

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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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

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*Inter Partes* Review No.: IPR2017-00807

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**PETITIONER'S RESPONSE TO PATENT OWNER'S  
MOTION FOR OBSERVATIONS ON CROSS-EXAMINATION OF  
PETITIONER'S REPLY WITNESSES: DR. ROBERT SCHLEIMER, DR.  
MAUREEN DONOVAN, AND JOHN C. STAINES, JR**

Petitioner Argentum Pharmaceuticals LLC (“Petitioner”) hereby responds to Patent Owner’s motion for observations regarding the cross-examinations of Dr. Robert Schleimer, Dr. Maureen Donovan, and John C. Stains, Jr. (Paper 44, hereafter “Mot.”). Office Patent Trial Practice Guide, 77 Fed. Reg. 48756 at 48767-68 (August 14, 2012).

**Observation #1:** Patent Owner’s assertion that Dr. Schleimer’s testimony is undermined by his adoption of the statements in footnote 1 of his second declaration (EX1144) misapprehends the deposition testimony and the claims. Footnote 1 made clear that Dr. Schleimer did not consider the specific limitations of claims 4 and 42-44 because “[Petitioner] asked a formulation expert to weigh in on them,” and that otherwise Dr. Schleimer considers “the combination of azelastine and fluticasone in a formulation suitable for nasal administration to be obvious for claims 4 and 42-44 for the same reasons as all the claims discussed [in the declaration].” EX1144, n.1. Claims 4 and 42-44 all depend from claim 1, making Dr. Schleimer’s opinions as to claim 1 relevant to claims 4 and 42-44.

**Observation #2:** Patent Owner’s assertions misapprehend Dr. Schleimer’s deposition testimony. Dr. Schleimer explained that from a layperson’s perspective, the clinical practice of conjunctive therapy most closely approximates the claimed invention. EX2179, 42:17-44:17. Dr. Schleimer also recognized that in the context of this legal proceeding where “prior art” might be restricted to printed

publications only, Segal and Cramer would be the strongest prior art. *Id.* Dr. Schleimer also noted that adoption of that prior art “does change [his] opinion” relative to his layman consideration of prior clinical use. *Id.*

**Observation #3:** Patent Owner’s assertions based on Dr. Schleimer’s testimony regarding Howarth and Nielsen both mischaracterize his testimony and ignore other relevant testimony. As to Howarth (EX2041), Dr. Schleimer explained that Howarth’s assertion of lack of clinical benefit was unsupported, and that Howarth overlooked the additivity of azelastine and fluticasone during the first two weeks of administration (EX2179, 66:2-20), which Dr. Schleimer explained in greater detail in his declaration (EX1144, ¶¶32-36). Regarding Nielsen (EX2042), Dr. Schleimer explained that the authors’ goal was to “definitively establish that steroids are superior to antihistamines, but when it came to discussing the combination, they kind of gave it short shift” and that “they begrudgingly admit that the combination has some marginal benefits but the cost is an issue” (EX2179, 73:6-9, 12-15), which was also discussed in more detail in Dr. Schleimer’s declaration (EX1144, ¶¶37-38). Dr. Schleimer also noted that one of Cipla’s own experts disagreed with the conclusions of these papers. *Id.*, ¶39.

**Observation #4:** Patent Owner’s assertions regarding what Dr. Schleimer explained in relation to Ratner 2008 (EX1045) grossly mischaracterizes the deposition testimony. The testimony ascribed to Dr. Schleimer only occurred

when he was asked to read aloud a quote from Ratner 2008 (EX2179, 96:13-19)—this was not Dr. Schleimer’s own testimony regarding Ratner. Instead, when asked “doesn’t this statement imply that six years later the authors were surprised by the efficacy of their regimen?” Dr. Schleimer explained that “[t]o me, as I’ve testified, a POSA would have anticipated an additivity, and a POSA would have looked at these results and thought, yeah, that makes sense” and “[w]hy they wrote it’s unanticipated and to what extent it truly reflects the views of all the authors, I cannot comment.” *Id.*, 98:2-21.

**Observation #5:** Patent Owner’s assertions that Dr. Schleimer relied on post-invention publications to support his obviousness conclusions mischaracterize the testimony and ignores other relevant testimony. Dr. Schleimer testified that it was well-known before the priority date that azelastine’s onset was 15-30 minutes. EX2179, 103:15-104:11, 109:11-13. Dr. Schleimer then explained that because Dr. Carr affirmatively contested the fast onset of azelastine, he felt it was important to find support both before and after the priority date showing that Dr. Carr’s arguments were incorrect. *Id.*, 104:19-105:22.

