitations 1(b) and 1(c) Through Rogueda Examples

While the Rogueda examples do not have both budesonide and formoterol included within the same formulation, a POSITA would understand that because the reference teaches "Symbicort™ (budesonide and formoterol)" that it informs a

POSITA of including budesonide and formoterol in the same formulation. (Ex. 1004, p. 3:5; Ex. 1005 (generally teaching combination of formoterol and budesonide); Ex. 1012, ¶ 95). A POSITA would understand that a budesonide and formoterol formulation could be achieved by adding the budesonide or formoterol API to any of the example or control formulation, or by combining example or control formulations with each other such that they have both APIs. (*Id.*)

Limitation 1(b) – "formoterol fumarate dihydrate . . . , wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml". (Ex. 1001, 8:17-23). **Limitation 1(c)** – "budesonide . . . wherein . . . the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml." (*Id.*, 8:18-24).

Rogueda's examples teach specific concentrations by weight of formoterol and budesonide. Examples 8 and 11 (right) show suspensions of formoterol in HFA 227 at concentrations by weight of around 0.016% or 0.017% w/w (Ex. 1004, pp. 24-25: Examples 8 and 11; Ex. 1012, ¶ 96 (quoting exact figures)). Rogueda teaches

Example 8

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Formoterol Fumarate Dihydrate	Methoxy-PEG-DSPE MW 2000	4HPFOH
8.1	0.017	0.174	17.3
8.2	0.0174	0.069	6.85
8.3	0.0169	1.04	11.9
8.4	0.0174	0.171	3.04
8.5	0.0172	0.521	12.0
8.6	0.0176	1.19	21.1

Example 11

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Fomoterol Fumarate Dihydrate	Glucamate DOE-120	1,1,2,2-tetrafluoroethyl-2,2,2-trifluoroethyl ether
11.1	0.017	0.063	6.98
11.2	0.017	0.159	18.4
11.3	0.016	0.198	3.16
11.4	0.016	0.587	12.1
11.5	0.017	1.10	12.1
11.6	0.017	1.3	22.2

that these formoterol suspensions could be incorporated into a 12 ml canister. (Ex. 1004, p. 22:13-14). Using the 12 ml canister figure, Dr. Beasley converts the formoterol fumarate dihydrate weight percentages into concentrations. (Ex. 1012, ¶ 96). His declaration states that between the 6 gram and 10 gram fill weights known to a POSITA, the concentrations of formoterol would be between 0.08 mg/ml and 0.15 mg/ml. (Ex. 1012, ¶¶ 65, 96). Accordingly, this anticipates limitation 1(b) of 0.09 mg/ml (as well as the formoterol limitation in Claims 12-15). (*Id.*, ¶ 96). This concentration is moreover anticipated at "multiple fill weights from around 6.0 grams to 6.5 grams"—and Dr. Beasley notes that a POSITA would expect a 12 ml canister to have a fill weight between 6 and 7 grams so in reality such a POSITA would not expect to test all the way up to 10 grams. (*Id.*).

Regarding the budesonide limitation, the Rogueda examples indicate that budesonide weight percentages, assuming the same fill weights of around 6 to 6.5 grams, will yield concentrations of around 1 mg/ml, anticipating limitation 1(c) and the budesonide limitation of Claim 12. (Ex. 1012, ¶ 97). (For example, at 6.3 gram fill weight, budesonide at around 0.25% or 0.26% by weight is the equivalent of around 1.3 or 1.4 mg/ml concentration.)

A POSITA reading Rogueda at the time of publication would understand that clinically significant molar ratios of formoterol to budesonide could be between 1:1 to at least as high as 1:60 or 1:100, with weight ratios similarly up to

about 0.98:100. (*See, e.g.*, Ex. 1005 (Carling), 6:30-36, and Ex. 1006 (Ekström), p. 8:1-3, 13:25-26 (both indicating the state of knowledge of a POSITA); Ex. 1012, ¶ 97 (converting clinically significant molar ratios to weight ratios)). Applying this known ratio would yield budesonide at concentrations with formoterol up to and above 8 mg/ml. (Ex. 1012, ¶ 97). Therefore, Rogueda's examples also anticipate the budesonide concentration in Claims 12-15. (*Id.*).

