

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC
Petitioner

v.

CIPLA LTD.
Patent Owner

Patent No. 8,168,620
Issue Date: May 1, 2012
Title: COMBINATION OF AZELASTINE AND STEROIDS

Inter Partes Review No.: IPR2017-00803

SECOND DECLARATION OF DR. MAUREEN D. DONOVAN, Ph.D.

TABLE OF CONTENTS

I.	Introduction.....	1
II.	The Basis For My Opinion	1
III.	Cipla's asserted meaning of "suitable for nasal administration" and "nasal spray" are MEANING OF "SUITABLE FOR NASAL ADMINISTRATION" AND "NASAL SPRAY"	3
IV.	A POSA would not be dissuaded by the non-aqueous "liquid formulations" identified by Smyth because the cited references actually encourage a POSA	5
V.	Azelastine would be understood as compatible with MCC and CMC.....	8
VI.	Cramer's Example III, while not the focus of a POSA's understanding, supports a POSA's reasonable expectation of successfully combining azelastine hydrochloride and fluticasone propionate into an aqueous nasal spray.....	13
A.	Dr. Govindarajan's recreations each showed physical stability, and Dr. Govindarajan's tested recreation provided a nasal spray.....	14
B.	Dr. Herpin did not make and test any of Dr. Govindarajan's examples because Dr. Herpin used a different HPMC.....	17
C.	Dr. Herpin's flawed attempt at Dr. Govindarajan's example produced a pH within the pH range stated by the '620 for a nasal spray "suitable for nasal administration," a fact acknowledged by Dr. Smyth during his deposition.	18
D.	Each of the Cramer Example III recreations falls within accepted osmolality values for nasal sprays according to the art submitted by both Petitioner and Patent Owner – including art specifically relied upon by Dr. Smyth	19
E.	Cipla's "recreations" of Cramer Example III are not representative of the routine work of a POSA	20
VII.	Patent Owner has relied on views in opposition to Dr. Smyth's when obtaining other patents claiming priority to the '620 patent.	22
VIII.	The prior art expressly provides for Dymista's preservative combination	24
IX.	Glycerine is a widely used excipient with known advantageous solubilizing properties as well as tonicity effects.....	28
X.	Meda's efforts were not that of a POSA and therefore do not show "failure by	

others,” especially when one of the two trials appears successful 31

I, Maureen Donovan, do declare as follows:

I. Introduction

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. I have been retained as an expert witness on behalf of Argentum Pharmaceuticals LLC for a *inter partes* review (IPR) for U.S. Patent No. 8,168,620 (Ex. 1001). I am being compensated for my time in connection with this IPR at my standard consulting rate, which is \$400 per hour for any consulting and \$600 per hour for any deposition appearances. I understand that my declaration accompanies a petition for *inter partes* review involving the above-mentioned U.S. Patent.

II. The Basis For My Opinion

3. In formulating my opinion, the documents I considered include Patent Owner's Response (Paper 21; "POR"), Dr. Smyth's Second Declaration (CIP2150), his deposition transcript (Ex. 1143), Dr. D'Addio's Second Declaration (CIP2148) and his deposition transcript (Ex. 1141), Dr. Herpin's Declaration (CIP2029), the documents cited in each of these, as well as other documents provided by Cipla and submitted as part of the Petitioner's Reply.

4. I understand that an obviousness analysis involves comparing a claim to the prior art to determine whether the claimed invention would have been obvious to

a person of ordinary skill in the art (POSA) in view of the prior art, and in light of the general knowledge in the art. I also understand that when a POSA would have reached the claimed invention through routine experimentation, the invention may be deemed obvious. I understand that a finding of obviousness for a specific range or ratio in a patent can be overcome if the claimed range or ratio is proven to be critical to the performance or use of the claimed invention.

5. I also understand that obviousness can be established by combining or modifying the teachings of the prior art to achieve the claimed invention. It is also my understanding that where there is a reason to modify or combine the prior art to achieve the claimed invention, there must also be a reasonable expectation of success in so doing. I understand that the reason to combine prior art references can come from a variety of sources, not just the prior art itself or the specific problem the patentee was trying to solve. And I understand that the references themselves need not provide a specific hint or suggestion of the alteration needed to arrive at the claimed invention; the analysis may include recourse to logic, judgment, and common sense available to a person of ordinary skill that does not necessarily require explication in any reference.

6. I understand that when considering the obviousness of an invention, one should also consider whether there are any secondary considerations that support the

nonobviousness of the invention. I understand from counsel that another expert has been retained to opine on secondary considerations not discussed in this declaration. Similar to my first declaration, counsel has informed me that because another expert has provided expert testimony on the obviousness of independent claims 1, 24, 25, I am to assume obviousness of those claims.

III. Cipla's asserted meaning of "suitable for nasal administration" and "nasal spray" are ambiguous

7. Cipla says that the claim terms "nasal spray" and "suitable for nasal administration" mean "pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited onto the nasal mucosa."

POR, 8-9; Ex. 2150, ¶21. Further, Dr. Smyth testifies that

Cipla also told the patent examiner that the term "suitable for nasal administration" was synonymous with the term "nasal spray," as used in the '620 patent. EX1002, 220 ("Likewise, independent claims 55 and 56 each recite a 'nasal spray'...").

Ex. 2150, ¶21.

8. However, all of the prior art references relied upon for Cipla's obviousness grounds are expressly directed to nasal sprays suitable for nasal administration. *E.g.*, Ex. 1007, 2:12-17; Ex. 1009, 32:57-60; Ex. 1010, 1; Ex. 1012, Abstract, 4-6. Indeed, Ex. 1007, Ex. 1009 and Ex. 1010 each teach commercially available nasal spray products. And Segal (Ex. 1012) and Cramer (Ex. 1011) each

teach aqueous compositions formulated as nasal drops or sprays that are both isotonic and pH adjusted that include both fluticasone and azelastine. Ex. 1012, 2, 3, 6; Ex. 1011, 3:7-9, 27-30, 43-45.

9. In addition, Cipla does not describe how long the claimed compositions must be homogenous. Must the formulation be homogenous perpetually, or 10 days, or three seconds, or does it merely have to be homogenous the instant it is made? If a formulation has settling but may easily be resuspended to become homogenous again, does it not meet Cipla's standard? Cipla does not provide any of this information.

