Paper No. ___
Filed: July 27, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC., TEVA PHARMACEUTICALS USA, INC. and AKORN INC.,[1]
Petitioners,
v.
ALLERGAN, INC.,
Patent Owner.

Case IPR2016-01127 (US 8,685,930 B2)
Case IPR2016-01128 (US 8,629,111 B2)
Case IPR2016-01129 (US 8,642,556 B2)
Case IPR2016-01130 (US 8,633,162 B2)
Case IPR2016-01131 (US 8,648,048 B2)
Case IPR2016-01132 (US 9,248,191 B2)

PETITIONERS' RESPONSE TO PATENT OWNER'S MOTION FOR OBSERVATIONS ON THE CROSS-EXAMINATION OF DR. ANDREW CALMAN

---

[1] Cases IPR2017-00576 and IPR2017-00594, IPR2017-00578 and IPR2017-00596, IPR2017-00579 and IPR2017-00598, IPR2017-00583 and IPR2017-00599, IPR2017-00585 and IPR2017-00600, and IPR2017-00586 and IPR2017-00601, have respectively been joined with the captioned proceedings. The word-for-word identical paper is filed in each proceeding identified in the caption pursuant to the Board's Scheduling Order (Paper 10).

Petitioner submits this Response to Allergan's Motion for Observations on the Cross-Examination of Dr. Andrew Calman ("Observations") pursuant to the Standing Order (Paper 9) and the Scheduling Order (Paper 10).

Dr. Calman's Opinions Regarding Thermodynamic Principles

Allergan's First Observation (Mot'n at 1-2) omits relevant testimony and mischaracterizes the cited testimony.

- Dr. Calman testified that he is capable of competently discussing the pharmacokinetic studies in a clinical context. EX2082 at 157:21–24 ("I believe I am qualified to discuss these issues and as well to put them in clinical context which neither of them [Drs. Amiji and Loftsson] is a clinician."); *Id.* at 158:8–16 ("[T]here are other aspects where I can provide a clinical context that's missing.").
- Dr. Calman testified that he would "defer to the formulators" regarding "any equations regarding thermodynamic activity," but that "with regard to the relationship of the bioavailability to the clinical efficacy, I'm a clinician and they're not." *Id.* at 158:12–16; *id.* at 158:2-22.
- In his declaration, Dr. Calman testified regarding the "internal pharmacokinetic studies" relied upon by Dr. Loftsson in support of his thermodynamics theory and relied upon by Dr. Attar for her

declaration. EX1039, ¶¶76-81. Dr. Calman testified that their presentation by Dr. Attar "is problematic" and "scientifically improper," with study designs that were "vastly different," including because one was a steady-state study and the other was a single-dose study. *Id.*, ¶77. Dr. Calman also testified that it was misleading to claim that "there are significant and material differences in the amount of CsA that each formulation delivered to the ocular tissue" because "each formulation delivered CsA to the cornea and conjunctiva ***well above the threshold required for therapeutic efficacy***" and "there was no 'dose-response' effect" between the CsA formulations. *Id.*, ¶¶78-81 (emphasis in original).

Allergan claims that Dr. Amiji "provided no opinions regarding thermodynamic principles in his declaration or deposition testimony."

- Dr. Amiji explained that each of the formulations in Example 1 of Ding '979 had a ratio of cyclosporin to castor oil sufficient to deliver therapeutic concentrations of CsA:

Ding '979 names "Examples 1A-1D" when discussing "formulations with cyclosporine" and the "cyclosporin containing castor oil emulsion," for which emulsions it reports finding therapeutic levels of cyclosporin, "no difference" in toxicity as compared to the emulsions without cyclosporin, and no crystallization of cyclosporin after nine

> months at room temperature. [EX1006] at col. 5, ll.18-30. Based on the disclosure of Ding '979, a person of ordinary skill in the art would expect that any of the CsA amounts disclosed in Example 1, in combination with any of the vehicles disclosed in Example 2, would yield a non-irritating emulsion, useful in the treatment of dry eye disease/KCS if the ratio of CsA to castor oil falls within the preferred range taught by Ding '979.

E.g., IPR2016-01127, EX1002, ¶71; *see also id.*, ¶¶67-68, 94, 105, 110, 113; EX1006, 3:15-28 ("No crystallization of cyclosporin was noticed after nine months at room temperature. Moreover, the cyclosporin emulsion is formulation in such a way that the drug has reasonably high thermodynamic activity, yet without the crystallization problem."); *id.*, 2: (describing problems with prior art "oily formulations' as including "the crystallization problem" and "a low thermodynamic activity (degree of saturation) of cyclosporin which leads to poorer drug bioavailability"); EX2023 at 160:23-161:3 (Dr. Amiji testifying that Ding '979's discussion of drawbacks of oily formulations is "just talking about dissolving cyclosporin in oil. They're not talking about emulsions here.").

- Dr. Amiji also confirmed that Ding '979's conclusions regarding therapeutic efficacy were based on "rabbit data," and that "Rabbit data are informative about the therapeutic efficacy as well as the safety." *Id.*, 158:4-158:13. Dr. Amiji also testified that Ding'979 patent describes performing "slit lamp analysis of the corneal tissue and they

also mention that they tested for ocular bioavailability and the therapeutic levels of cyclosporin." *Id.*, 158:19-159:14.

Dr. Calman's Opinions Regarding Sall Figure 2

Allergan's Second Observation (Mot'n at 2-3) omits relevant testimony and mischaracterizes the cited testimony.

- With regard to Allergan's terminology "numerically superior," Calman stated: "Well, I --'numerically superior' is a little bit of a loaded term. It is not statistically significantly different. The number, the average number, the mean is higher. All of these are very small changes. But the number -- the change is slightly higher for .05 on this particular time point." EX2082 65:15–21.
- Dr. Calman also states:

> To put that [Sall Fig. 2] in context, this is categorized Schirmer values with pitfalls that I discussed at length, as did Dr. Bloch, in our declarations, measured with anesthesia at the -- at a time point that -- and which was measured only at two time points in contrast to most of the other measures. And at the time point that was not the key time point of six months as identified by Allergan, none of these emulsions achieve any significant change or seen -- none of these emulsions achieve a significant change compared to baseline at Month 3. But there was a statistically significant difference between .05 and vehicle but not between .05 and .1.

Id. at 57:15–58:6.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.