

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

MEDA PHARMACEUTICALS, INC. and
CIPLA LTD.

Plaintiffs,

v.

APOTEX, INC. and APOTEX CORP.

Defendants.

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Civil Action No. 14-1453 (LPS)

EXPERT REPLY REPORT OF MAUREEN D. DONOVAN, PH.D.

TABLE OF CONTENTS

	<u>Page</u>
I. SUMMARY OF OPINIONS	2
II. LEGAL STANDARDS	5
III. ANALYSIS	5
A. A POSA would not need to choose between a solution and a suspension, because every suspension is already a combination of dissolved materials in solution and undissolved materials in suspension.	5
B. The core issue is whether any ingredient necessary for the dissolution of azelastine hydrochloride would be expected to be incompatible with the ingredients necessary for the suspension of fluticasone propionate—Dr. Smyth gives no example or reason to think that any such an incompatibility exists or was thought to exist.....	9
C. As of June 2002, it would have been obvious to a POSA formulator how to formulate an azelastine hydrochloride-fluticasone propionate product and a POSA would have had an expectation of success.....	11
D. It would have been obvious to a POSA which excipients to try for a successful formulation.....	13
E. Dr. Herpin’s studies were conducted with impermissible hindsight and do not prove that Cramer III is not enabled.	18
i. Dr. Herpin did not act as a formulator POSA as of 2002.	18
ii. Dr. Herpin does not prove that Cramer is inoperable.	19
IV. CONCLUSION	23

1. I, Maureen Donovan, have been retained by Defendants Apotex, Inc., and Apotex Corp. as an expert to analyze certain aspects of U.S. Patent Nos. 8,163,723 (“the ’723 patent”); 8,168,620 (“the ’620 patent”); and 9,259,428 (“the ’428 patent”), in connection with this lawsuit.

2. I submitted an opening expert report on June 30, 2016, opining that the asserted claims of the patents-in-suit are obvious. I also submitted a rebuttal report on July 29, 2016, and I incorporate both reports by reference. I have been asked to respond to the report of Hugh David Charles Smyth, Ph.D., submitted by plaintiffs on July 29, 2016, in rebuttal to my opening report. I reserve the right to amend or supplement my opinions in light of evidence presented by or on behalf of Meda Pharmaceuticals and Cipla Ltd., or in connection with additional information that may be made available to me in the future.

3. In addition to the information, materials and opinions discussed in this report, I may use demonstrative exhibits at trial to the extent useful for explaining and understanding the opinions I set forth in this report.

4. I may testify at trial about background scientific concepts related to my opinions to the extent that is useful for understanding my opinions.

5. I am being compensated for my time on this matter at a rate of \$250/hour for general document and background review, \$400/hour for preparing reports, and \$600/hour for testifying at trial or depositions. Those are my standard consulting rates. My compensation is in no way dependent on the outcome of this case.

6. My professional background and the bases for my opinion are set forth in my opening expert report.

I. SUMMARY OF OPINIONS

7. Dr. Smyth’s rebuttal report rests on two fundamental misconceptions. First, he opines that one cannot merely assume that a formulator would have sought to combine azelastine

hydrochloride and fluticasone propionate and then proceed to determine how to go about formulating the two active ingredients. This, he claims, would “be nothing more than hindsight: starting at the end of the process by considering the obvious way a formulator POSA would proceed if she were to make a combination nasal spray that uses azelastine hydrochloride and fluticasone propionate.” Smyth ¶ 2. Rather, Dr. Smyth claims, “a formulator first would consider formulation issues when selecting an active ingredient,” and by doing so “would be counseled away from trying an intranasal antihistamine and steroid combination.” ¶ 3. A formulator would be counseled away, he argues, because “given the formulation challenges of a solution-suspension system, such a combination would not have been obvious to try, and in June 2002, a formulator POSA would not have had a reasonable expectation of success in combining those systems into a new type of nasal dosage form.” ¶ 5.

8. Dr. Smyth’s hindsight argument, however, assumes the conclusion that a co-formulation would in fact have been difficult to achieve. My opinion, as I explained in my opening report, is that there would be no readily apparent difficulties in such a formulation, and hence it would be obvious for a formulator to combine the two ingredients if that is what was desired. Assuming that such a combination is desired, as Dr. Schleimer opines without the use of hindsight, only then determining how to formulate it is not hindsight on my part or the part of any other expert whose report I have read on behalf of Apotex. Dr. Smyth, on the other hand, relies entirely on hindsight to dig through the literature finding what he says are reasons the claimed combination formula may not have worked. That inquiry makes no sense and is not how scientists work. A formulator tasked with making the combination product would have known that it was fully possible and would have had a reasonable expectation of success—even if not guaranteed success—based on the teachings of the prior art.

9. Second, Dr. Smyth's entire report is based on his opinion that formulating azelastine hydrochloride and fluticasone propionate would be difficult because it would require creating "a new dosage form: a solution/suspension" (§ 61)—or as he puts it elsewhere, a "dosage form that is both a solution and suspension" (§ 50). *See also, e.g.,* §§ 1, 4, 5, 23, 37, 59, 68, 69, 74–78, 84, 88, 104, 105, 107 (making similar statements). This is incorrect. Every suspension is a "dosage form that is both a solution and suspension." § 50. That is because every suspension includes materials that are in solution as well as materials that are undissolved. Flonase[®], for example, is actually ~99.95% fluid vehicle with dissolved materials and less than 0.05% undissolved particles in suspension. Opening Report § 93. Hence Dymista[®] is actually properly categorized—as Dr. Smyth notes in paragraph 55—as an "aqueous suspension" and not as some hybrid, "new" dosage form.