10. Furthermore, Cipla does not indicate what osmolality values for a composition are "tolerable." Cipla states an osmolality of 529 mOsm/kg is "unacceptable" in dismissing the relevance of Cramer. Ex. 2150, ¶ 38. Cipla and Dr. Smyth provide no art reference to support this (Ex. 2150, ¶ 38) and, in fact, the reference on which they rely identifies 200-600 mOsm/kg as an acceptable osmolality range (Ex. 2112, 19). Somehow, despite the art, 529 mOsm/kg is outside what Cipla considers tolerable. Yet Cipla does not provide a mOsm/kg range that is acceptable, only venturing to state that one particular value – 300 mOsm/kg – is acceptable. *See* Ex. 2150, ¶38.

11. Cipla does not provide an unambiguous statement of what time period

and situations should be considered for “homogeneous” and does not provide an unambiguous statement of what range in mOsm/kg is “tolerable” according to the claims of the ’620 patent. *See* Ex. 2150, ¶23. All that Cipla tells us is that art is not relevant or applicable because it does not meet these undisclosed standards. Under such terms one would have to contact Cipla, formulation by formulation, to ever know if a particular formulation met the claims of the ’620 patent.

IV. A POSA would not be dissuaded by the non-aqueous “liquid formulations” identified by Smyth because the cited references actually encourage a POSA

12. A POSA would not be dissuaded in combining fluticasone with another active ingredient in an aqueous system. Dr. Smyth claims CIP2111 and CIP2004 undercuts a POSA’s motivation to combine fluticasone with another active ingredient in a “liquid formulation,” where he relies on discussions for non-aqueous liquid systems. CIP2150, ¶¶ 34-35. What Dr. Smyth ignores is that CIP2044 even describes the drug-containing complexes formed in a non-aqueous liquid system as avoiding deposition (CIP2044, 2), and, importantly, ignores that CIP2111 describes that in an aqueous system the complex was even better at avoiding deposition (CIP2111, 9-10).¹

¹ While these references make many statements about potential molecular interactions, I am not stating that this particular mechanistic description is accurate – rather, I discuss how the references expressly contradict the assertions made by Cipla

13. Dr. Smyth relies on discussions from CIP2044, but does not address that the liquid used in the studies described in this reference is CFC-113 – a chlorofluorocarbon. CIP2044, 1-2. Moreover, this reference explicitly states that

“The hetero-aggregation [in the chlorofluorocarbon media] results in reduced drug deposition onto the MDI surfaces as compared with that observed with the individual drug formulations. This phenomenon could be an advantage from a pharmaceutical point of view, i.e. the combination formulation shows a decrease in the total loss of the drugs due to deposition on to the internal surfaces of the MDI.”

CIP2044, 2. The study in CIP2044 was directed to further exploring this heteroaggregation behavior in the chlorofluorocarbon media. *Id.*, 2, 10. While noting “creaming” in the chlorofluorocarbon solvents – where the drug particles migrate to the air/liquid surface of the sample resulting in a decreased drug concentration at the bottom of the sample over time – these experiments did not attempt to re-suspend the particles. *Id.*, 9. The authors found that in CFC-113 “[t]he interparticulate binding between salmeterol xinafoate and fluticasone propionate is a reversible process” – *i.e.*, there was no irreversible caking in this solvent. *Id.*, 8. Dr. Smyth avoids these explicit discussion of favorable aspects of the non-aqueous

when citing to these references.

inhaler system to focus on “aggregation,” implying any aggregation is discouraging – which, as discussed below, it is not.

14. Dr. Smyth provides no discussion or explanation why a POSA would look to a non-aqueous solvent, or why a POSA would rely on information provided from a non-aqueous solvent-based pulmonary inhaler when considering an aqueous nasal spray system. Dr. Smyth simply cites claim 5 of the ’620 patent for “aqueous suspension” to somehow justify his reliance on the chlorofluorocarbon solvent of CIP2044. Ex. 2150, ¶ 34. However, his cited references themselves expressly state that the solvent medium is important in determining the behavior of the combination. CIP2044, Abstract, 5, 6, 10.

15. Moreover, Dr. Smyth ignores teachings of CIP2111 that contradict his assertion, where the authors describe that the complex of salmeterol and fluticasone propionate provides “less deposition” in aqueous media compared to the single, uncomplexed drug species. CIP2111 also explicitly describes the differences between the chlorofluorocarbon CFC-113 and an aqueous solvent for the combination of salmeterol and fluticasone propionate. CIP2111, 9-10.

16. Therefore, while Dr. Smyth cites to CIP2111 to support his proposition, he conspicuously ignores this statement and how it undercuts his arguments, especially in equating flocs with undesirable caking. CIP2150, ¶34. Instead,

CIP2111 states that the floc of salmeterol and fluticasone propionate provides “less deposition” as compared to the single, uncomplexed drug species – a desirable characteristic in a pulmonary inhaler.

17. Therefore, a POSA would not be dissuaded from combining fluticasone with another active ingredient in an aqueous system.

V. Azelastine would be understood as compatible with MCC and CMC

18. Well before the '620 patent, a POSA understood that MCC and CMC were compatible with hydrochloride salts of drugs. In particular, Avicel® RC 591 (a mixture of CMC and MCC) was known and understood to provide aqueous pharmaceutical suspensions that include monovalent cationic drugs. Instead of looking to the actual product guides for Avicel® RC 591 or in the art for particular discussion regarding Avicel® RC 591, Dr. Smyth instead relies solely on selected citations in Lieberman (CIP2113) to assert a POSA would regard azelastine hydrochloride as incompatible with MCC and CMC. CIP2150, ¶¶45-47. However, Dr. Smyth omits what Lieberman's basis is for such statements.

19. Lieberman's citations are to the product guides from the producers of MCC and CMC – in particular, FMC for Avicel® RC 591. At these places, Lieberman cites to two references, both from the 1984: *Cellulose Gums Chemical and Physical Properties*, Hercules, Inc. Wilmington (1984), and B. Idson and A. J. Scheer, Suspensions. In: *Problem Solver and Reference Manual*. FMC Corp.,

Philadelphia (1984). CIP2113, 24, 61 n.51. Note that for Avicel® RC 591, Liebermann cites to a reference by FMC Corp., the manufacturer of Avicel® RC 591.

20. A POSA would be well-versed on updated source material for Avicel® RC 591, including the 2001 FMC publication (Ex. 1146) discussing Avicel® RC 591. This 2001 FMC publication at page 8 specifies CMC is incompatible with di- and trivalent salts. *See also* Ex. 1033, 10. A POSA would expect if an incompatibility with monovalent cations existed, the 2001 FMC publication would list this along with the specific recitation of divalent salts and trivalent salts. Monovalent salts are not called out as problematic for Avicel® RC 591, but are for carbomer. Ex. 1146, 8.