**Observation #6:** Patent Owner’s assertion that Dr. Donovan undermined her credibility when she stood by her trial demonstratives is false. Dr. Donovan explained that the purpose of the chart in EX2177 was not to communicate to the Court the advantages and drawbacks of all of the tonic agents shown. EX2178,

55:11-18. Dr. Donovan also testified on numerous occasions regarding the fact that while all of the listed materials were obvious tonicity agents, there were advantages to glycerine and drawbacks to sodium chloride and dextrose that would cause a POSA to prefer glycerine over the other choices. EX2178, 44:16-45:5; 45:17-46:3; 54:15-55:6; 56:1-19; *see also* EX1145, ¶¶68-70 (same).

**Observation #7:** Patent Owner's assertion that Dr. Donovan's deposition testimony contradicts her testimony that a motivation existed to "use the three preservatives as recited in claims 42-44" and to "avoid using dextrose" mischaracterizes the testimonial record. When asked if there was no need for dextrose when using the preservatives from Flonase in a combination fluticasone azelastine formulation, Dr. Donovan testified that a "POSA always holds out the possibility that they will have some undesired failure of their system and then the dextrose will serve as a great growth media." EX2178, 66:20-67:13. Dr. Donovan's declaration also explains that "[s]ugars like dextrose are known for aiding bacterial growth when used in low concentrations." EX1145, ¶69. This is further corroborated by Dr. Donovan in her deposition. EX2178, 71:18-72:7. Additionally, Dr. Donovan also testified that there is "always a concern that your antimicrobial preservatives will fail under some use challenge" and that one can "address that concern through the use of adequate antimicrobial preservatives." *Id.*, 67:4-9; 73:5-8.

**Observation #8:** Patent Owner’s assertion that Dr. Donovan’s deposition testimony relating to whether two amine structures in azelastine are tertiary amines undercuts her testimony that azelastine is a monovalent cation misapprehends the testimony. Dr. Donovan testified that azelastine contains only one functional group that would be characterized as a tertiary amine. EX2178, 124:7-125:1; 126:5-8, 16-19. Dr. Donovan also testified that unless the pH were extreme (e.g., below 0 or 1, or near 14 and above), azelastine contains only a single protonation site. *Id.*, 128:16-130:1. In her declaration, Dr. Donovan also referenced Dr. Smyth’s opinion that “[i]n a pharmaceutical aqueous solution, the tertiary amine of azelastine will have a [singular] positive charge,” which translates to azelastine behaving like a monovalent cationic drug in solution. EX1145, ¶28; EX2150, ¶47. The testimony highlighted by Patent Owner relates to counsel’s questions asking what the other two amines in azelastine would be called, *i.e.*, what technical term would be used to describe those other functional groups. EX2178, 125:12-16. That issue was not within the scope of Dr. Donovan’s testimony or expertise (*id.*, 126:1-4, 15-16), nor is it relevant.

**Observation #9:** Dr. Donovan’s testimony that a final formulation must administer the dose that was intended to be administered is irrelevant to her disagreement with Dr. Smyth’s construction of a “dosage form that is suitable for nasal administration.” Dr. Donovan testified that a dosage form is suitable for

nasal administration if it is able to administer the dose that was intended to be administered and to do so, a POSA would use chemical analysis to determine the amount of drug the spray was delivering. EX2178, 138:19-139:2; 163:21-164:17. Dr. Donovan's testimony does not support Dr. Smyth's proffered claim construction of "pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited on the nasal mucosa." Dr. Donovan's declaration explains in detail that Dr. Govindarajan's recreations of Cramer Example III were physically stable and provided a successful nasal spray, which were the relevant issues with respect to these tests. EX1145, ¶¶34-40.