10. The question for a POSA as of June 2002—just as it would be for a POSA today when making any formulation with similar goals—is whether adding azelastine hydrochloride to the Flonase[®] formulation would be expected to be incompatible with fluticasone propionate or any of the excipients in Flonase[®]. That is the question that would have determined, as of June 2002, whether formulating a combined azelastine hydrochloride-fluticasone propionate product would have been obvious to a POSA. Dr. Smyth does not give a single example of such an incompatibility. His report fails to show that a POSA would foresee any difficulty in formulating a suspension of fluticasone propionate that includes dissolved azelastine hydrochloride.

11. As I explained in my opening report, a POSA would have expected none. It was known how to formulate azelastine hydrochloride from the Astelin[®] product, it was known how to formulate fluticasone propionate from the Flonase[®] product, and a POSA would have

expected no obvious incompatibility by combining the products, and if any unexpected incompatibility did arise, adjusting with known excipients and optimization techniques would have been a matter of routine experimentation.

II. LEGAL STANDARDS

12. I note that throughout his report, Dr. Smyth appears to assume that the legal standard for obviousness is that a POSA must have expected success to a complete certainty. He states that a formulator must have a “reasonable expectation of success,” but claims that there would be no such expectation because “a formulator POSA attempting to combine fluticasone propionate and azelastine hydrochloride would be unable to predict how the two actives interact with each other.” ¶ 80. The factual premise of his conclusion is incorrect, as I have explained in detail elsewhere. A POSA would have no reason to expect that there would be any material, negative interaction between the two active ingredients, and indeed there is no material, negative interaction between them. But Dr. Smyth appears to conflate the actual standard—a reasonable expectation of success—with the proposition that a POSA must be able to predict every interaction in its entirety and to a certainty in order for something to be obvious. I do not believe that proposition is consistent with the standard. As I explained in my opening report and as I explain again below, much was and is known about each ingredient and excipient in Astelin[®] and in Flonase[®] and a POSA would fully have expected a satisfactory formulation containing azelastine hydrochloride and fluticasone propionate and no incompatibilities—even if she were unable to know in advance to an absolute certainty.

III. ANALYSIS

- A. A POSA would not need to choose between a solution and a suspension, because every suspension is already a combination of dissolved materials in solution and undissolved materials in suspension.**

13. As summarized above, Dr. Smyth’s entire opinion that it would not be obvious to

formulate a combination product with azelastine hydrochloride (which is FDA-approved in dissolved form and sold as the nasal spray Astelin[®]) and fluticasone propionate (which is FDA-approved as a suspension dosage form and sold as the nasal spray Flonase[®]) is based on a misconception—that a POSA would not be led to combine a solution and suspension because such a combination would be novel. He writes: “[T]he formulator POSA would have understood that nasal solutions and nasal suspensions referred to two separate dosage forms and therefore would have selected one or the other. To combine the two dosage forms would have required a leap in the state of the art, as I am not aware of any art that describes a successful solution/suspension nasal spray that combines two actives in a single dosage form available as of June 2002.” ¶ 23.

14. Elsewhere he opines: “A formulator POSA seeking to develop a new drug product would use one of the existing dosage forms available, especially because literature and guidance were available only for existing dosage forms.” ¶ 37. Thus, “a formulator POSA would not have had a reasonable expectation of success in developing a dosage form that is both a solution and a suspension.” ¶ 59. He subsequently reiterates: “Combining azelastine hydrochloride and fluticasone propionate [in] a single nasal spray in 2002 would require developing a new dosage form: a solution/suspension in which the azelastine hydrochloride is in solution, while the fluticasone propionate remains in suspension.” ¶ 61.

15. He adds that a POSA would have looked to several resources on existing dosage forms, but no such guidance was available “at that time for a formulation that would be both a nasal solution and a nasal suspension.” ¶ 68. “A formulator POSA, therefore, would have little to no information on the challenges, problems, or potential ways to formulate a nasal solution/suspension combination product.” *Id.* It would not have been obvious to formulate

“such a product given the lack of any working examples or literature describing how to formulate such a product.” ¶ 69. For example, he claims, “Cramer does not provide useful guidance to a formulator POSA trying to develop a combination nasal solution/suspension product.” ¶ 74. Similarly, “[t]he Segal reference provides no guidance at all on how to formulate a combination nasal solution/suspension product.” ¶ 75.

16. Dr. Smyth repeats similar statements in paragraphs 5, 50, 60, 78, 88, 104, 105, 107, and elsewhere in his opinion, which depends on this proposition. Dr. Smyth concludes: “In my opinion, the technical knowledge necessary to create a new dosage form goes well beyond ordinary creativity to create a new dosage form.” ¶ 76. “In my opinion, discovering a formulation that would lead to a stable and useful nasal spray that combined a solution and a suspension could not have been done by routine optimization as of June 2002.” ¶ 77. “It is my opinion that the asserted claims of the patents-in-suit are not obvious, for at least the reason that the invention required combining two different and incompatible dosage forms.” ¶ 1. “Solutions and suspensions are two different dosage forms, and the literature did not set forth ways to make a combination of these two distinct dosage forms.” ¶ 4.

