

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

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CASE IPR2017-00807  
Patent 8,168,620

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

***Mail Stop "PATENT BOARD"***  
Patent Trial and Appeal Board  
U.S. Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450

Patent Owner Cipla Ltd. (“Cipla”) deposited Petitioner’s reply witness, Dr. Maureen Donovan, on March 27, 2018, and files concurrently the deposition transcript and a previously unfiled exhibit as exhibits CIP2178 and CIP2177, respectively. Cipla deposited Petitioner’s reply witness, Dr. Schleimer, on March 30, 2018, and files the deposition transcript concurrently as Exhibit CIP2179. Finally, Cipla deposited Petitioner’s reply witness, Mr. Staines, on April 4, 2018, and files concurrently the deposition transcript as Exhibit CIP2180 and a previously unmarked exhibit that was marked by Petitioner as EX1171. Cipla files its Motion for Observations on Cross-Examination in accordance with Due Date 4 (Paper 36, 1). All emphasis is added unless otherwise noted.

**I. Observation #1: Dr. Schleimer previously offered no evidence of a motivation to combine the four references listed in Ground 3.**

In CIP2179, at 27:9-32:18, Dr. Schleimer testified that, with the exception of water, he “did not” discuss in his reply declaration (EX1144) any of the limitations in claims 42-44, *i.e.*, the claims of Ground 3. Dr. Schleimer further confirmed that footnote 1 of EX1144 is his sole response to Dr. Carr’s testimony that Dr. Schleimer’s first declaration (EX1003) failed to mention claims 42-44 or any motivation to combine the references of Petitioner’s Ground 3. This testimony is relevant to Dr. Schleimer’s obviousness conclusions pertaining to claims 42-44 and Petitioner’s arguments because it undercuts their position that a motivation existed in 2002 for a person of ordinary skill to combine the art cited in Ground 3.

EX1144, ¶5, n.1; Reply, 15-18.

**II. Observation #2: Petitioner and its declarant did not agree on the closest prior art.**

In CIP2179, at 42:17-44:17, Dr. Schleimer, when asked if Cramer and Segal are the closest prior art, testified, “[n]o, that’s not correct” but that he “was convinced that from a legal perspective that Segal and Cramer are perhaps more persuasive to a patent board than my view.” This testimony is relevant to Dr. Schleimer’s obviousness conclusions and Petitioner’s arguments because it undercuts Dr. Schleimer’s credibility and undermines his conclusions that Dymista<sup>®</sup> does not exhibit unexpected results compared to the closest prior art. EX1144, ¶¶52-60; Reply, 18-23. This is also relevant to the weight and credibility the Board should afford Dr. Schleimer’s testimony.

**III. Observation #3: Dr. Schleimer testified that multiple authors concluded that co-administration of antihistamines and steroids yielded no clinical benefit.**

In CIP2179, at 58:3-74:15, Dr. Schleimer testified regarding the various co-administration studies he cited, as well as meta-analyses published before the invention date. He testified that Howarth (CIP2041) concluded that there was no “clinical benefit” to co-administration. He also testified that Nielsen (CIP2042) found that “[c]ombining antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis does not provide any additional effect to intranasal corticosteroids.” This testimony is relevant to Dr. Schleimer’s obviousness

conclusions and Petitioner's arguments because it undermines Dr. Schleimer's credibility by contradicting his testimony regarding the views of skilled artisans before the invention date and further undermines his conclusions regarding how a POSA would interpret the co-administration studies he cites. EX1144, ¶¶ 10-39, 52-86; Reply, 3-10, 18-23.

**IV. Observation #4: The clinical efficacy of co-administered azelastine and fluticasone was surprising in 2008.**

In CIP2179, at 8:5-13, 80:15-19, and 93:9-98:12, Dr. Schleimer testified the authors of Ratner 2008 (EX1045) had concluded that co-administration of azelastine and fluticasone "produced an unanticipated magnitude of improvement in rhinitis symptoms." This testimony is relevant to Dr. Schleimer's obviousness conclusions and Petitioner's arguments because it undercuts Dr. Schleimer's conclusions regarding the clinical efficacy a POSA would have expected on the invention date because it confirms the independent views of skilled artisans years after the date of invention. EX1144, ¶¶ 52-67, 83-86; Reply, 18-21.