21. Further, a POSA would be aware of multiple aqueous suspension formulations that included at least one or more monovalent cationic drugs and utilizing a mixture of CMC and MCC such as Avicel® RC 591, including art describing aqueous nasal spray suspensions including both a monovalent cationic drug and Avicel® RC 591 (*see infra*).

22. In 1972 aqueous suspensions including monovalent cationic drugs and a mixture of CMC and MCC were described in U.S. 3,636,200 (Ex. 1152). This reference discloses “stable” pharmaceutical suspensions that include a CMC/MCC

mix and hydrochloride salts of 8 different therapeutic agents. U.S. 3,636,200, 1:10-22; 3: 1-37. Examples 2-4 list specific aqueous suspensions utilizing Avicel® RC and 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine hydrochloride (Example 2), 4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl)benzylamine hydrochloride (Example 3), and 2-chloro-9-(3-dimethylaminopropylidene)thioxanthene hydrochloride (Example 4), and Example 5 provides an aqueous suspension utilizing Avicel® RC and a monovalent cationic drug in the form of a hydrobromide salt. U.S. 3,636,200, 5:55 – 6:18.

23. U.S. 5,196,436 (Ex. 1153), issued in 1993, provides five aqueous compositions that include varying amounts of dextromethorphan hydrobromide and Avicel® RC 591. U.S. 5,196,436, Examples I, IV, V, VI, and VII; claims 1, 5.

24. U.S. 5,658,919 (Ex. 1154) issued in 1997, provides stable aqueous pharmaceutical suspensions that contain acetaminophen as well as at least one other pharmaceutical active, specifically naming at least four that are monovalent cationic drugs in aqueous solution: chlorpheniramine maleate, diphenhydramine hydrochloride, dextromethorphan hydrobromide and pseudoephedrine hydrochloride. U.S. 5,658,919, 2:10-16 ,4:21-36. This patent particularly highlights that pseudoephedrine hydrochloride, chlorpheniramine maleate, and dextromethorphan hydrobromide are generally in solution in the aqueous phase of

the suspension. U.S. 5,658,919, 4:37-42.

25. In fact, U.S. 5,658,919 provides a specific example of an aqueous suspension that includes three monovalent cationic drugs with Avicel® RC 591 (Example 2) and three specific aqueous suspension examples with two monovalent cationic drugs together with Avicel® RC 591 (Examples 1 and 3-4).

26. Moreover, an aqueous nasal spray suspension including both a monovalent cationic drug and Avicel® RC 591 was known. U.S. 6,565,832 (Ex. 1155) was filed January 31, 2000 and issued on May 20, 2003. This patent highlights the use of Avicel® RC 591 “in compositions which otherwise have no suspended particulates, i.e., which compositions are [absent Avicel® RC 591] solutions.” U.S. 6,565,832, 3:54-56. Several aqueous nasal spray compositions that include oxymetazoline hydrochloride and Avicel® RC 591 are detailed. U.S. 6,565,832, Examples 1-3.

27. Based on the actual guidance provided by the manufacturer of Avicel® RC 591 and the multiple known aqueous suspensions utilizing Avicel® RC 591 with many different types of monovalent cationic drugs – including two or three monovalent cationic drugs in the same Avicel® RC 591 suspension – a POSA would not be dissuaded from using Avicel® RC 591 to provide an aqueous suspension that also included monovalent cationic drug. In fact, an aqueous nasal spray suspension

including a monovalent cationic drug and Avicel® RC 591 was already known in the art. U.S. 6,565,832, Examples 1-3.

28. Azelastine hydrochloride in water below a pH of 8 provides a monovalent cationic drug. Ex. 1008, 2. As stated by Dr. Smyth, “[i]n a pharmaceutical aqueous solution, the tertiary amine of azelastine will have a [singular] positive charge, thereby giving azelastine the behavior of a cationic drug.” CIP2150, ¶47. Therefore, once azelastine hydrochloride dissociates in solution, it would behave as a monovalent cationic drug.

29. Therefore, a POSA would possess a reasonable expectation of success generating a suspension with both Avicel® RC 591 and azelastine hydrochloride

- (i) because an aqueous nasal spray suspension including a monovalent cationic drug and Avicel® RC 591 was already known in the art (U.S. 6,565,832, Examples 1-3);
- (ii) because azelastine hydrochloride would be understood to dissociate to a monovalent cation in an aqueous media (*supra*);
- (iii) based on the actual guidance provided by the manufacturer of Avicel® RC 591(Ex. 1146), where Lieberman cites the same manufacturer for the proffered understanding of Avicel® RC 591 (CIP2113, 203);
- (iv) because multiple aqueous suspensions utilizing Avicel® RC 591 with

many different types of monovalent cationic drugs, as well as including two or three monovalent cationic drugs in the same Avicel® RC 591 suspension, were well-known.

Dr. Smyth fails to account for this understanding of a POSA, not even attempting to refer to the underlying citations of Lieberman or refer to art actually describing monovalent cationic drugs with Avicel® RC 591. Ex. 1143, 40:9-21.

VI. Cramer’s Example III, while not the focus of a POSA’s understanding, supports a POSA’s reasonable expectation of successfully combining azelastine hydrochloride and fluticasone propionate into an aqueous nasal spray.

30. Dr. Smyth opines that recreations of Cramer’s Example III by Dr. Ram Govindarajan, Dr. Matthew Herpin, and co-inventor Geena Malhotra were each (1) “physically unstable”, (2) “highly acidic,” (3) “unacceptably high osmolality.” Ex. 2150, ¶ 41.

31. Yet, Dr. Govindarajan’s recreations each showed physical stability. Ex. 2030, 4 (¶ 13-14). Dr. Herpin’s report purports to make and test Dr. Govindarajan’s example tested for acceptability as a nasal spray, but this is not the case: Dr. Herpin used a different HPMC grade than used by Dr. Govindarajan. While Dr. Herpin immediately saw different results in the initial steps, neither Dr. Herpin nor Dr. Smyth seem to question this when concluding Dr. Govindarajan’s recreations were physically unstable and unsuitable as a nasal spray.

32. However, even Dr. Herpin's flawed attempt at Dr. Govindarajan's example produced a pH within the pH range stated by the '620 patent as "suitable for nasal administration." *See* Ex. 1143, 79: 9-20.