17. Each of these statements and the opinions they support in paragraphs 1, 4, 5, 23, 37, 59, 61, 68, 69, 74–78, 84, 88, 104, 105, 107, and elsewhere in the report rest on the misconception that combining an active ingredient in solution with an active ingredient in suspension would be a “new dosage form.” This is incorrect. Every suspension is in fact already a combination of solution and suspension. That is because many suspensions have numerous ingredients —indeed, *most* ingredients—in solution. Only a small fraction of the total weight is undissolved particles. Flonase®, for example, which is a “suspension” because the active ingredient fluticasone propionate is suspended, is in fact ~99.95% fluid vehicle with dissolved

materials and less than 0.05% undissolved materials in suspension. Opening Report ¶ 93. Indeed, even some of the fluticasone propionate is dissolved in solution. It thus “combines a solution and suspension.” There is no such thing as the “new” dosage form that supposedly would be required before azelastine hydrochloride and fluticasone propionate could be combined. That is why Dymista[®]—the very combination of azelastine hydrochloride and fluticasone propionate that is the embodiment of the patents-in-suit—is categorized as a suspension, as Dr. Smyth himself notes in his report. ¶ 55.

18. Indeed, the key pharmaceutical textbook, Remington’s (2000), defines a suspension as follows (p. 743, emphasis supplied): “The physical chemist defines the word ‘suspension’ as a *two-phase system* consisting of a finely divided solid dispersed in a solid, liquid, or gas. The pharmacist accepts this definition and can show that *a variety of dosage forms fall within the scope of the preceding statement*. There is, however, a reluctance to be all-inclusive, and it is for this reason that the main emphasis is placed on solids *dispersed in liquids*.” In other words, any POSA would understand that a suspension by definition is a “two-phase system,” typically containing a solid phase dispersed in a liquid phase.¹

19. It is telling that Dr. Smyth makes the following observation in support of his opinion: “The textbooks that Dr. Donovan relies upon support my opinion because each discusses solutions and suspensions in different sections. I would expect that if the formulation considerations were related they would have been discussed together.” ¶ 60. However, a single chapter in Remington’s (Chapter 39: “Solutions, Emulsions, Suspensions, and Extracts”) discusses both solutions and suspensions. But what is more, Remington’s discusses the science

¹ Some amount of the solid phase is dissolved in the liquid phase where it reaches a concentration equal to the equilibrium solubility in the system. Any excess material remains in the solid form. Other materials, alone or in combination, can be added to the suspension to improve its performance or organoleptic characteristics, including its taste or color, its resistance to bacterial or fungal growth, or its ability to slow the settling of the particles due to gravity, for example.

of tonicity in Chapter 18, of rheology in Chapter 23, and of drug absorption in Chapter 57. These are not discussed with either the section on solutions in Chapter 39 or the section on suspensions in that same chapter, but knowledge of all these subjects would have been crucial for a POSA in order to formulate either a solution or a suspension—and a POSA would have known to consider them. The section in Chapter 39 on suspensions also explains (p. 744) that the principles outlined in Chapters 20 and 22 govern the formulation of suspensions—yet these are in separate parts of the textbook. Dr. Smyth’s main observation in support of his claim that a solution/suspension would be a new dosage form is nothing but a non-sequitur.

B. The core issue is whether any ingredient necessary for the dissolution of azelastine hydrochloride would be expected to be incompatible with the ingredients necessary for the suspension of fluticasone propionate—Dr. Smyth gives no example or reason to think that any such an incompatibility exists or was thought to exist.

20. An important question for a POSA as of June 2002 in determining how to proceed with formulating *any* suspension *or* solution is whether any of the ingredients is expected to be incompatible with any of the others. Dr. Smyth says that when a formulator seeks to enhance the solubility of a particle, she will normally look to different ingredients than if she were looking to enhance the suspendability of a particle. But Dr. Smyth seems to assume that these opposing objectives are sought for the same particle. Yet different active ingredients can have vastly different properties, including vastly different solubilities. There was no reason to think that azelastine hydrochloride even needed the assistance of a solubility-enhancing excipient (because Astelin[®] had no such excipient), and if it did that such an excipient would have any meaningful impact on the suspendability of fluticasone propionate. A POSA would select excipients to accomplish the desired endpoints—and would certainly evaluate whether such excipients might hinder or change the properties of the other drug—but there is a reasonable expectation that a

POSA would be able to find excipients that are perfectly compatible with both objectives.