**V. Observation #5: A POSA could not have known about Han and Corren "unless they had a time machine."**

In CIP2179, at 103:13-104:6 and 107:4-109:13, Dr. Schleimer testified that he could not find any data from before the priority date to support a fast onset of azelastine, so he cited Han (EX1148) and Corren (EX1160). He further explained that a POSA as of the invention date could not have been aware of the data

conveyed in those two references “unless they had a time machine.” This testimony is relevant to Dr. Schleimer’s obviousness conclusions and Petitioner’s arguments because Dr. Schleimer’s reliance on post-invention publications to support his reading of onset undermines Dr. Schleimer’s conclusion that POSA in 2002 would have expected Dymista<sup>®</sup>’s onset of action. EX1144, ¶¶68-73; Reply, 21-22.

**VI. Observation #6: Dr. Donovan previously believed that sodium chloride and dextrose were obvious tonicity adjusters to use in an azelastine hydrochloride/fluticasone propionate combination formulation.**

In CIP2178, at 46:7-55:6 and 56:20-57:14, Dr. Donovan stood by her trial demonstratives from the related proceedings before the the District Court for the District of Delaware that her trial demonstratives (*see* CIP2177) that “list as an obvious tonicity adjuster to use—to include in this combination formulation, dextrose and sodium chloride.” According to Dr. Donovan, in CIP2178, at 58:17-59:4, “they [sodium chloride and dextrose] were all materials that – that were identified as obvious materials to include in a combination formulation” of azelastine hydrochloride and fluticasone propionate. Dr. Donovan’s direct testimony demonstratives from the related proceeding are filed concurrently as CIP2177. CIP2177 and the above cited testimony in CIP2178 are relevant to Dr. Donovan’s obviousness conclusions and Petitioner’s Reply arguments because they directly contradict her testimony in the present proceeding that a POSA would

have sought to “avoid” dextrose and sodium chloride and/or undermine her credibility. EX1145,<sup>1</sup> ¶¶68-69; Reply, 17-18. This testimony is also relevant to the weight and credibility the Board should afford Dr. Donovan’s conclusions.

**VII. Observation #7: Flonase<sup>®</sup> contains antimicrobial preservatives that have been shown to adequately control bacterial growth in the dextrose component.**

In CIP2178, at 61:4-63:17, Dr. Donovan testified that “in the chemical manufacturing controls package for an FDA-approved project [sic] that you have to demonstrate that your antimicrobial preservative for a multidose system is adequate.” In CIP2178, at 65:1-16, Dr. Donovan confirmed that “by 2002 Flonase was a multidose nasal spray that was FDA approved” and “contained the preservatives benzalkonium chloride and phenyl ethyl alcohol.” In CIP2178, at 66:9-19, Dr. Donovan testified: “Flonase contains antimicrobial preservatives that have been demonstrated to maintain the lack of growth. They kill or – or render harmless, somewhat harmless, bacteria that – that can enter into that formulation. So there’s likely no bacteria there to need the dextrose to feed off of.” This testimony is relevant to Dr. Donovan’s obviousness conclusions and Petitioner’s Reply arguments because it contradicts her testimony that a motivation existed in 2002 to (1) use the three preservatives as recited in claims 42-44, and (2) avoid

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<sup>1</sup> Citations to EX1145 also apply equally to EX1165, a public redacted copy of EX1145.

using dextrose. EX1145, ¶¶59-66, 69; Reply, 17-18.

**VIII. Observation #8: Dr. Donovan did not know whether azelastine could be a di- or trivalent cation.**

In CIP2178, at 125:2-16, when asked whether two additional amine structures in azelastine would be classified as tertiary amines, Dr. Donovan testified that “identifying functional groups in—in chemical molecules is not something I’m prepared to do about azelastine or other structures today.” In CIP2178, at 125:17-126:8, Dr. Donovan further testified: “I haven’t made a systematic analysis of the other functional groups contained in azelastine to both name them and be able to tell you what sort of electronic structure contributions they make.” And in CIP2178, at 127:13-128:1, when asked whether the two additional amine structures contained in azelastine would protonate to form a di- or trivalent cation, Dr. Donovan testified: “Well, a formulator acting as a POSA wouldn’t be the person doing that. I haven’t been asked to provide an opinion on how a formulator or a chemist would go about doing that. So at this point in time I am not prepared to – to start describing accurately how that would be accomplished.” This testimony is relevant to Dr. Donovan’s obviousness conclusions and Petitioner’s Reply argument because it undercuts her testimony that azelastine is a monovalent cation. EX1145, ¶¶18-29; Reply, 11-12. This testimony is also relevant to the weight and credibility the Board should afford Dr. Donovan’s conclusions.