Anticipation of Limitations 1(b) and 1(c), Rogueda Control Samples

The control samples are understood in Rogueda to be the base formulation for experimenting with polar fluorinated molecules to test for increased stability. (Ex. 1012, ¶ 98). A POSITA would understand that the components in these control formulations could be used, by adding additional ingredients, to form a final medicament formulation. (*Id.*). Moreover, a POSITA would understand that the Rogeuda specification discloses adding either budesonide and/or formoterol to certain of the base control samples to create a Symbicort® formulation with a certain base level stability (*i.e.*, sufficient stability that it was used as a control for attempting to find a more stable formulation). (*Id.*).

Limitation 1(b) – "formoterol fumarate dihydrate . . . , wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml". (Ex. 1001, 8:17-23).

Limitation 1(c) – "budesonide . . . wherein . . . the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml." (*Id.*, 8:18-24).

In Rogueda, the control samples teach formoterol in a concentration by weight of 0.0167%, and budesonide in a concentration by weight of 0.259% or 0.260%. (Ex. 1004, p. 25:9, p. 25:13, p. 26:1, p. 26:22, p. 26:26, & p. 26:30). Again assuming 6.3 gram fill weight as previously used (while noting that Dr. Beasley finds there are actually multiple acceptable fill weights around 6 to 6.5 grams fill for the 12 ml canister (Ex. 1012, ¶¶ 96, 99)), then after rounding to the same significant figures as the '328 Patent, the formoterol in the Rogueda control sample is at a concentration of 0.09 mg/ml. (*Id.*, ¶ 99).

Applying the same calculation to the budesonide yields a concentration of 1.4 mg/ml, or 1 mg/ml in the same significant figures as the '328 Patent. (Ex. 1012, ¶¶ 100-01). Because a POSITA at the time of the Rogueda publication would have known that formoterol to budesonide weight ratios range from 0.98:1 to 0.98:100 (Ex. 1006 (Ekström), p. 8:1-3, 13:25-26; Ex. 1012, ¶¶ 97, 115), then keeping formoterol constant at 0.09 mg/ml would allow the budesonide concentration to go up to and above 8 mg/ml. (Ex. 1012, ¶ 97 (explaining that a POSITA would understand it to be as high as 8.8 mg/ml). Accordingly, the Rogueda control samples anticipate limitations 1(b) and 1(c), and the budesonide limitations in Claims 12-15.

Limitation 1(d) – "PVP K25 (polyvinyl pyrrolidone with a nominal K-value of 25) . . . , wherein . . . the PVP K25 is present at a concentration of 0.001% w/w." (Ex. 1001, 8:19-25). Rogueda teaches a PVP K25 in a list of "[s]uitable excipients" and in a list of "preferred excipients" for an HFA medicament formulation. (Ex. 1004, p. 8:30 – p. 9:13; p. 10:5-24; Ex. 1012, ¶ 103). Nothing in the reference indicates that the PVP K25 is not critical to the invention, and in fact it is repeated in the specification, the claims, and in the control samples. (*Id.*; Ex. 1004, p. 20:23-24, 30; p. 30:23; p. 31:20-21; p. 32:1-5; p. 43:12; p. 44:21).

Concentrations of PVP K25 in formulations are shown several times in the Rogueda reference, including the control samples—the concentration of PVP K25 is the same each time in Rogueda, 0.001% by weight. (Ex. 1004, p. 26:3, p. 26:33, p. 30:29 (0.00099%, rounded to one significant figure as the '328 Patent uses, is 0.001%), & p. 32:3; Ex. 1012, ¶ 105). (Note that concentrations in Table 2 are not formulations and were based on an "arbitrary" limit. (*See* Ex. 1004, pp. 15:34-17).) The repetition of this precise concentration of 0.001% indicates its critical importance to the invention, and to stability (with which Rogueda is concerned). (Ex. 1004, p. 2:10-12; p. 29:14-18; p. 29:31-32 ("All suspensions had improved stability properties in the range of concentrations studied."); Ex. 1012, ¶ 106). Moreover, nothing in the reference indicates that it is not of critical importance, and in fact it is in line with (and happens to be the very lower bound of) the

concentrations that Rogueda teaches for all excipients, *i.e.*, "suitably from 0.001% to 1%" by weight. (Ex. 1004, p. 11:15; Ex. 1012, ¶ 104).