21. For example, Dr. Smyth states that “[t]o prevent dissolution” of suspended particles, “a formulator must select the appropriate vehicle and avoid excipients that may promote partial dissolution of the active ingredient” and that “[s]uspensions generally require additional excipients to ensure a uniform and stable dispersion of the suspended particles, unlike what occurs with a solution.” ¶ 62. He then states that to ensure the dissolution of an active ingredient in solution, “a formulator may select excipients that promote solubility, including solubilizing excipients, co-solvents, among others,” and that “[a] formulator may promote solubility by modifying the pH of the solution, for example.” ¶ 63.²

22. But, crucially, Dr. Smyth does not give a single example or reason to think that any of the ingredients known from the Astelin[®] formulation (indeed, Astelin[®] does not have any solubility enhancing excipients at all) would be incompatible with any of the ingredients known from the Flonase[®] formulation to be useful for the suspension of fluticasone propionate. That is the core issue, and it is one on which Dr. Smyth offers nothing but a vague generality: “a formulator POSA would recognize that techniques used to promote solubility of an active ingredient in a formulation *could potentially adversely affect* the acceptability of a suspended active ingredient in the same formulation.” ¶ 64 (emphasis added). What Dr. Smyth does not acknowledge is that those “techniques used to promote solubility” to which he refers were already known from the Astelin[®] formulation (and in fact, no solubility enhancers are necessary), and the techniques used to promote the suspension of fluticasone were already known from the Flonase[®] formulation, *and a POSA would have no reason to believe any of these were incompatible with each other*. Thus, a POSA would have had a reasonable expectation of

² Indeed, Dr. Smyth’s observation here fully supports the argument in my rebuttal report that MedPointe did not make a serious attempt at formulation—because it did not undertake any of these obvious steps to enhance the solubility of azelastine, even assuming that azelastine was not dissolved in the supernatant.

success in attempting to combine azelastine hydrochloride and fluticasone propionate in a single suspension product.

- C. As of June 2002, it would have been obvious to a POSA formulator how to formulate an azelastine hydrochloride-fluticasone propionate product and a POSA would have had an expectation of success.**

23. Not only does Dr. Smyth offer no reason to expect that any of the considerations for formulating azelastine hydrochloride in solution would be incompatible with any of the considerations for formulating fluticasone propionate in suspension, but as explained in my opening report a POSA would expect no such incompatibilities. The reason a POSA would expect no significant incompatibilities or barriers to formulation is because it was already known how to formulate azelastine hydrochloride in a successful formulation (Astelin[®]) and it was already known how to formulate fluticasone propionate in a successful formulation (Flonase[®]). A formulator would have begun with Flonase[®] because suspensions are generally more difficult to formulate, and then added azelastine hydrochloride. Because Astelin[®] had no solubility-enhancing ingredients, a POSA would not have been concerned about the opposing considerations to which Dr. Smyth refers. If there were unanticipated incompatibilities, they could be accommodated with routine optimization or by selecting alternative known excipients with similar functions.

24. Thus, paragraphs 24-52 & 66-67 of Dr. Smyth's report detailing the many steps in formulating various dosage forms such as tablets, powders, and emulsions—suggesting that a POSA would have to wade through all of these possibilities—is beside the point, because as of June 2002 a formulator already knew how successfully to formulate azelastine hydrochloride and how successfully to formulate fluticasone propionate as nasal sprays for local treatment of allergy.

25. Indeed, as the patents at issue here state, “It would be highly desirable . . . to provide a treatment that combines the effects of anti-histamine treatments and steroid treatments” ’620 Patent at 1:34-36. Thus, a POSA would have started with the known treatments, including Astelin[®] and Flonase[®]. Moreover, a POSA would not have looked to formulate a tablet because, as Dr. Kaliner recognizes in his rebuttal report, “the use of corticosteroids supplanted antihistamines as the most effective treatment option for allergic rhinitis; by 2002, corticosteroids were recognized as the most potent treatment option.” Kaliner Rebuttal Report ¶ 36; *see also* Kaliner Opening Report ¶ 52 (“At the time of invention, intranasal corticosteroids were generally recognized as the best treatment option for allergic rhinitis.”). A POSA, in other words, would know to start with an intranasal steroid. If she were looking to formulate a combination product, she would look to *intranasal* antihistamines, which can be combined with the intranasal steroid.

26. Dr. Smyth argues, however, that starting with Flonase[®] “would not lead to a workable product” because, as he previously described, “formulating a solution requires vastly different considerations than formulating a suspension” and “at several critical points, those considerations directly compete with each other.” ¶ 96. But as before, Dr. Smyth has given no example that the known requirements for dissolving azelastine in solution were incompatible with the known requirements for suspending fluticasone—and a POSA would have expected none.

27. Dr. Smyth next relies on MedPointe’s purported failure to formulate a combination product in 2006. ¶¶ 97-101. But as explained in my rebuttal report to Dr. Smyth’s opening report, MedPointe’s short-lived experiment—terminated within a few days once MedPointe discovered Cipla’s intellectual property—cannot be considered a serious attempt to

formulate a combination product. I incorporate my rebuttal report into this reply.

28. Dr. Smyth claims that even if MedPointe “could have determined how to successfully dissolve azelastine in a suspension system, it would have needed to conduct numerous additional tests to verify a successful formulation” (§ 100) and “would have then needed to analyze whether the formulation was a suitable nasal spray (§ 101). Any POSA would have to run tests and analyses if she were trying to develop a product for commercialization following FDA approval. Dr. Smyth’s implication that such tests would somehow render a formulation attempt nonobvious merely goes to show that MedPointe’s formulation attempt in 2006—in which they conducted not a single test, and in fact likely did successfully dissolve azelastine—was not a serious one.

29. Regardless, MedPointe’s “failure” to formulate in 2006, even if it was a failure, is merely hindsight on the part of Dr. Smyth, and would not factor into a POSA’s expectation of success in 2002.