**IX. Observation #9: Dr. Donovan admits that a “dosage form suitable for nasal administration” is a final formulation that must administer the dose that was intended to be administered.**

In CIP2178, at 138:19-139:2, Dr. Donovan testified that a dosage form is suitable for nasal administration if it “at the time that it’s administered that it [is] able to administer the dose that was intended to be administered.” In CIP2178, at 159:10-22, Dr. Donovan admitted that the time a POSA would know that a formulation delivers the amount of the drug intended to be administered “would likely be the time at which I’ve decided on my final formulation components, their final concentrations, my final device, my final – and what my – probably close to what my manufacturing specifications would be.” In CIP2178, at 163:21-164:17, Dr. Donovan admitted that to determine whether a multidose drug suspension administered the amount of drug that was intended to be administered, she would have to “chemically analyze for the amount of drug that was sprayed into whatever container I sprayed it into.” This testimony is relevant to the claim construction issue in Dr. Donovan’s declaration and Petitioner’s Reply because it undermines Dr. Donovan’s disagreement with Dr. Smyth’s claim construction testimony and supports Cipla’s proffered claim construction: “pharmaceutical formulations that are tolerable to patients, that are homogeneous, and that can be suitably deposited on the nasal mucosa.” EX1145, ¶¶7-11; Reply, 1-3. This testimony is also relevant to Dr. Donovan’s obviousness conclusions and Petitioner’s Reply because it



undermines her claims that Dr. Govindarajan's recreations of Cramer Example III were successful. EX1145, ¶¶30-41; Reply, 13-15.

**X. Observation #10: Dr. Donovan confirmed that Dr. Govindarajan's recreations of Cramer Example III were not a "dosage form suitable for a nasal administration."**

In CIP2178, at 195:3-8, Dr. Donovan testified that Dr. Govindarajan "was approaching [his recreations of Cramer Example III] as a POSA beginning a formulation development activity." In CIP2178, at 197:11-198:9 and 199:2-8, Dr. Donovan testified that Dr. Govindarajan's recreation of Cramer Example III "was not a formulation" but instead was "his first mixing of materials that were listed as a composition." And, in CIP2178, at 159:10-22, Dr. Donovan testified that the time a POSA would know that a formulation delivers the amount of the drug intended to be administered "would likely be the time at which I've decided on my final formulation components, their final concentrations, my final device, my final – and what my – probably close to what my manufacturing specifications would be." This testimony is relevant to Dr. Donovan's obviousness conclusions and Petitioner's Reply because it undercuts Dr. Donovan's testimony that Dr. Govindarajan's recreations of Cramer Example III were suitable for nasal administration. EX1145, ¶¶30-40; Reply, 13-15.

**XI. Observation #11: 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.**

In CIP2178, at 171:4-20, Dr. Donovan testified that her expert report in the related Apotex case (*see* CIP2016) “call[ed] into question” certain aspects of Dr. Herpin’s recreations of prior art Cramer Example III. Despite this, in CIP2178, at 174:11-175:10, Dr. Donovan admitted that her expert report from the related Apotex case *did not* call into question the HPMC viscosity grades used by Dr. Herpin, despite the fact that the ’620 patent was a part of both this proceeding and the related Apotex case. This testimony is relevant to Dr. Donovan’s obviousness conclusions and Petitioner’s Reply because it undermines Dr. Donovan’s testimony that Dr. Herpin did not recreate Dr. Govindarajan’s recreations of Cramer Example III. EX1145, ¶¶41-45; Reply, 14-15. This testimony speaks to the weight and credibility the Board should afford Dr. Donovan’s conclusions.

**XII. Observation #12: Dr. Donovan admitted that in aqueous environments azelastine hydrochloride dissociates into electrolytes.**

In CIP2178, at 117:2-118:19 and 119:16-120:7, Dr. Donovan admitted that, below the solubility limit of the solution, azelastine hydrochloride will dissociate into electrolytes when placed in an aqueous environment at a reasonable pH. This testimony is relevant to Dr. Donovan’s testimony because it undermines her conclusion that azelastine hydrochloride would not have been viewed by a POSA as incompatible with MCC/CMC. EX1145, ¶¶18-29; Reply at 11-12.