Limitation 1(e) – "PEG-1000 (polyethylene glycol with an average molecular weight of 1000), wherein . . . the PEG-1000 is present at a concentration of 0.3% w/w." (Ex. 1001, 8:20-26).

Rogueda teaches PEG 1000 in a list of "[p]referred excipients" and as a "[s]uitable excipient," and also teaches the addition of lubricants (as noted in the analysis of limitation 1(e) in Mistry, PEG is a common lubricant and acts as a valve lubricant in an inhaler). (Ex. 1002, p. 281-87; Ex. 1004, p. 8:30 – p. 9: 13, p. 10:5-37 ; Ex. 1012, ¶ 108). A POSITA would understand that PEG could be added with other excipients or inactive ingredients. (Ex. 1002, p. 281-87; Ex. 1012, ¶ 109). As with PVP K25, the Rogueda references teaches PEG 1000 multiple times in the specification, and again in the claims; there is nothing in Rogueda indicating that it was not critical to the invention (Ex. 1004, 9:13, 10:5, 10:24-25, 20:23-24, 20:30, 26:1-5, 26:32, 43:12-13, 44:21-22 (dependent claim 11); Ex. 1012, ¶ 108).

The concentration of PEG 1000 taught by Rogueda is anticipatory to the '328 Patent. PEG 1000 is taught at a concentration of 0.3% w/w twice. (Ex. 1004, p. 26:31; p. 32:1 (0.299%, rounded to one significant figure as the '328 Patent uses, is 0.3%); Ex. 1012, ¶ 110). In a control sample, PEG 1000 is taught at 0.3%

w/w in an HFA 227 formulation with PVP K25 and budesonide all within the ranges claimed by Claim 1 in the '328 Patent. (Ex. 1001, 8:17-26; Ex. 1004, p. 26:30-34; Ex. 1012, ¶ 110). Broadly in the specification, Rogueda teaches the concentration of PEG as an excipient "preferably" from "0.01 to 1%." (Ex. 1004, p. 11:15; Ex. 1012, ¶ 109).

Therefore, the Rogueda reference teaches each and every claim limitation of Claims 1, and 12-15 and therefore these claims are invalid. (Ex. 1012, ¶ 111).

3. Claims 4-7

Claim 4 – "The method of treating symptoms of a respiratory disorder, comprising administering to a patient the pharmaceutical composition according to claim 1, wherein the respiratory disorder is asthma, rhinitis, or chronic obstructive pulmonary disease (COPD)." (Ex. 1001, 8:32-36). **Claim 5** – "The method of claim 4, wherein the respiratory disorder is asthma." (*Id.*, 8:37-38). **Claim 6 –** "The method of claim 4, wherein the respiratory disorder is rhinitis." (*Id.*, 8:39-40). **Claim 7** – "The method of claim 4, wherein the respiratory disorder is COPD." (*Id.*, 8:41-42).

Rogueda anticipates each and every limitation of Claims 4-7, which all depend from anticipated Claim 1, by teaching that the "pharmaceutical formulations of the present invention" are useful for the treatment of diseases. (Ex. 1004, p. 11:22-32). Rogueda further states that "[t]he present invention also

provides . . . a method for treatment of a patient in need of therapy, comprising administering to said patient a therapeutically effective amount of the pharmaceutical aerosol formulation of the present invention." (*Id.*, p. 11:24-29). Finally, Rogueda expects to use the pharmaceutical aerosol formulation of the present invention to treat, *inter alia*, "inflammatory diseases in the respiratory tract, for example asthma, rhinitis, [and] COPD." (*Id.*, p. 11:30; see also p. 12:9-10; p. 44:1-2 (claiming "A pharmaceutical aerosol formulation as claimed in any of the claims 1 to 11 for use in the treatment of asthma, rhinitis or COPD"; p. 37:20 (specifying "Symbicort™" in claim 4)). Therefore, Rogueda anticipates each and every limitation of Claims 4-7. (Ex. 1012, ¶ 113).