30. Dr. Smyth’s only remaining argument that formulating a combination product would have been nonobvious is that “effects of small changes in a formulation are unpredictable.” §§ 79-94. That does not affect a POSA formulator’s expectation whether combining known elements would be successful. A POSA would have fully expected success in attempting to co-formulate azelastine hydrochloride and fluticasone propionate, expected that some unanticipated problems might arise, and expected that, should any such problem arise, they could be resolved with known optimization and excipient-selection techniques.

D. It would have been obvious to a POSA which excipients to try for a successful formulation.

31. Dr. Smyth specifically claims that it would not have been obvious how to account for the pH of a combined formulation, or for the preservatives, tonicity agent, suspending agent,

or the concentrations of the active ingredients in a co-formulated product. He is wrong on each count.

32. With respect to pH, he writes: “Astelin® uses a buffer system to ensure that the pH of the formulation is stable and compatible with the nasal mucosa. Flonase®, on the other hand, does not use a buffer system because fluticasone propionate is stable with the formulation’s pH range.” ¶ 82. Nothing in this paragraph suggests a POSA would expect any problem with respect to pH. A POSA would combine the active ingredients and then determine whether the pH needed to be adjusted or controlled as in Astelin®, or not, as in Flonase®. If adjustment were necessary, a POSA would have no difficulty finding a buffer compatible with both of these active ingredients. In particular, a POSA would start with the buffer used in Astelin®. Further, a POSA would anticipate no incompatibility between fluticasone propionate and any known buffer used in nasal spray formulations. As with adjusting tonicity, adding buffers to solutions or suspensions is not novel—it is what formulators do every day and what their education and experience train them to do.

33. As for preservatives, Dr. Smyth writes: “There would be many choices of preservatives that could have been used for nasal products in 2002” ¶ 83. But a POSA would have initially selected the preservatives in Astelin® and Flonase®—both included benzalkonium chloride, a very common preservative. Two other routinely used preservatives were phenylethyl alcohol and edetate disodium—the former of which was present in Flonase® and the latter of which was present in Astelin®. A POSA would not have expected any challenges in terms of creating an adequate preservative system.

34. Next, Dr. Smyth opines that glycerin would not have been an obvious choice. He writes: “I see no particular reason why using glycerine or the claimed range of glycerine would

have been obvious or routine to a POSA seeking to formulate a combination azelastine hydrochloride and fluticasone propionate product. Glycerine was not used in either Astelin® or Flonase®.” ¶ 85. Here, Dr. Smyth undermines the rest of his argument—he acknowledges that if glycerin had been used in either Astelin® or Flonase®, that would have been a reason why using it would be obvious. But every *other* excipient claimed by the asserted claims in this case *was* in either Astelin® or Flonase®. Thus, Dr. Smyth effectively concedes that the inclusion of those other ingredients would have been obvious.

35. As for glycerin itself, Dr. Smyth ultimately opines that “a formulator had no information on how glycerine interacts with fluticasone propionate.” ¶ 86. But that would not have deterred a POSA from using glycerin. A POSA would have had any number of known tonicity-adjusting agents to choose from and would have no reason to *expect* that any of them would have any kind of negative interaction with fluticasone propionate. To the extent that any tonicity-adjusting agent did have a negative interaction with another ingredient, it would have taken routine experimentation to choose another agent that had no such interaction. I understand from counsel that routine experimentation does not amount to nonobviousness.

36. For this same reason, Dr. Smyth’s argument that using microcrystalline cellulose and carboxymethylcellulose (“MCC-CMC”) would not have been obvious—a “POSA had no experience with how any excipients would interact with the selected ingredients,” ¶ 87—gets it exactly backward. MCC-CMC was known to be perfectly acceptable in the Flonase® formulation, and there was no reason for a POSA to think the inclusion of azelastine hydrochloride would be incompatible. Dr. Smyth offers no reason why a POSA would not have expected success by the inclusion of the obvious choice of MCC-CMC, already in the Flonase® formulation, except for his refrain that you never know for sure until you try.

37. Each of the above points fails to demonstrate that formulating a combination product would not be obvious. As I explained in my opening report, developing formulations with suitable preservatives, tonicity, and a suitable pH is something formulators do every day using common and known ingredients. What is more, Dr. Smyth's opinion appears to assume that a formulator would have known virtually nothing about azelastine hydrochloride or fluticasone propionate and their interactions with various excipients. Quite the opposite was true. Much was known about the pharmacological and chemical properties of these drugs, both of which were successfully formulated using common and known excipients in Astelin[®] or Flonase[®]. For example, as Meda recognized in its own development documents—citing to Bryson & Faulds (1992) and Wiseman & Benfield (1997)—“[t]here are . . . exhaustive published summaries on the pharmacological properties of [fluticasone propionate] available.” MEDA_APTX02502947. A POSA deploying all of this knowledge would have had no reason to doubt that a combination of azelastine hydrochloride and fluticasone propionate could be successfully formulated.