33. In addition, Dr. Govindarajan's recreations, as well as each of the other Cramer Example III recreations, fall within accepted osmolality values for nasal sprays according to the art submitted by both Petitioner and Cipla – including art specifically relied upon by Dr. Smyth (Ex. 2150, ¶ 38 (citing to CIP2112,19)). While Dr. Smyth's position is that these examples show unacceptable osmolality, Dr. Smyth has no citation but merely asserts it must be true. Ex. 2150, ¶ 38. Even Ms. Malhotra's statements regarding unacceptable osmolality only rely on "preferred" ranges and simply states that the osmolality of her recreation is "undesirable." Ex. 1002, 287 ((C)).

A. Dr. Govindarajan's recreations each showed physical stability, and Dr. Govindarajan's tested recreation provided a nasal spray.

34. Dr. Govindarajan's recreations of Cramer's Example III (which were submitted by Cipla) each were found to be physically stable. These three batches were 1345-004, 1345-008, and 1345-011. Ex. 2030, 24. For each batch, Dr. Govindarajan utilized Hypromellose, Type 2910, Pharmacoat 606. Ex. 2030, 27; *see also* Ex. 2150, ¶ 42 (Dr. Smyth acknowledging this is the HPMC used by Dr. Govindarajan); Ex. 2105, 4-6. As noted by Dr. Smyth, this grade of HPMC has an

apparent viscosity of 6 cP according to the USP method for determining viscosity.

Ex. 2150, ¶ 42; Ex. 2105, 8.

35. Dr. Govindarajan describes preparing Batch 1345-004 on pages 28-31, where HPMC was added to a pre-mixed solution of azelastine hydrochloride, sodium chloride, and benzalkonium chloride where during the addition the solution was stirred vigorously forming a vortex “to hydrate and disperse the hypromellose to yield a clear solution.” Ex. 2030, 30 (emphasis added). The remaining components were subsequently added as detailed by Dr. Govindarajan. Ex. 2030, 30-31.

36. Upon forming the final suspension formulation it was stored overnight, after which Dr. Govindarajan identified a fine settled solid that “easily redispersed upon gentle agitation by overturning the vial 3-4 times” where the solid was “readily and uniformly resuspended.” Ex. 2030, 31.

37. Batch 1345-008 was prepared by a different method than Batch 1345-004, but like Batch 1345-004 also presented a “clear solution” upon addition of hypromellose. Ex. 2030, 33. Upon forming the final suspension formulation, Dr. Govindarajan found that “settling of the suspended solid occurred over time, but the sediment was easily and uniformly resuspendable.” Ex. 2030, 34.

38. Batch 1345-011 was a 500 mL preparation where, similar to the previous two batches, Dr. Govindarajan found settled solid was easily and readily

resuspended by gentle inversion of the container. Ex. 2030, 38. In this section Dr. Govindarajan also highlights that samples of 1345-004 and 1345-008 that were left undisturbed for 3 days had some sediment that was also easily and readily resuspended by gentle inversion of the container. Ex. 2030, 38.

39. Batch 1345-011 was tested for spray delivery tested in a nasal spray pump where delivery by the spray pump was visually observed and the delivery pattern recorded on video. Ex. 2030, 39. Dr. Govindarajan included two videos of the mist produced in his report (Ex. 2030, 4 (¶ 14)), but Cipla conspicuously declined to provide these videos. Based on his observations and these videos, Dr. Govindarajan found that Batch 1345-011 “delivered a fine spray.” Ex. 2030, 4 (¶ 14); 39. Dr. Govindarajan also found that Batch 1345-011 had an osmolality of 529 mOsm/kg. Ex. 2030, 39.

40. Based on the data obtained from his recreations, Dr. Govindarajan concluded that such suspensions are acceptable as nasal sprays, where “[t]here was some settling, but no settling or sedimentation in the product that would make it pharmaceutically unacceptable” and that such suspensions “could be delivered as a fine spray using a nasal spray pump.” Ex. 2030, 4 (¶ 13-14). Indeed, these exact behaviors are cited by Dr. Smyth for a pharmaceutically acceptable suspension. Ex. 2150, ¶ 35 (citing to Ex. 2113, 5; Ex. 2103, 12; 2104, 6-7).

B. Dr. Herpin did not make and test any of Dr. Govindarajan's examples because Dr. Herpin used a different HPMC grade.

41. Dr. Herpin purports to formulate and test Cramer Example III using three processes: the process of Cramer's description, "the process Geena Malhotra describes in her August 12, 2011 declaration," and "the first process Dr. Govindarajan used in his June 30, 2016 report." Ex. 2029, 2 (¶ 6).

42. However, Dr. Herpin does not use the grade of HPMC utilized by Dr. Govindarajan. Dr. Herpin uses an HPMC that has a viscosity of 3 cP in his single attempt to replicate Dr. Govindarajan's first process. Ex. 2029, 3 (¶ 8-10). But this is clearly not correct, because Dr. Govindarajan used an HPMC with a viscosity of 6 cP. Ex. 2030, 27; Ex. 2150, ¶ 42; Ex. 2105, 4-6. It is not clear how this was missed – in fact, Dr. Smyth admits that he developed Dr. Herpin's protocols: "He followed protocols and procedures that I wrote out for the testing of Cramer Example III." Ex. 2021, 171: 19-20. Nonetheless, the fact that Dr. Herpin did not use the correct grade of HPMC means that Dr. Herpin did not recreate Dr. Govindarajan's first recreation.

43. It seems warning signs that Dr. Herpin and Dr. Smyth had made a mistake were evident early on. Dr. Herpin, in attempting to follow Dr. Govindarajan's procedure for Batch 1345-004, observes that in adding the hypromellose it "did not form a clear solution." Ex. 2029, 52. This was prior to

adding triamcinolone acetonide – the active pharmaceutical ingredient to be suspended. *Id.* Such a clear discrepancy with Dr. Govindarajan’s observations should have given Drs. Herpin and Smyth pause, especially because hypromellose has “high solubility” in water. Ex. 2105, 9. Instead, there is no discussion regarding this clear discrepancy.

44. In addition, Dr. Herpin (and thus also Dr. Smyth) chose Dr. Govindarajan’s first process that resulted in Batch 1345-004 and did not attempt to generate Batch 1345-011, Dr. Govindarajan’s recreation that was used to test the ability to spray the composition. Ex. 2030, 28-31; 38-39. The reason for this avoidance is also unclear.