**Observation #10:** Patent Owner's assertion that Dr. Donovan conceded that Dr. Govindarajan's recreations of Cramer Example III were not a "dosage form suitable for a nasal administration" is a misstatement of the record. Dr. Donovan's declaration explains in detail that Dr. Govindarajan's recreations "could be delivered as a fine spray using a nasal spray pump." EX1145, ¶40. Dr. Donovan testified that Dr. Govindarajan's first recreation of Cramer Example III was "his first mixing of materials" in response to a question on whether visual observation "doesn't foreclose the possibility that the composition is not uniformly resuspended." EX2178, 197:11-198:9. Dr. Donovan further explained that each of the three batches Dr. Govindarajan recreated were found to be physically stable and exhibited behaviors of a pharmaceutically acceptable suspension. EX1145,

¶¶34, 40. The relevance of Dr. Govindarajan’s recreations of Cramer Example III relates only to the fact that the formulations were adequately suspended and stable, and could be adequately sprayed, not whether they were in a “dosage form suitable for a nasal administration.” Dr. Donovan was never asked at her deposition and never testified that Dr. Govindarajan’s recreations of Cramer Example III were not in a “dosage form suitable for a nasal administration.”

**Observation #11:** Patent Owner’s assertion that Dr. Donovan did not “call into question” in the related district court proceeding the difference in the grades of viscosity of HPMC used by Drs. Herpin and Govindarajan mischaracterizes the testimonial record. Dr. Donovan testified that she “was certainly aware of” the HPMC viscosity grade difference for the *Apotex* case, but simply could not “recall a paragraph that speaks directly to the viscosity grade of the HPMC.” EX2178, 172:19-173:10; 174:6-9. Dr. Donovan denied the suggestion that this issue was not meaningful enough to point out in her reply report in the *Apotex* case. *Id.*, 173:20-22. Instead, Dr. Donovan testified repeatedly that the *Apotex* case involved other issues, other experts, was “a different litigation.” *Id.*, 173:8-10, 14-19; 174:19-175:3.

**Observation #12:** Patent Owner’s assertion that Dr. Donovan’s testimony regarding azelastine dissociating into electrolytes undercuts her conclusion that azelastine hydrochloride would not have been viewed by a POSA as incompatible



with MCC/CMC is false and unsupported by the testimonial record. Dr. Donovan's declaration explains that azelastine hydrochloride would be understood to dissociate to a monovalent cation in an aqueous media. EX1145, ¶28. Dr. Donovan also testified only that cations and anions are "broadly classified as electrolytes." EX2178, 120:4-7. As to the compatibility of azelastine hydrochloride with MCC/CMC, Dr. Donovan explained in her declaration that MCC/CMC are compatible with monovalent cationic drugs like azelastine. EX1145, ¶¶18-29. Patent Owner cites no other evidence to support its conclusion in this observation, nor is any connection apparent.

**Observation #13:** Patent Owner's assertion that Dr. Donovan admitted that the two-preservative combinations in Astelin<sup>®</sup> and Flonase<sup>®</sup> were sufficient to inhibit bacterial growth mischaracterizes the deposition testimony. Dr. Donovan testified that there is "always a concern that your antimicrobial preservatives will fail under some use challenge," and that one can "address that concern through the use of adequate antimicrobial preservatives." EX2178, 67:4-9; 73:5-8. Dr. Donovan further explains in her declaration why a POSA would have been motivated to select the three preservatives used at issue here. EX1145, ¶¶59-66.

**Observation #14:** Patent Owner's assertion that Dr. Donovan's failure to rely on "prior art" to support a pH of 3 or below being "suitable for nasal administration" speaks to the weight and credibility of Dr. Donovan's conclusions

is without merit. Dr. Donovan cites both to claim 45 of the '620 patent as well as Dr. Smyth's own deposition testimony to support her conclusion that a pH of 3 or below is suitable for nasal administration. EX1145, ¶46; EX1143, 79:9-20; EX1001, claims 1, 45.

**Observation #15:** Patent Owner's assertion that Dr. Donovan "admitted that Dr. Govindarajan's visual observations alone are insufficient to show a uniform suspension" misstates the testimonial record. Dr. Donovan never testified that visual observations alone are insufficient to show a uniform suspension. Dr. Donovan testified that she would "use whatever information I'm provided and discern whether I think it makes logical sense." EX2178, 196:21-197:1. She further testified that when recreating Cramer Example III, Dr. Govindarajan used a methodology entirely consistent with how she believes a POSA would approach the problems he was given, and that she has no reason to not believe the notations Dr. Govindarajan recorded. EX2178, 197:2-9. Dr. Donovan also testified that a chemical analysis is "not what one does with the first formulation mixing attempt that you undertake as a formulation development scientist." *Id.*, 197:17-198:9; *see also* 195:6-8. Lastly, Dr. Donovan testified that she was "willing to believe" that Dr. Govindarajan readily and uniformly resuspended the solid. *Id.*, 196:3-9.