38. Lastly, Dr. Smyth opines that the concentration of azelastine hydrochloride and fluticasone propionate would not have been obvious because the labeling in Astelin[®] recommended 8 doses a day (two per nostril, twice daily) but the labeling in Flonase[®] recommended 4 doses per day. ¶¶ 90-94. Thus, Dr. Smyth argues, using two sprays per nostril twice daily of a combination product as per Astelin[®]'s label would lead to 1096 µg of azelastine per day but 400 µg of fluticasone—twice the daily limit recommended by the Flonase[®] label. But this misses the point. First, it would have been obvious to include the concentrations described in the Astelin[®] and Flonase[®] labels because those concentrations were known to be successfully formulated in Astelin[®] and Flonase[®]. Second, a POSA would know that the

concentrations from Astelin[®] and Flonase[®] would be safe and effective as those concentrations were already FDA approved. I understand from Dr. Schleimer that although the Astelin[®] label recommended use twice daily, all that was required for the immediate antihistaminic and anti-inflammatory effects was a single dose. A second dose later in the day could be added as needed, but the first dose would have been effective. Meda itself recognized in its development documents that “the US Product Information of Astelin[®] Nasal Spray provides details on the US pivotal clinical studies confirming its efficacy when given 1 *or* 2 sprays per nostril twice daily,” MEDA_APTX02502947, which would lead to half the amount per day that Dr. Smyth implies was necessary from the label.

39. Moreover, the Hettche reference, of which Astelin[®] is the commercial embodiment, did not teach that 1096 µg per day was required for effectiveness. Critically, the patent taught that anywhere from “0.03 to 3 mg of azelastine base should be released per spray.” Hettche at 2:20-22. That’s as few as 30 µg per spray, which would require over 36 sprays per day to reach the 1096 µg per day that Dr. Smyth implies incorrectly was required by the prior art. Hettche teaches that a preferred embodiment is 0.1% azelastine hydrochloride—the exact concentration in both Astelin[®] and the combination product—and makes no mention of how many times a day such a product could be used. Rather, Hettche (and Astelin[®]) taught that 0.1% azelastine hydrochloride, or 137 µg of azelastine hydrochloride, was effective.

40. Moreover, none of the asserted claims of the patents-in-suit depends on this dosing differential. That is because the asserted claims specify a broad concentration range for fluticasone propionate, the narrowest range being 50 µg to 0.15 mg (or 150 µg) per actuation. This upper limit of 150 µg per actuation is *three times* the amount in Flonase[®]—more than the double concentration resulting from administration of a combination product twice daily that Dr.

Smyth claims would have deterred a POSA. The asserted claims, in other words, do not claim to have discovered anything novel about the efficacy or safety of particular concentrations of fluticasone propionate.

E. Dr. Herpin’s studies were conducted with impermissible hindsight and do not prove that Cramer III is not enabled.

41. Dr. Smyth opines that EP 0780127 Example III of Cramer, which discloses a combined aqueous suspension of an antihistamine and a steroid, is “inoperable.” Dr. Smyth bases his opinion primarily on testing done by Dr. Matthew Herpin, a former graduate student of his, in which Dr. Herpin attempts to formulate Cramer’s example using a variety of methods. Dr. Smyth also critiques the testing completed by Dr. Govindarajan, which I relied on in part for my opinion that Cramer discloses an operable nasal spray formulation. My opinion remains unchanged.

i. Dr. Herpin did not act as a formulator POSA as of 2002.

42. As an initial matter, after review of both the Malhotra Declaration and Dr. Herpin’s testing, I note that Ms. Malhotra did not perform a majority of the tests that Dr. Herpin performed. Ms. Malhotra appropriately limited her enablement analysis to the types of tests a formulator would perform to determine if Cramer disclosed a useable nasal formulation. By contrast, Dr. Herpin’s tests were more focused on characteristics that support a formulation being developed into a commercial product. Dr. Herpin’s tests thus go well beyond what is required of the claims, and are therefore irrelevant regardless of his conclusions.

43. Further, Dr. Herpin’s analysis was fundamentally flawed in that he was tasked with recreating the Cramer reference with both Dr. Govindarajan’s results in hand and nonenablement in mind. Dr. Herpin did not act as a POSA formulator would have in 2002—he performed a series of experimental “recreations,” determined that the resulting products had

certain characteristics, and then stopped. A POSA formulator in 2002 would have continued the formulation process if she thought the characteristics of the initially resulting formula were unsuitable by performing known formulation adjusting steps (e.g., pH buffering) to achieve more preferred results. Put simply, Dr. Herpin was tasked with disproving Dr. Govindarajan, and stopped the formulation process after he believed he achieved that goal. Dr. Govindarajan, on the other hand, was only given the Cramer reference and asked to formulate a product that was suitable for nasal administration using nothing other than the prior art and the knowledge of a POSA in 2002. On balance, Dr. Govindarajan was put in a real world situation where the only task was to formulate, and in contrast Dr. Herpin stopped when he got a product that he determined would not meet the requirements for a commercially successful formulation.

ii. Dr. Herpin does not prove that Cramer is inoperable.

44. Turning to the alleged substance of his opinions, Dr. Smyth begins by criticizing Dr. Govindarajan's choice of a hydroxypropyl methylcellulose ("HPMC") grade, which Dr. Smyth argues has too low of a viscosity to suspend a steroid. Smyth ¶¶ 115. Further, in his discussion of Dr. Herpin's tests, Dr. Smyth notes that Dr. Herpin's attempt at Dr. Govindarajan's method produces a formulation that "cakes" after 7 days. ¶ 133. Dr. Smyth argues that this "caking" is due to the HPMC grade not being able to suspend the steroid, *i.e.*, the steroid, unsuspended, "cakes" at the bottom of the container. *Id.* I disagree.