45. Because Dr. Herpin’s testing was not performed on any of Dr. Govindarajan’s recreations, especially not the one used to test spray, Dr. Herpin’s testing does not contradict Dr. Govindarajan’s findings.

C. Dr. Herpin’s flawed attempt at Dr. Govindarajan’s example produced a pH within the pH range stated by the’620 for a nasal spray “suitable for nasal administration,” a fact acknowledged by Dr. Smyth during his deposition.

46. Dr. Herpin’s attempt at Dr. Govindarajan’s Batch 1345-004 exhibited a pH of 3.04. Ex. 2029, 53. The claims of the’620 patent do not state when in time the formulation must be suitable for nasal administration. While Dr. Smyth asserted that a pH of 3 was below the pH of an acceptable nasal formulation, claim 45 of the

'620 patent states that claim 1 formulation "suitable for nasal administration" may be "a pH from 3 to 7" (Ex. 1001, claims 1, 45). At his deposition, Dr. Smyth admitted such a pH range would have to be suitable for nasal administration. Ex. 1143, 79: 9-20.

D. Each of the Cramer Example III recreations falls within accepted osmolality values for nasal sprays according to the art submitted by both Petitioner and Cipla – including art specifically relied upon by Dr. Smyth

47. Dr. Smyth's assertion that all the Cramer Example III recreations show unacceptable osmolality is not supported by the art. In fact, for this contention Dr. Smyth has no citation but merely asserts it must be true. Ex. 2150, ¶ 38. Dr. Smyth's own reference identifies 200-600 mOsm/L as an acceptable osmolality range (Ex. 2112, 19), where Dr. Smyth admits the Cramer Example III recreations are within this range (Ex. 2150, 23 (fn. 10)). Even Ms. Malhotra's statements regarding osmolality only rely on "preferred" ranges and simply states her recreation had an osmolality that was "undesirable." Ex. 1002, 287 ((C)).

48. While Dr. Smyth tries to allege that the side effects listed for Imitrex would be associated with Imitrex's osmolality of 742 mOsm/kg (Ex. 2150, ¶ 38), Azelastin® Nasal Spray (Ex. 1008, 3148) and Flonase® Nasal Spray (Ex. 1010, 7) each exhibit the same side effects as do the placebo vehicle. Dr. Smyth's association of these side effects with Imitrex's osmolality lacks support in the art.

49. Each of the Cramer Example III recreations therefore exhibited osmolality values within ranges taught by the art of record – the same ranges a POSA would view as acceptable for a nasally administered pharmaceutical suspension.

E. Cipla’s “recreations” of Cramer Example III are not representative of the routine work of a POSA

50. Dr. Smyth tries to characterize the recreations of Cramer Example III as “routine modifications” (Ex. 2150, ¶¶36, 42) and that Cramer Example III could not provide a formulation suitable for nasal administration “even after routine modifications (Ex. 2150, ¶43). Thus, in addition to ignoring Dr. Govindarajan’s successful recreations, Dr. Smyth also incorrectly asserts the few recreation efforts he designed (carried out by Dr. Herpin) and the one sample by Ms. Malhotra are representative of the routine modifications that would be employed by a POSA.

51. However, there are multiple routine modifications commonly employed by a POSA that were never attempted by Dr. Herpin or Ms. Malhotra (whose focus was recreation, not generating a successful formulation). Just four of these routine modifications are (i) modification of the HPMC by assessing multiple commercial grades of HPMC, (ii) modification of the amount of HPMC used, (iii) modification of the amount of sodium chloride used, and (iv) modification of the type of spray device employed – none of which was performed by Dr. Herpin or Ms. Malhotra.

52. For HPMC, Cipla's own references show multiple grades of HPMC were available for providing suspensions. CIP2105, 11; CIP2040, 4; *see also* Ex. 1033, 23. The prior art also describes the selection of the grade as well as amount of HPMC to achieve the desired viscosity of a suspension. *See, e.g.*, Ex. 1033, 23; Ex. 1011, 4:56-5:5. Neither Dr. Herpin nor Ms. Malhotra attempted to modify the amount of HPMC used, and Dr. Herpin tried only two grades of HPMC. Ex. 2029, 3.

53. For sodium chloride, if osmolality was truly a concern, a POSA would reduce the amount of sodium chloride used, *i.e.*, use less of the particular tonicity adjuster. *See, e.g.*, CIP2112, 4; Ex. 1007, 31-50; Ex. 1012, 4:4-7. Neither Dr. Herpin nor Ms. Malhotra attempted what may be the simplest approach to reducing the osmolality of their attempts at Cramer Example III: use less sodium chloride.

54. A POSA would also modify the spray device including the pump mechanism as well as the nasal adapter. Ex. 1168, 6-8. Importantly, neither Dr. Herpin nor Ms. Malhotra attempted or provided any discussion regarding the different types of spray devices that may be used with a formulation – a topic on which Dr. Smyth is also silent. Ms. Malhotra performed one attempt with one undisclosed spray pump device (Ex. 1002, 286); Dr. Herpin also used only one type of spray pump device (Ex. 2029, 18, 22, 27, 32, 37, 163, 167, 172, 177, 182).

55. Because Dr. Herpin and Ms. Malhotra together failed to perform even these few routine modifications well-described in the art, Cipla's "recreations" of Cramer Example III are far afield from the routine work of a POSA.

VII. Cipla has relied on views in opposition to Dr. Smyth's when obtaining other patents claiming priority to the '620 patent.

56. In support of their position regarding the abilities of a POSA, Cipla relies on Dr. Smyth's testimony that the '620 patent's recitation at column 7, line 67 through column 8, line 2 is that a "POSA would have viewed this sentence to be limited to the examples listed in the '620 Patent which set out the specific formulation ingredients and concentrations." Ex. 2150, ¶ 32. Dr. Smyth reiterated at his deposition that this relates only to the specific examples, where the ingredients are given and the amounts are given, where such examples would be processed and prepared by techniques that are well known in the art. Ex. 1143, 113: 15-21. This reasoning is also the basis for Dr. Smyth and Cipla's contention that Hettche, Phillips, Segal, and Cramer lack "meaningful guidance." Ex. 2150, ¶ 24-33.