**XIII. Observation #13: Dr. Donovan admitted that the two-preservative combinations in Astelin<sup>®</sup> and Flonase<sup>®</sup> were sufficient to inhibit bacterial growth.**

In CIP2178, at 207:1-17, Dr. Donovan agreed that Astelin<sup>®</sup> and Flonase<sup>®</sup>, because they were FDA-approved by 2002, “had passed the preservative challenge test or had sufficiently shown to the FDA that they inhibited bacterial growth.” In CIP2178, at 208:17-209:8, Dr. Donovan further agreed that given the available information about Astelin<sup>®</sup> and Flonase<sup>®</sup> in 2002, “the person of ordinary skill would know that those preservatives and those concentrations would be able to pass a preservative challenge[] test or at least gain FDA approval.” This testimony is relevant to Dr. Donovan’s obviousness conclusions (*see* EX1145, ¶¶59-66) and Petitioner’s Reply (*see* Reply at 17-18) because it directly contradicts Dr. Donovan’s testimony that a person of ordinary skill would seek to use three preservatives instead of the two-preservative combinations found effective in Astelin<sup>®</sup> and Flonase<sup>®</sup>. EX1145, ¶¶59-66; Reply, 17-18.

**XIV. Observation #14: Dr. Donovan failed to rely on any prior art to support a pH of 3 or below being “suitable for nasal administration.”**

In CIP2178, at 165:9-166:6, Dr. Donovan confirmed that she cited to no prior art to support her conclusion in EX1145, ¶46 that a pH of 3 or below was “suitable for nasal administration.” This testimony is relevant to Dr. Donovan’s obviousness conclusions and Petitioner’s Reply because it raises a concern about whether Dr. Donovan conducted a proper obviousness analysis. EX1145, ¶46;

Reply, 15. This testimony speaks to the weight and credibility the Board should afford Dr. Donovan's conclusions about whether a POSA would have had a reasonable expectation of arriving at a dosage form "suitable for nasal administration" as claimed.

**XV. Observation #15: Dr. Donovan admitted that Dr. Govindarajan's visual observations alone are insufficient to show a uniform suspension.**

In CIP2178, at 195:3-8, Dr. Donovan confirmed that Dr. Govindarajan used visual observations to assess his recreations of Cramer Example III, rather than analytical tests. In CIP2178, at 197:11-199:8, Dr. Donovan agreed that Dr. Govindarajan's visual observations alone did not foreclose the possibility that his recreations were not in fact uniform when analyzed further. This testimony is relevant to Dr. Donovan's obviousness conclusions (EX1145, ¶¶ 30-40) and Petitioner's Reply (Reply at 13-15) because it undermines her testimony that Dr. Govindarajan's recreations of Cramer Example III were a "dosage form suitable for nasal administration."

**XVI. Observation #16: Mr. Staines could not identify the proportion of Dymista<sup>®</sup> sales that were attributable to rebates and copayment programs.**

In CIP2180, at 18:5-19:8, Mr. Staines testified: "I don't think I could, attribute, you know, quantitatively what proportion of the sales were due to" Dymista<sup>®</sup>'s rebate program. Similarly, in CIP2180, at 21:17-22:13, Mr. Staines testified that he did not look to see whether copayment programs were offered for

competing products and that he could not “estimate a precise percentage, or even a general percentage” of the sales attributable to Dymista<sup>®</sup>’s copayment card program. This testimony is relevant to Mr. Staines’s commercial success conclusions and Petitioner’s Reply because it undercuts Mr. Staines’s credibility and undermines his conclusions that rebates and copayment card programs were primary drivers of Dymista<sup>®</sup>’s sales. EX1140, ¶¶119-125; Reply, 23-24, 27-28.