4. Claims 8-11

Claim 8 – "The method of claim 4, wherein the concentration of budesonide is 1 mg/ml." (Ex. 1001, 8:43-44). **Claim 9** – "The method of claim 4, wherein the concentration of budesonide is 2 mg/ml." (*Id.*, 8:45-46). **Claim 10** – "The method of claim 4, wherein the concentration of budesonide is 4 mg/ml." (*Id.*, 8:47-48). **Claim 11** – "The method of claim 4, wherein the concentration of budesonide is 8 mg/ml." (*Id.*, 8:49-50).

These claims are anticipated by Rogueda for the same reason that claim limitation 1(c) for budesonide is anticipated. (Ex. 1012, ¶ 115). The values 1 mg/ml through 8 mg/ml are all included in the ranges disclosed in the analyses of

anticipation for limitation 1(c). (*Id.*). In particular, a POSITA's knowledge of the ratio of formoterol to budesonide, given the reference to "Symbicort™" and the therapeutic uses of the invention, would enable the POSITA to scale up the budesonide up to and above 8 mg/ml. (Ex. 1012, ¶ 115).

C. Ground III: Mistry in View of Rogueda and Carling Renders Obvious Claims 1 and 4-15

1. Motivation to Combine

A POSITA employed in the pharmaceutical industry would be motivated to develop shelf-stable drugs to treat common respiratory disorders. (Ex. 1012, ¶ 118). Such a motivation to develop these drugs ultimately would come from the pharmaceutical company's interest in a profit derived from legally selling such drugs. (*Id.*). The POSITA would have knowledge of Carling's budesonide and formoterol treatment effectiveness, or potential for treatment, and would seek to adapt the Carling invention to a non-CFC pressurized inhaler. (*Id.*). A POSITA with knowledge of Carling would be aware of the changing legal requirements regarding CFCs from the Montreal Protocol, which is why he or she would seek a non-CFC pressurized aerosol formulation. (*Id.*; *see also* Ex. 1003, 1:21-31 (describing background of Mistry invention). This provided a strong motivation for reformulation using a new propellant and other excipients.

To find a non-CFC formulation with which to adapt the budesonide and formoterol invention of Carling, the POSITA would look to Mistry. (Ex. 1012,

¶ 119). Mistry provides a non-CFC inhaler medicament formulation by using HFA instead. (*Id.*; Ex. 1003, 1:42-44, 2:62-65). Moreover, Mistry teaches the HFA formulation with the active ingredients from Carling, *i.e.*, budesonide and formoterol. (Ex. 1012, ¶ 119; Ex. 1003, 2:62-65, 3:27-42). Through selecting PVP and PEG, Mistry achieved stability and appropriate lubrication. (Ex. 1003, 1:65-67, 2:3-11; 2:30-37). Stability is important for drugs that are distributed through a supply chain and need to sit on the shelf while maintaining their efficacy, and the proper lubrication is important for how long the inhaler can function and deliver the proper medicament during actuation. (Ex. 1012, ¶ 119).

Looking for further stability inventions for HFA formulations of budesonide and formoterol, a POSITA would look to Rogueda to avoid time-intensive, though routine, formulation efforts to determine whether the PVP K-values, PEG molecular weights, and concentrations of both, could be further limited. (Ex. 1012, ¶ 120). Ultimately, Rogueda also teaches a POSITA better specifics about commercializing the invention of Carling and Mistry, for which a POSITA also would be searching. Rogueda teaches improved stability, and precise characterizations in its experimental and control samples of the concentrations of budesonide, formoterol, PVP, and PEG. (*See* Ground II Analysis). It also provides a specific K-value to use for the PVP, and a specific average molecular weight for

the PEG. Rogueda even provides a canister size for packaging of the formulation in a consumer inhaler. (Ex. 1012, ¶ 120).