57. However, this is inconsistent with Cipla's actions in two continuation applications of the '620 patent, namely U.S. 8,304,405 and U.S. 8,933,060 (Exs. 1167 and 1166, respectively). These patents have claims directed to compositions "suitable for nasal administration" that include azelastine and ciclesonide—a steroid essentially insoluble in water (Ex. 1151). Ciclesonide, like triamcinolone acetonide

of Cramer, is a steroid. Like fluticasone, an aqueous nasal spray suspension of ciclesonide was known. Ex. 1156. These patents also have the same description and working examples as the '620 patent. Like the '620 patent, U.S. 8,304,405 and U.S. 8,933,060 contain no working examples with azelastine and ciclesonide. Despite this, Cipla pursued independent claims that merely include azelastine and ciclesonide (absent any amounts, suspending agents, etc.) in a composition suitable for nasal administration.² Cipla must have regarded these claims as supported by the application if they submitted such claims, which could only be the case if Cipla was relying on the understanding and skill of a POSA to generate such compositions absent any working examples or description of such amounts.

58. Yet this position is contrary to Cipla's position in this proceeding. While Cipla and Dr. Smyth assert that Hettche, Phillips, Segal, and Cramer lack "meaningful guidance" (Ex. 2150, ¶ 24-33), Cipla relied on as much or less guidance in pursuing U.S. 8,304,405 and U.S. 8,933,060. Therefore, it appears Cipla has only asserted Smyth's view when convenient to exclude art.

² Such pursuit contrasts with Cipla's position here, such as Dr. Smyth's criticisms of Segal "Unlike the formulation examples of the '620 patent, Segal contains no formulation examples and therefore would not be understood by a POSA to "list" "the ingredients of the formulation according to [Segal's invention]"—indeed, no formulations are listed." Ex. 2150, ¶ 32.

VIII. The prior art expressly provides for Dymista's preservative combination

59. As I stated in my first declaration, it was well known to a POSA in 2002 that multi-dose nasal spray formulations must be preserved against microbial contamination. Ex. 1004, ¶ 52. In particular, if a product contains water (like Flonase®, Astelin®, and Dymista®), “it is almost mandatory to include a preservative in the formulation.” Ex. 1149, 2.

60. The use of edetate disodium (“EDTA”), benzalkonium chloride (“BAC”), and phenylethyl alcohol as preservatives in a formulation that combines the active ingredients in the FDA-approved Flonase® label (Ex. 1010) and the Hettche patent (Ex. 1007) (Astelin® is the commercial embodiment) would be readily appreciated because Flonase® and Hettche use the same active ingredients and contain overlapping preservatives. Flonase® is an aqueous based product that includes the preservatives benzalkonium chloride and phenyl ethyl alcohol. Ex. 1010, 1:3. Hettche (Example I)/Astelin® is also an aqueous based product and includes the antimicrobial agents benzalkonium chloride and edetate disodium. Ex. 1007, 6:6-18; Ex. 1008, 2. Claims 42-44 of the '620 patent recite the same active ingredients in Flonase® and Hettche (Example I)/Astelin® and the preservatives EDTA, BAC, and phenylethyl alcohol. Dymista® is an aqueous based product that includes these same active ingredients and three preservatives. Ex. 2066, 12-13.

The table below further illustrates this. A formulator would reasonably expect using all three preservatives in a formulation combining the active ingredients in Flonase® and Hettche (Example I)/Astelin® would result in successfully passing a preservative challenge test by preventing the growth of bacteria and fungi, because the preservatives were already successfully used in Flonase® and Hettche (Example I)/Astelin®.

	Flonase® Label	Hettche	'620 Patent Claims 42-44
Active Ingredient(s)	Fluticasone propionate	Azelastine HCl	Fluticasone Propionate Azelaastine HCL
Vehicle	Water	Water	Water
Preservatives	(1) Benzalkonium chloride; (2) Phenyl ethyl alcohol	(1) Benzalkonium chloride; (2) EDTA disodium	(1)Benzalkonium chloride (2) Phenyl ethyl alcohol (3)EDTA disodium
Surfactants	Polysorbate80	None needed	Polysorbate80
Thickening Agents	MCC/CMC	HPMC	MCC/CMC
Tonicity Adjustor	Dextrose	Sodium chloride	Glycerine

61. A skilled formulator would have also considered *Remington: the Science of Practice of Pharmacy* (“*Remington*”), which lists ethanol, propylene glycol, chlorobutanol, phenylethyl alcohol, benzoic acid, sorbic acid, parabens, and

BAC as well-known preservatives. Ex. 1149, 2-3. It is well known that some preservatives are useful only in certain pH ranges, so when deciding which preservatives to use a skilled formulator would have considered that Flonase® and Hettche/Astelin® disclose formulation pH ranges of between 5 and 7 and 6.8 ± 0.3 , respectively. Ex. 1010, 1; Ex. 1007, 5:6-7; Ex. 1008, 2. A skilled formulator would not have selected benzoic acid as a preservative in a formulation with a pH range between 5-7 and/or 6.8 ± 0.3 , because benzoic acid's "use is restricted to preparations with a pH below 4.5." Ex. 1149, 2.

62. Accordingly, because the formulation to be made is aqueous based with a preferable pH range between 5-7 and/or 6.8 ± 0.3 , the only preservatives taught by *Remington* that a skilled formulator would have considered when combining the active ingredients in Flonase® and Hettche (Example I)/Astelin® are ethanol, propylene glycol, chlorobutanol, phenylethyl alcohol, sorbic acid, parabens, and BAC. Given the choice of seven preservatives, Hettche (Example I)/Astelin® label, and the Flonase® label, it would have been obvious to a skilled formulator to select phenylethyl alcohol and benzalkonium chloride. Additionally, as I highlighted in my first declaration, a formulator would have considered the *Handbook of Pharmaceutical Excipients* ("Handbook"), which states synergistic effects were reported when BAC and phenylethyl alcohol are combined. Ex. 1004, 54; Ex. 1033,

5 and 27.

63. A POSA would be motivated to add EDTA to the formula containing phenylethyl alcohol and benzalkonium chloride. Not only does Hettche (Example I)/Astelin® include EDTA, but EDTA is a well-known chelating agent (*i.e.*, “sequestering agent”). [REDACTED]

[REDACTED] *Remington* also discloses the use of citric acid or EDTA in aqueous formulations for use as a sequestering/chelating agent to minimize the effect of trace metals in formulations. Ex. 1149, 2. Moreover, the thickening/suspending agent Avicel® RC 591 (a mixture of CMC and MCC) is used in the formula and the guidelines for using the product suggest including EDTA as a sequestering agent. Ex. 1146, 9. Additionally, as I previously stated, a skilled formulator would have considered the *Handbook*, which states that when EDTA is used with certain other antimicrobial preservatives it “demonstrates a marked synergistic effect in its antimicrobial activity.” Ex. 1004, 54; Ex. 1033, 16. The *Handbook* also states synergistic effects were reported when BAC and EDTA are combined. Ex. 1004, 54; Ex. 1033, 5 and 27.