**XVII. Observation #17: Dr. Staines admitted that the evidence he relied on did not actually contain the information he said it did.**

In CIP2180, at 32:11-36:1 and 37:20-40:4, Mr. Staines conceded that the documents he relied upon to conclude that Meda’s salesforce was constrained from selling to primary care physicians but not to allergy and asthma specialists whom Meda was targeting, did not say that. Indeed, Mr. Staines agreed that “there’s no discussion of that” in two Meda documents (CIP2074 and CIP2064) he relied upon, and that he was “mistaken” in thinking that CIP2053 provided that information. This testimony is relevant to Mr. Staines’s commercial success conclusions and Petitioner’s Reply because it undercuts Mr. Staines’s credibility and undermines his conclusion that Meda’s salesforce and its increased share of voice were a primary driver of Dymista<sup>®</sup>’s sales. EX1140, ¶¶126-135; Reply at 23-24, 27-28.

**XVIII. Observation #18: Mr. Staines was not sure whether Dymista®'s 23% and 31% rebates were atypical in the pharmaceutical market.**

In CIP2180, at 66:19-70:11, when asked to compare Dymista®'s 23% rebate in 2012 and 31% rebate in 2013 to the typical rebates in the pharmaceutical market in 2012, Mr. Staines testified that he had not “formed an opinion on that” and would need to “study it a little more” to determine whether those rebates were typical. This testimony is relevant to Mr. Staines’s commercial success conclusions and Petitioner’s Reply because it undercuts Mr. Staines’s credibility and undercuts his conclusions that Dymista’s 47% rebate in 2015 was atypical. EX1140, ¶¶63, 124, Ex. 2a; Reply, 23-24, 27-28.

**XIX. Observation #19: Mr. Staines does not know what a “blocking patent” is.**

In CIP2180, at 86:11-87:21, Mr. Staines testified that his blocking patent argument “is not my opinion” and, when asked if he knew what a blocking patent was, said “I don’t think I really do.” Further in CIP2180, at 88:6-90:15, Mr. Staines testified: “I don’t have an opinion on whether they [EX1007 and EX1009] actually do block or not” and that it “seem[ed] reasonable” that competitors could have developed and received regulatory approval for a combination azelastine/fluticasone product in 2012. This testimony is relevant to Mr. Staines’s commercial success conclusions and Petitioner’s Reply because it undercuts Mr. Staines’s credibility and undermines his conclusions that blocking patents negate a

commercial success. EX1140, ¶¶108; Reply at 23-24, 27-29.

**XX. Observation #20: Mr. Staines admitted that he did not know the novel features of the claimed invention for his nexus analysis.**

In CIP2180, at 61:21-63:12 and 83:19-84:17, Mr. Staines explained his nexus analysis as follows: “[i]f there is an alternative [product] that can do the same thing [as Dymista<sup>®</sup>], then I would consider that not a novel feature.” In CIP2180, at 83:19-86:7, Mr. Staines further testified that (1) he did not know what the novel features of the claimed invention were, (2) he “assumed that all of the features of Dymista [were] in some way or form claimed in the patent,” and (3) he had “no opinion” on the novel features of the invention from a legal sense. This testimony is relevant to Mr. Staines’s commercial success conclusions and Petitioner’s Reply because it undermines Mr. Staines’s conclusions that the novel features of the claimed invention were not primary drivers of Dymista<sup>®</sup>’s sales. EX1140, ¶¶109-135; Reply at 23-24, 27-28.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Dennies Varughese (Reg. No. 61,868)  
Lead Attorney for Patent Owner

Date: April 10, 2018  
1100 New York Avenue, N.W.

Washington, D.C. 20005-3934  
(202) 371-2600

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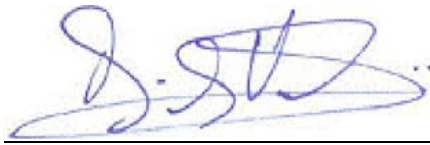


**CERTIFICATE OF SERVICE (37 C.F.R. §§ 42.6(e))**

The undersigned hereby certifies that the above-captioned "CIPLA LTD.'S MOTION FOR OBSERVATIONS ON CROSS-EXAMINATION," was served in its entirety on April 10, 2018, upon the following party via electronic mail:

Michael R. Houston: mhouston@foley.com  
Joseph P. Meara: jmeara@foley.com  
James P. McParland: jmcparland@foley.com  
Andrew R. Cheslock: acheslock@foley.com  
Tyler C. Liu: TLiu@agpharm.com  
ARG-dymista@foley.com

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Date: April 10, 2018

Dennies Varughese (Reg. No. 61,868)  
Lead Attorney for Patent Owner

1100 New York Avenue, N.W.  
Washington, D.C. 20005 - 3934  
(202) 371-2600