45. First, Dr. Herpin's observed "caking" occurs over the course of 7 days. ¶ 132. Yet the Cramer reference, along with the patents-in-suit, do not require stability for any length of time. Dr. Govindarajan made a product that was suitable for pharmaceutical use at the instant it was made and dispersed, which is what a POSA formulator would have done in 2002. And Dr. Govindarajan noted that even if there was any settling over a short length of time, it was easily

remedied by a light 3-4 shakes of the bottle. This is exactly what a POSA formulator in 2002 would have expected after preparing a suspension. Moreover, if there were any stability limitations put on the POSA formulator, she would have been able to perform routine steps to remedy the expected sedimentation problem to keep the formulation stable for a reasonably desired length of time.

46. Second, Dr. Govindarajan's selection and use of a lower grade HPMC, along with all of Dr. Govindarajan's formulation steps, was well within what a POSA would have done in 2002, and Dr. Govindarajan's overall formulation did produce a suspension, as shown by his observations. But if a POSA was concerned about shelf life, which Dr. Smyth seems to be, she would have simply reformulated using a different grade of HPMC to achieve a suspension with a slower settling rate. A POSA, such as Dr. Govindarajan, would not be overly concerned about shelf life at an early formulation stage. A POSA would be concerned with making a usable product, and a POSA would know to adjust the formulation to accommodate any commercial limitations put on her formulation (*e.g.*, shelf-life, spray geometry, etc.). Cramer simply discloses a working pharmaceutical composition—it does not disclose a perfect commercial product.

47. Third, even if there were some commercially unacceptable “caking” in Cramer III, a POSA would know to use a different grade of HPMC to achieve a higher viscosity. There is a finite number of HPMC grades that a POSA could use to achieve a viscosity for the pharmaceutical product's desired use. *See Handbook of Pharm. Excipients* (1994) at 229 (listing four available grades of HPMC). This is presumably why Cramer did not include a grade of HPMC—because a POSA in 2002 knew to pick the grade of HPMC that would achieve the best result for her intended product. Indeed, the specific HPMC grade is commonly undisclosed in

many formulation labels or specifications, including the patents-in-suit, because any formulator knows how to select that particular grade that is required of her particular needs. *See, e.g.,* '620 patent at 3:52-54.

48. Dr. Smyth also argues that the pH levels obtained from Dr. Herpin's formulations are too acidic. But pH is easily adjusted using pH buffers. The Cramer reference itself teaches this by stating that the disclosed compositions "are preferably provided as isotonic aqueous solutions, suspensions or viscous compositions *which may be buffered to a selected pH.*" Cramer at 3:8-9 (emphasis added). This is a routine process known to a POSA in 2002 that Dr. Herpin chose not to perform. *See* Loyd V. Allen, *The Art, Science, and Technology of Pharmaceutical Compounding* (1998) at 235. As I stated earlier, this is an example of Dr. Herpin refusing to conduct routine formulation steps and stopping the formulation process because he had already supposedly achieved his goal of disproving Dr. Govindarajan.

49. Dr. Smyth next argues that Dr. Govindarajan's Cramer formulation showed an "unacceptable osmolality" of 529 mOsm/kg. ¶ 120. But in the next paragraph of Dr. Smyth's report he acknowledges that "an acceptable range of osmolality for nasal administration was 200 to 600 mOsm/kg." ¶ 121. So by Dr. Smyth's own admission, Dr. Govindarajan's Cramer formulation was acceptable. Still, Dr. Smyth argues that, while "acceptable," Dr. Govindarajan's osmolality would only be for "acute" treatments. *Id.* This is a red herring. Cramer's formulations are not limited to treating "acute" or "chronic" symptoms. And the portion of Block et al, *Inorganic Medicinal and Pharmaceutical Chemistry*, that Dr. Smyth cites does not make the distinction between chronic and acute symptoms—it just states that isotonicity is required for nasal preparations. This cannot be the case, because as I describe in my opening report and as Dr. Smyth recognizes, non-isotonic formulations are also acceptable. Imitrex was

not isotonic and was still administered as a nasal spray. Opening Report at ¶187.

50. Finally, Dr. Smyth opines that Dr. Govindarajan did not follow the Cramer “method” as taught in Cramer Example I. Specifically, Dr. Smyth believes that Dr. Govindarajan’s mixing steps are not taught by Cramer, and that neither myself nor Dr. Govindarajan provide explanation of his three homogenization steps of the Cramer formulation. But homogenization was well known in the art as of 2002, and would be seen as “mixing” within the context of the instructions of Cramer Example I. A POSA seeing any sedimentation would know to homogenize as a quality control step in order to ensure that the formulation was homogeneously dispersed. The Cramer reference leaves many routine protocol design choices to the formulator, and Dr. Govindarajan’s formulation steps were routine choices left to a 2002 formulator POSA. This is also illustrated by the three different tests Dr. Herpin performed—Dr. Govindarajan, Ms. Malhotra, and Dr. Herpin all had their own approach to formulating Cramer, and those routine formulation decisions would have been left to a POSA.