64. A POSA would understand that having a combination of preservatives with multiple synergies means a greater chance of successfully providing a nasal spray unable to support the growth of bacteria or fungi as evaluated by preservative

challenge testing.

65. Finally, I agree with Dr. Smyth that there is no reason to believe that phenylethyl alcohol and azelastine hydrochloride are incompatible or that EDTA and fluticasone propionate are incompatible. Ex. 2021, 191:1-14. Rather, as I previously stated, Hettche discloses using 2-phenylethanol (an alternative name for phenylethyl alcohol) in combination with azelastine hydrochloride. Ex. 1004, 53.

66. Dr. Smyth's reasoning to deviate from the known three preservative agents in Flonase® and Hettche (Example I)/Astelin® is flawed. Dr. Smyth asserts "Segal discloses that '[p]reservative-free compositions are preferred due to reduced sensitivity and increased patient compliance.'" Ex. 2150, 52 (citing Ex. 1012, 6:17-20). In stating this, Segal is referring to compositions that "can be prepared in unit dose or systems which prevent contamination of the reservoir of solution." Ex. 1012, 6:17-20. Claims 42-44 do not refer to unit dose compositions or special systems that prevent contamination, and Dymista® is a multi-dose composition that "provides 120 metered sprays, after priming." Ex. 2066, 13.

IX. Glycerine is a widely used excipient with known advantageous solubilizing properties as well as tonicity effects

67. As I previously explained, Hettche discloses that glycerine is suitable for azelastine hydrochloride formulations and is also useful for its functions as a solvent and humectant. Ex. 1004, 56; Ex. 1007, 2:35-39; Ex. 1012, 4:8-10; Ex.

1008, 3147. In fact, Hettche refers to Example I (the commercial embodiment formulation) and states “it is possible to use instead of NaCl per 100 ml of solution, for example:... glycerine 2.2 g.” Ex. 1007, 4:45-48. A skilled formulator would have considered glycerin because Hettche discloses its suitability for use with azelastine formulations.

68. Although Hettche (Example I)/Astelin® uses sodium chloride as a tonicity adjuster, a POSA would have been motivated to *avoid* sodium chloride when combining azelastine hydrochloride and fluticasone propionate. Flonase®, which includes fluticasone propionate, is an aqueous based suspension that uses the suspending agent Avicel® RC 591 (a mixture of CMC and MCC) (referred to in claims 42-44 of the '620 patent as a “thickening agent”). Similarly, when combining azelastine hydrochloride and fluticasone propionate a POSA would know that a suspending agent is likely necessary as I’ve discussed above. *Supra*. When preparing a suspension with MCC/CMC, a POSA would avoid adding any additional electrolytes (*e.g.*, sodium chloride) if uncharged equivalents are available. In fact, because MCC is “practically insoluble in water” (Ex. 1033, 13), a POSA would look to uncharged tonicity adjusters to enhance the stability of the suspension – for which glycerin was known for preventing “the crystallization of solubilized solids in an aqueous suspension” (CIP2113, 29). Because a suspending agent is likely needed in

a suspension formulation with fluticasone propionate, and because high concentrations of additional electrolytes like sodium chloride would be avoided with the suspending agent MCC/CMC, when preparing a suspension formulation combining azelastine hydrochloride and fluticasone propionate a POSA would preferably avoid using sodium chloride as a tonicity adjuster.

69. Although Flonase® uses dextrose as a tonicity agent, a POSA would be motivated to avoid using dextrose in a formulation. Sugars like dextrose are known for aiding bacterial growth when used in low concentrations. Ex. 1149, 9 (“In dilute solutions sucrose provides an excellent nutrient for molds, yeasts and other microorganisms.”), 22. If a POSA is formulating a multi-dose composition containing azelastine hydrochloride and fluticasone propionate, dextrose would preferably be avoided to prevent aiding bacterial growth.

70. Dr. Smyth asserts that “a POSA would have faced many options if they sought to use an isotonicity agent other than sodium chloride or dextrose,” but fails to acknowledge that the other listed isotonicity/tonicity agents do not have the same solvent and humectant properties that make glycerine have added attractiveness. A POSA would have been motivated to use an tonicity agent like glycerine that adds to the comfort of the nasal spray.

71. At low concentrations glycerine would not render an

azelastine/fluticasone formula too thick. Cipla asserts “[e]ven if a POSA were to consider glycerine’s other properties, a POSA would know that glycerine is used to thicken formulations and thus would potentially render the azelastine/fluticasone too thick.” Patent Owner’s Response, 45. I disagree. At 5% w/w glycerine in water at 20 °C has a viscosity of 1.143 mPas (1 mPas = 1 cPs). Ex. 1033, 21. Water at 20 °C has a slightly lower viscosity of 1.002 mPas. If glycerine is used in water at a low concentration as taught by Hettche (2.2% w/w glycerine; Ex. 1007, 4:45-50) [REDACTED], a POSA would estimate such addition would result in a glycerine solution with a viscosity nearly the same as water. Dr. Smyth admits the viscosity of water provides a good nasal spray. Ex. 1143, 56: 7-15. Thus, inclusion of such an amount of glycerine in an aqueous suspension would not be expected to render such a suspension too thick to be suitable as a nasal spray. Furthermore, a POSA would know to adjust the concentration of glycerine to achieve the desired viscosity, and they would also likely know the viscosity tolerances of the spray actuators they were considering.

72. Finally, I agree with Dr. Smyth that there is no reason to believe that glycerine and fluticasone propionate are incompatible. Ex. 2021, 191:15-19.

X. Meda’s efforts were not that of a POSA and therefore do not show “failure by others,” especially when one of the two trials appears successful

73. I understand that failure of others can be evidence of non-obviousness,

where competitors tried and failed to develop the claimed invention. I understand that Cipla has argued failure of others by relying on Meda's experiments in 2006. To support their arguments, I understand Cipla has submitted a declaration by Dr. D'Addio, who worked at Meda during this time period. Ex. 2148.

74. Having reviewed Dr. D'Addio's declaration (Ex. 2148) and deposition transcript (Ex. 1141), I am of the opinion that Meda has not shown that it "failed" to develop a combination azelastine and fluticasone formulation. Dr. D'Addio's declaration and the accompanying lab notebook (Ex. 2061) shows that Meda conducted only four days of experimentation and only two trials.