2. Claim 1

Limitation 1(a) – "A pharmaceutical composition comprising . . . 1,1,1,2,3,3,3-heptafluoropropane (HFA227)". (Ex. 1001, 8:17-19). As discussed in both Grounds I and II, Mistry and Rogueda teach an HFA formulation. (*See* Ground I, Limitation 1(a) and Ground II, Limitation 1(b) herein; Ex. 1012, ¶ 122).

Limitation 1(b) – "formoterol fumarate dihydrate . . . , wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml". (Ex. 1001, 8:17-23). **Limitation 1(c)** – "budesonide . . . wherein . . . the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml." (*Id.*, 8:18-24).

In 2002, over a year before the PCT filing of the '328 Patent, a POSITA aware of and motivated to commercialize Carling in a non-CFC formulation would be aware of Symbicort, and even impending or completed clinical trials of budesonide and formoterol formulations. (Ex. 1005 (Carling, the original Symbicort patent); Ex. 1004, p. 3:5 (teaching Symbicort); Ex. 1012, ¶ 123). Mistry would teach the POSITA a non-CFC formulation using HFA to which the Carling invention of budesonide and formoterol could be adapted. And Rogueda would teach the appropriate concentration by weight of formoterol fumarate dihydrate. (*See* Limitations 1(b) and 1(c) Analysis from Ground II). A POSITA, filling a

12 ml canister, would know that the fill weights could be between 6 grams and 10 grams (although a POSITA would expect between 6 grams and 7 grams)—the formoterol mass and mass of the other components would stay the same or similar from Rogueda, and the POSITA would simply optimize for stability by altering the fill weights of HFA over this range of final mass. (Ex. 1012, ¶ 124). This is obvious to a POSITA and is exactly the type of routine formulation work expected to be carried out for such a medicament. (Ex. 1012, ¶ 39 (identifying equipment used for testing formulations in the '328 patent specification as "well known within the prior art"), 40-48, 119).

Limitation 1(d) – "PVP K25 (polyvinyl pyrrolidone with a nominal K-value of 25) . . . , wherein . . . the PVP K25 is present at a concentration of 0.001% w/w." (Ex. 1001, 8:19-25). **Limitation 1(e) –** "PEG-1000 (polyethylene glycol with an average molecular weight of 1000), wherein . . . the PEG-1000 is present at a concentration of 0.3% w/w." (*Id.*, 8:20-26).

Mistry teaches a POSITA to use a PVP over a certain K-value range for stability, and teaches using PEG over a certain average molecular weight range for lubrication. A POSITA searching for an example of such a K-value would find it in Rogueda, where only a handful of PVP K-values are taught, and only PVP K25 and PVP K30 are shown in the experimental and control samples. (Ex. 1012, ¶¶ 125, 127). Mistry teaches PEG as the preferred lubricant excipient (*e.g.*, Ex.

1003, 2:33-37, 12:33-34, 12:41-42 (dependent claims 8 and 11)), and specifically refers to PEG 1000 in formulation examples with HFA 227 (Ex. 1003, 11: 28-30, 11:40, 11:54, 11:58). (*See* Ground I Limitation 1(e) Analysis). A POSITA seeking to cut down on time spent during routine optimization of PEG average molecular weight and concentration would look for PEG formulations adapting the invention of Carling and Mistry, and would find Rogueda.

In Rogueda, as discussed above, only PVP K25 and PVP K30 are taught in the experiment and control samples, and they are combined with PEG 1000 and PEG 600, respectively. (Ex. 1004, p. 19:23-24; p. 19:30; p. 25:2-3; p. 25:31-32; p. 29:29 (table); p. 30:20-21; p. 31:1-4; p. 32:1-3; p. 33:1-3; Ex. 1012, ¶ 127). Given these two options to apply the teachings of Mistry, a POSITA would try both, along with their concentrations, and determine the same formulation and stability findings as the ’328 Patent. (*See* Grounds I and II, Limitations 1(d) and 1(e) Analysis; Ex. 1012, ¶¶ 128-133). Accordingly, the formulation of Claim 1 of the ’328 Patent would be obvious to a POSITA in light of the prior art.