51. Overall, Dr. Herpin’s testing was done using a product development approach rather than that of a POSA formulator in 2002. It seems that Dr. Herpin was very concerned with spray geometry and sedimentation. While those characteristics may be commercially important, they would not have been important to a POSA formulator tasked with trying to simply make a pharmaceutical composition, which Dr. Govindarajan did. Ultimately, counsel has instructed me that for a reference to be enabled, a person of ordinary skill in the art must be able to make and use the invention without undue experimentation. They do not need to be able to make it so that it is a fully optimized, FDA-approvable, commercializable product. I reiterate my opinion that Dr. Govindarajan, as a 2002 POSA formulator, made and used Cramer Example III after routine experimentation.

IV. CONCLUSION

52. In conclusion, a POSA formulator tasked with combining azelastine hydrochloride and fluticasone propionate into a single combination product would have known how to do so. Each ingredient had been successfully formulated in an FDA-approved product using known excipients that are also common in the art. No science suggested that either active ingredient would be incompatible with the other, or that any excipient necessary to improve the suspendability of fluticasone propionate would be incompatible with the solubility of azelastine hydrochloride. To the extent any unanticipated difficulties arose in terms of stability, tonicity, or pH, a formulator would use routine optimization techniques well known in the art to adjust the formulation. Even if a formulator would not have had a certainty of success, she most certainly would have had a reasonable expectation of success.

DECLARATION

I declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true.

Date: August 19, 2016

By: 

Maureen Donovan, Ph.D.

Materials Considered for the Reply Expert Report of Maureen Donovan

Description	Begin Bates	End Bates
Block, J., et al., "Inorganic Medicinal and Pharmaceutical Chemistry," 1986, cover, publication, and preface pages plus p. 100, Indian Edition, Varghese Publishing House, Bombay, India	APOTEX_AZFL 0059681	APOTEX_AZFL 0059684
Bryson, et al., "Intranasal fluticasone propionate: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in allergic rhinitis," Drugs, 1992, vol. 43, No. 5, pp. 760-775	APOTEX_AZFL 0059695	APOTEX_AZFL 0059713
Declaration of Geena Malhotra (July 6, 2005)	CIP_DYM_00060301	CIP_DYM_00060350
Declaration of Geena Malhotra (September 23, 2010)	MED_DYM_00000654	MED_DYM_00000682
Lloyd V. Allen, The Art, Science, and Technology of Pharmaceutical Compounding, Chapter 20 (1998)	APOTEX_AZFL 0132304	APOTEX_AZFL 0132325
Module 2.5 Clinical review on the fixed drug combination of azelastine hydrochloride and fluticasone propionate nasal spray for allergic rhinitis (June 30, 2011)	MEDA APTX02502922	MEDA APTX02502987
Remington: The Science and Practice of Pharmacy, 2000, 20th edition, vol. 1, Chapter 18, Tonicity, Osmoticity, Osmolality, and Osmolarity (2000)	APOTEX_AZFL 0130673	APOTEX_AZFL 0130689
Remington: The Science and Practice of Pharmacy, 2000, 20th edition, vol. 1, Remington, Chapter 22: "Rheology"	MEDA_APTX03505007	MEDA_APTX03505029
Remington: The Science and Practice of Pharmacy, 2000, 20th edition, vol. 1, Chapter 23 Rheology (2000)	APOTEX_AZFL 0132197	APOTEX_AZFL 0132219
Remington: The Science and Practice of Pharmacy, 2000, 20th edition, vol. 1, Chapter 39, Solutions, Emulsions, Suspensions, and Extracts	APOTEX_AZFL 013942	APOTEX_AZFL 013973
Remington: The Science and Practice of Pharmacy, 2000, 20th edition, vol. 1, Remington, Chapter 57: "Drug Absorption"	APOTEX_AZFL 0135183	APOTEX_AZFL 0135212
U.S. Patent No. 5,164,194 (Hettche)	APOTEX_AZFL 0054360	APOTEX_AZFL 0054365
U.S. Patent No. 8,163,723	CIP_DYM_0054179	CIP_DYM_0054192

Description	Begin Bates	End Bates
U.S. Patent No. 8,168,620	CIP_DYM_0054193	CIP_DYM_0054206
U.S. Patent No. 9,259,428	MEDA_APTX03490368	MEDA_APTX03490383
Wade, A., et al., Handbook of Pharmaceutical Excipients (1994)	APOTEX_AZFL 0132041	APOTEX_AZFL 0132077
Wiseman, L., et al., "Intranasal Fluticasone Propionate: A Reappraisal of its Pharmacology and Clinical Efficacy in the Treatment of Rhinitis," Drugs, 1997, vol. 53, No. 5, pp. 885-907, Adis International Limited.	APOTEX_AZFL 0061890	APOTEX_AZFL 0061902
Expert Report of Dr. Ramprakash Govindarajan (June 30, 2016)	N/A	N/A
Expert Report of Robert Schleimer (June 30, 2016)	N/A	N/A
Rebuttal Expert Report of Matthew Herpin, Ph.D. (July 29, 2016)	N/A	N/A
Rebuttal Expert Report of Michael Kaliner, Ph.D. (July 29, 2016)	N/A	N/A
Rebuttal Expert Report of Robert Schleimer (July 29, 2016)	N/A	N/A
Rebuttal Expert Report of Charles Hugh Smyth, Ph.D. (July 29, 2016)	N/A	N/A
All documents cited in my rebuttal expert report	N/A	N/A