75. Further, Meda tries to avoid the fact that one of their three trials – the first trial ("Trial 1") – did not exhibit the "precipitation" Cipla now claims is failure for a different trial. Starting on April 24, 2006, Meda describes combining Flonase® with Astelin®. Ex. 2148, ¶22; Ex. 2061, 17. As admitted by Dr. D'Addio, this simple addition resulted in a combination where no precipitation was observed. Ex. 2148, ¶22; Ex. 2061, 17. Meda tries to move on from this by saying it "was only a screening experiment" (Ex. 2148, ¶22), but fails to even describe this Trial 1 as a failure.

76. The next day, April 25, 2006, Meda centrifuged the Flonase® product and then filtered through a 0.45 micrometer filter where "the force required to filter

this sample was more than the filter could withstand” leading to a spill and loss of this sample. Ex. 2148, ¶23; Ex. 2061, 18. Therefore, this second of the total three trails in April never even included azelastine hydrochloride, and so doesn’t even count as an attempt to include azelastine hydrochloride.

77. Meda attempted the trial again the next day on April 26, 2006 in initially centrifuging Flonase® for one hour to remove solids and provide a supernatant, then successively passing the supernatant through a 5 micrometer filter, a 2 micrometer filter, and finally a 0.45 micrometer filter “slowly and with difficulty.” Ex. 2148, ¶23; Ex. 2061, 18. To the resulting sample was added 0.1% w/v azelastine hydrochloride with stirring and the mixture was allowed to stir overnight (“Trial 2”). Ex. 2148, ¶23; Ex. 2061, 18. The next day (April 27, 2006), Meda asserts they visually inspected the sample and concluded “a major portion of the azelastine hydrochloride [] had not gone into solution.” Ex. 2148, ¶23; Ex. 2061, 18. Meda then put Trial 2 through alternating cycles of heating and cooling from which the sample became “white and opaque” and subsequently left to sit overnight. Ex. 2148, ¶24-28; Ex. 2061, 18. The next day (April 28, 2006), Meda observed “some of solid has, in fact, precipitated,” and Meda deemed it “necessary” to analyze the sample. Ex. 2061, 18. Results from those sample analyses have not been provided by Meda, if those samples actually underwent such analysis.

78. From beginning to end, Meda's development efforts lasted only four days from April 24, 2006 until April 28, 2006 with only two trials: Trial 1 and Trial 2. Meda's short-lived experimentation cannot be considered a serious attempt to formulate a combination product.

79. In fact, it appears that Meda only stopped its efforts to develop a combination fluticasone and azelastine formulation after discovering Cipla's published patent application "in May 2006." *Id.*, ¶26. In his declaration, Dr. D'Addio does not describe any other experiments being performed between April 28, 2006 and the unspecified date "in May 2006" when Meda discovered Cipla's patent application. No experiments are disclosed in Dr. D'Addio's declaration after discovering Cipla's patent application.

80. Furthermore, Meda's development efforts are incomplete at best. Dr. D'Addio claims that in the four days of testing, Meda could not dissolve azelastine into the Flonase® nasal spray vehicle. *Id.*, ¶24. However, no testing was ever performed to determine whether the undissolved material was in fact azelastine hydrochloride. Ex. 2148, ¶24; Ex. 2061, 18. The results of the assay of the solid precipitate are not disclosed in Dr. D'Addio's declaration (Ex. 2148, ¶25), and Dr. D'Addio testified that "I don't know if the sample was ever tested." Ex. 1141, 36:3-8. A POSA would have performed the analyses in order to determine if azelastine

was in fact the solid that precipitated out of that particular experiment. Furthermore, Meda never attempted to adjust the amount of any excipient, to use a different grade of the same excipient, include a solubility enhancer such as glycerine, or otherwise attempt to modify the composition of the sample. *See supra*, Section VI(E).

81. Moreover, Dr. D’Addio himself has testified that he has previously spent more than a couple of months developing other pharmaceutical compositions at Meda that were ultimately patented. Ex. 1141, 44:13-45:8. Dr. D’Addio is a named inventor on one such patent, U.S. Patent No. 6,417,206, which was assigned to MedPointe³ and issued on July 9, 2002. Ex. 1056. Given that Meda has previously spent months developing other pharmaceutical formulations around the same time period, Meda’s attempt to formulate a combination azelastine and fluticasone formulation after only three days of testing cannot be considered a development effort. This is consistent with Dr. D’Addio’s testimony that the shortest amount of time Meda has spent developing a viable product took “[p]robably months” because “[t]ypically you have to perform a lot of testing on the formulation to be able to decide if you’ve made a viable formulation.” Ex. 1141 at 47:15-48:6.

82. Dr. D’Addio has also testified that after entering into a product

³ In 2007, Meda acquired MedPointe Pharmaceuticals. As done by Dr. D’Addio in his declaration, I will refer to both companies as “Meda.”

agreement with Cipla, both Meda and Cipla engaged in further formulation development efforts. Ex. 1141, 62:17-64:7. Dr. D’Addio testified that “a minor modification” to the final formulation of reducing the amount of an antioxidant alone took “more than a day or two.” *Id.*, 64:5-7. Tellingly, Meda spent roughly the same amount of time developing a combination azelastine and fluticasone formulation (three days) that it took Meda to make “a minor modification” to the final Cipla formulation (more than a day or two).

83. Lastly, I am aware that Dr. Smyth has claimed that both Duonase and Dymista are formulations that are “tolerable to patients, that are homogenous, and that can be suitably deposited onto the nasal mucosa,” but neither Dr. Smyth nor Dr. D’Addio have disclosed that Duonase and Dymista do not present the same settling that Meda had encountered in its three days of testing. Ex. 2150, ¶¶63; Ex. 2148, ¶¶22-25. Meda never discussed attempting to resuspend the Trial 2 composition to form a homogenous suspension.

84. Therefore, Meda has not shown any failure because (1) Trial 1, according to Meda and Cipla’s standards, appears to have been a successful combination; (2) Meda’s mere four-day, two trial attempt was not a full development effort; (3) Meda did not attempt to resolve any perceived difficulties; and (4) Cipla and Meda do not explain whether Duonase or Dymista exhibit settling in the same

Patent No. 8,168,620

manner as Meda's Trial 2.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: March 6, 2018

A handwritten signature in cursive script, reading "Maureen D. Donovan". The signature is written in dark ink and is positioned above the printed name.

Maureen D. Donovan, Ph.D.