3. Claims 4-7

Claim 4 – “The method of treating symptoms of a respiratory disorder, comprising administering to a patient the pharmaceutical composition according to claim 1, wherein the respiratory disorder is asthma, rhinitis, or chronic obstructive pulmonary disease (COPD).” (Ex. 1001, 8:32-36). **Claim 5** – “The method of

claim 4, wherein the respiratory disorder is asthma." (*Id.*, 8:37-38). **Claim 6 –** "The method of claim 4, wherein the respiratory disorder is rhinitis." (*Id.*, 8:39-40). **Claim 7** – "The method of claim 4, wherein the respiratory disorder is COPD." (*Id.*, 8:41-42).

A POSITA aware of the Carling, Mistry and Rogueda prior art would understand that budesonide and formoterol in an aerosol formulation has treatment potential for respiratory disorders, including asthma, rhinitis, and COPD. (*See, e.g.*, Ex. 1003, 1:7-9, 3:27-42; Ex. 1004, p. 11:29-32 ("It is expected that inflammatory diseases in the respiratory tract, for example asthma, rhinitis, COPD, . . . can be treated using the present pharmaceutical aerosol formulation."), p.12:9-10, p. 45:1-2; Ex. 1005, Abstract (general application to "the treatment of an inflammatory respiratory disorder"), 2:56-60; Ex. 1012, ¶ 134; *see also* Ex. 1015, p. 6, Table 15-3 (identifying asthma as a form of COPD)). Moreover, the POSITA would be motivated to create the formulation to sell to consumers and the healthcare industry for such treatment. (*Id.*).

4. Claims 8-15

As discussed above, these claims have the same budesonide limitation as in limitation 1(c). A POSITA would know that the budesonide can be scaled up at higher ratios, up to 0.98:100 by weight. (*See* Ekström, Ex. 1006, p. 8:1-3; p. 12:11-12; Ex. 1012, ¶¶ 27, 97). Accordingly, A POSITA would understand that he or she

could scale up the budesonide to 8 mg/ml and above (up to around 8.8 mg/ml according to Dr. Beasley, Ex. 1012, ¶ 97), satisfying the budesonide concentration limitations in Claims 8-15 and rendering them obvious. (Ex. 1012, ¶ 135).

D. Ground IV: Mistry, in View of Rogueda, Meade, and Lewis Renders Obvious Claims 2 and 3

In developing a budesonide and formoterol HFA formulation for an inhaler, a POSITA would continue to look for improvement ideas. Dr. Beasley states that the Meade reference teaches an improved HFA formulation "for the treatment of respiratory diseases with decreased side effects," and with additional active ingredients. (Ex. 1007, ¶¶ 0002, 0006, 0008, 00014; Ex. 1012, ¶ 136). Moreover, Meade teaches PVP and PEG in its formulations, in line with Mistry and Rogueda, allowing a POSITA to properly combine the reference to try to achieve decreased side effects. (Ex. 1007, ¶ 0050, Ex. 1012, ¶ 136).

The Lewis reference teaches a more stable HFA formulation comprising PEG, PVP, budesonide, and formoterol, which interacts less with the interior of canisters than prior art formulations. (*See, e.g.*, Ex. 1008, 3:6-11, 3:27-67 (teaching HFA 227, PVP, PEG), 4:5-15 (teaching APIs including budesonide and formoterol "and their combinations"), 4:40-46 (statement of novelty about interior canisters); Ex. 1012, ¶¶ 140-41). Because a POSITA would continue to look for improvements, he or she would be motivated to improve stability by incorporating the invention of Lewis with Mistry and Rogueda. (*Id.*).

Claim 2 – "A pharmaceutical composition according to claim 1, in which formoterol fumarate dihydrate is the R, R-enantiomer." (Ex. 1001, 8:27-29).