**Observation #16:** Patent Owner's assertion that Mr. Staines' deposition testimony undercuts his credibility and undermines "his conclusions that rebates

and copayment programs were primary drivers of Dymista® sales”

mischaracterizes the testimonial record. Mr. Staines’ declaration explains in detail how rebates and copayment programs resulted in low net prices for Dymista, and that analysis does not rely on identification of specific portions of sales. EX1040, ¶¶119-125. As to impact of Dymista rebates, and comparison to other drugs, Mr. Staines testified that he analyzed Dymista’s rebates using documentation and his experience (EX2180, 15:15-16:4), which can be found in his declaration at paragraphs 63 and 124, and Ex. 2a. Similarly, Mr. Staines testified about the impact of Dymista’s copayment program including the existence of other common copayment programs that do not reduce prices to those close to generics. EX2180, 22:19-24:14.

**Observation #17:** Patent Owner’s assertion that Mr. Staines conceded that documents he relied upon did not provide support for his assertions regarding constraints of Meda’s salesforce in paragraph 127 of his declaration mischaracterizes the deposition testimony. Paragraph 127 specifically references the 2015 GlobalData study (EX2053), and Mr. Staines specifically recited that study when asked “what was your basis for characterizing Mr. Jarosz's opinions as being limited to primary care physicians?” *See* EX2180, 36:2-37:19. While Mr. Staines acknowledged there was no explicit statement in EX2053 regarding Primary Care Physicians, he explained there is an inference that “if [Meda] have a

good presence with respiratory market, that means that [in] the other market, [Meda] doesn't." EX2180, 39:13-15.

**Observation #18:** Patent Owner's assertion that Mr. Staines' deposition testimony relating to the 2012 and 2013 Dymista discount rates "under cuts Mr. Staines' credibility and undercuts his conclusions that Dymista's 47% rebate in 2015 is atypical" misapprehends the deposition testimony relative to Mr. Staines' declaration. Mr. Staines stated in his declaration that "[t]he discounts through 2015, however, are comparatively large for brand drugs," not that those in 2012 and 2013 were atypical. EX1040, ¶124. As for "atypical," Mr. Staines specifically testified that the "47% discount is atypically large for innovative brand pharmaceuticals that have no bioequivalent generic competitors." EX1040, ¶63.

**Observation #19:** Patent Owner's assertion regarding Mr. Staines' deposition testimony relating to blocking patents misapprehends the testimony relative to Mr. Staines' declaration. Mr. Staines' statement that the ultimate opinion as to blocking "is not my opinion" is consistent with his declaration, which explains the basis of his assumption that the blocking patents existed. EX1040, ¶108. Consistent with his declaration, Mr. Staines testified "[i]t's possible that [the blocking patents] could [block]. I could foresee that they would inhibit or impede somebody from developing a product if they're not sure when somebody is going

to launch or when they're going to be able to launch, and that would be an impediment or disincentive to develop." EX2180, 89:21-90:5.

**Observation #20:** Patent Owner's assertions regarding Mr. Staines' testimony relating to "novel features" misapprehends his deposition testimony and the testimony provided in his declaration. Regarding "novel features," Mr. Staines explained that "when I say something is novel, I'm using it in a layman's sense" and that "to the extent that 'novel' has some patent law implication here, I'm not using it in that sense, and I don't have an opinion in that way." EX2180, 86:1-7. This is consistent with his declaration which states "[i]n other words, there must be a causal correlation, or 'nexus,' between the purported merits of the claimed invention and the success of the product," where Mr. Staines testified during his deposition that he assumed "all the features of Dymista are in some way or form claimed in the patent, but I don't have a technical knowledge of what specific things." EX1140, ¶106; EX2180, 85:7-11.

Respectfully submitted,

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**CERTIFICATION OF SERVICE**

The undersigned hereby certifies that a copy of the foregoing  
**PETITIONER'S RESPONSE TO PATENT OWNER'S MOTION FOR  
OBSERVATIONS ON CROSS-EXAMINATION OF PETITIONER'S  
REPLY WITNESSES: DR. ROBERT SCHLEIMER, DR. MAUREEN  
DONOVAN, AND JOHN C. STAINES, JR** was served on April 24, 2018, on  
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