An enantiomer is an optical isomer, or a stereoisomer that is a mirror image of another molecule. The "R,R-" designation is part of the nomenclature for enantiomers and designates the molecule's configuration in three dimensional space. Stereoisomers are important in pharmaceuticals because a different three dimensional configuration of what is essentially the same molecule can yield different physiological effects.

As Dr. Beasley, describes, the Meade reference refers to "betamimetics," a class of drug that includes bronchodilators and the active ingredient formoterol, which is a "common example." (Ex. 1007, ¶ 0010; Ex. 1012, ¶ 138). Meade teaches "R,R-formoterol" and that the "enantiomeric salts" of "R,R-formoterol are of particular importance". (Ex. 1007, ¶ 0010; Ex. 1012, ¶ 138). Meade also teaches that the hydrates of these salts may be used, and later teaches formoterol fumarate dihydrate. (Ex. 1007, ¶ 1010 (referencing hydrates of formoterol salts), ¶ 0097; Ex. 1012, ¶ 138). Moreover, Meade teaches that they may be added to an inhalable formulation that could be used for propellants. (Ex. 1007, ¶ 0050, Ex. 1012, ¶ 136).

Claim 3 – "A pharmaceutical composition according to claim 1, in which the budesonide is the 22R-epimer." (Ex. 1001, 8:30-31).

An epimer is either of two stereoisomers differing in the configuration of a group based on a single carbon atom. The "22R-" designates which carbon atom is the stereocenter, *i.e.*, the point where the molecule's configuration differs. Lewis teaches that the active ingredient may be present in a single epimer. (*See, e.g.*, Ex. 1008, 4:12-15; 5:13-15 (defining budesonide 22R-epimer "dexbudesonide" for the specification); Ex. 1012, ¶ 140). For budesonide, a POSITA would understand Lewis to teach that the 22R-epimer of budesonide would allow for greater stability in certain canister interiors, *e.g.*, those of epoxy-phenol lacquered aluminum. (*Id.*; Ex. 1008, 4:40-46; 6:16-25 (example 4)).

Accordingly, the combination of Mistry, Rogueda, Lewis, and Meade render Claims 2 and 3 obvious.

E. Statement of Non-Redundancy

While Petitioner believes that Claims 1, and 4-15 of the '328 Patent are anticipated by Mistry or Rogueda alone, Petitioner urges the Board to institute IPR based on both of these references, and also based on obviousness in view of Mistry, Rogueda, and Carling. Moreover, Petitioner submits only one ground for challenging Claims 2 and 3, *i.e.*, Mistry, in View of Rogueda, Meade, and Lewis. Petitioner submits that the closeness of the prior art in this application, and the fact that much of it is owned by AstraZeneca, presents an opportunity for a complete

invalidity challenge on an important drug formulation that may in fact belong to the public.

In addition, the Board has acknowledged that instituting on multiple grounds involving the same references may lead to a fair and efficient resolution. (*See Geotab Inc. et al v. PerdiemCo LLC.*, IPR2016-01062, paper 19, p. 8, (PTAB December 6, 2016) (stating that "[c]oncerns of fairness and efficiency in this case persuade us to institute not only on the ground of anticipation by Fast, but also on any ground of obviousness for which Fast serves as the primary basis of the challenge")).

VIII. Conclusion

This Petition demonstrates "a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition." 35 U.S.C. § 314(a). Because all elements of the challenged claims are taught in the prior art as explained in the proposed Grounds for Unpatentability, Petitioner requests *inter partes* review, and ultimate cancellation of the challenged claims.

IX. Certification of Compliance

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that Microsoft Word counts 11994 words in this Petition.

Respectfully submitted,

HILL, KERTSCHER & WHARTON, LLP

Date: Jan. 9, 2017

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CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing Petition and supporting materials (included all exhibits, notice of related matters, and power of attorney documents) were served via e-mail on January 9, 2017 pursuant to 37 C.F.R. § 42.105, in its entirety on Patent Attorneys of the Agent/Attorney of Record (MORGAN LEWIS & BOCKIUS LLP (WA); 1111 PENNSYLVANIA AVENUE NW; WASHINGTON DC 20004) at the following email addresses:

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