UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ETON PHARMACEUTICALS, INC.,
Petitioner

v.

EXELA PHARMA SCIENCES, LLC,
Patent Owner

Case PGR2020-00068
Patent No. 10,583,155

PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE

EXHIBIT LIST

Exhibit No.	Description
2001	Declaration of Dr. Robert J. Kuhn
2002	Aileen B. Sedman et al., *Evidence of Aluminum Loading in Infants Receiving Intravenous Therapy*, 312 NEW ENG. J. MED. 1337 (1985)
2003	Nicholas J. Bishop et al., *Aluminum Neurotoxicity in Preterm Infants Receiving Intravenous-Feeding Solutions*, 336 NEW ENG. J. MED. 1557 (1997)
2004	ELCYS® Label, Exela Pharma Sciences, LLC
2005	Amended Complaint (Redacted), *Exela Pharma Sciences, LLC v. Sandoz, Inc.*, No. 1:20-cv-00645-MN (D. Del. June 1, 2020), ECF No. 12
2006	Amended Complaint, *Exela Pharma Sciences, LLC v. Eton Pharmaceuticals, Inc.*, No. 20-365-MN (D. Del. July 28, 2020), ECF No. 14
2007	Declaration of Mark Hartman (Redacted), *Exela Pharma Sciences, LLC v. Sandoz Inc.*, No. 19-cv-00318-MR (W.D.N.C. Dec. 6, 2019), ECF No. 26-1
2008	Megan Fortenberry et al., *Evaluating Differences in Aluminum Exposure Through Parenteral Nutrition in Neonatal Morbidities*, 9 NUTRIENTS 1249 (2017)
2009	Kathleen M. Gura, *Aluminum Contamination in Parenteral Products*, 17 CURR. OPIN. CLIN. NUTR. & METAB. CARE 551 (2014)
2010	Gordon L. Klein et al., *Hypocalcemia Complicating Deferoxamine Therapy in an Infant with Parenteral Nutrition-Associated Aluminum Overload: Evidence for a Role of Aluminum in the Bone Disease of Infants*, 9 J. PED. GASTR. & NUTR. 400 (1989)
2011	Jay M. Mirtallo, *Aluminum Contamination of Parenteral Nutrition Fluids*, 34 J. PARENTERAL & ENTERAL NUTR. 346 (2010)
2012	Robert L. Poole et al., *Aluminum Exposure From Pediatric Parenteral Nutrition: Meeting the New FDA Regulation*, 32 J. PARENTERAL & ENTERAL NUTR. 242 (2008)
2013	Eton Pharmaceuticals, Inc., Amendment No. 1 to Sales/Marketing Agreement (Form S-1/A, Exhibit 10.18) (Sept. 25, 2018)

Patent Owner files this sur-reply pursuant to the Board's Order of October 14, 2020 (Paper 7).

I. THE PETITION LACKS PARTICULARITY

The Petition continues to suffer from a lack of particularity. Eton says it is relying on the "four-corners of the Sandoz label" as a printed publication and admits that the label does not disclose every element of the claimed compositions. Paper 8 (Petitioner's Reply ("Reply")) at 1–2; Paper 1 ("Petition") at 52. Eton relies on the "knowledge of a POSITA" to fill in the gaps. Pet. at 42–45. But what is this alleged "knowledge?" This is where the lack of particularity comes in. In its Petition, Eton relies on the properties of a ***product*** as measured shortly after manufacture by Allergy Labs and before it is accessible to the public. *See, e.g.,* Pet. at 50-51. Not only does this conflate two separate categories of prior art, but it refers to information to which a person of ordinary skill would not have been privy.

In its Reply, Eton now points to the Geissler Declaration, which includes aluminum data of an L-cysteine product manufactured in ***June 2019*** (i.e., after Exela's invention date) by a ***different entity*** (Avara) at a ***different facility*** (Boucherville, Canada) than the "Sandoz Label" of Eton's Grounds. Ex. 1116 at 6 ¶ 12, 44–45, 48–49. Eton's addition of this 2019 Avara product to what it considers the "Sandoz Label" further compounds the lack of particularity and

undermines Eton's own "four corners" argument.

Moreover, Eton's reliance on the Geissler Declaration actually supports Exela's position. First, the Geissler Declaration shows only "release testing" data for the Avara product, which means testing done before the Avara product was released to the public—again, information to which a person of ordinary skill would not have been privy. Ex. 1116 at 6, 44–45, 48–49. Moreover, the only aluminum data in the Declaration is for an Avara product made in June 2019, which is *after* Exela's invention date and thus not prior art. *Id.* at 44–45, 48–49. Finally, the Geissler Declaration shows that at release in August 2019—with nearly 22 months of shelf-life (and aluminum leaching) to go—the Avara product already contained up to 375 ppb of aluminum. *Id.* at 44–45, 48–49 (August 2019 release testing results for 2 batches of Avara product, both manufactured in June 2019 and expiring in June 2021).

In short, this different, later, non-prior art Avara L-cysteine product had precisely the same problem as the Sandoz Label product of Eton's grounds. *See* Paper 6 (Patent Owner Preliminary Response ("POPR")) at 1–2, 12–13; Ex. 2001 (Kuhn Decl.) ¶¶ 15, 21–24. It was the inventors who solved this problem by developing a stable, low aluminum L-cysteine composition that is safe for administration to vulnerable infants over the shelf life of the product.

Eton continues to characterize this inventive work as mere "routine optimization" in its Reply. Although the Board *explicitly denied* Eton's request to address its "routine optimization" argument in its Reply, Eton still did so under the guise of addressing Exela's particularity argument. Order at 2–3; Reply at 2–4.

Eton's "routine optimization" arguments mischaracterize the problem the inventors discovered and solved by treating the solution as if it involved two independent variables: (1) removing head space and dissolved oxygen to prevent oxidation of L-cysteine[1] and (2) storing the product in a coated glass vial to prevent aluminum from leaching into the composition. *See* Reply at 2–4. In its POPR, Exela showed—based on Eton's own references—how and why L-cysteine parenteral solutions are sensitive to an array of multivariate and interrelated interactions. *See* POPR at 53–57. Balancing these interactions is integral to Exela's solution to the aluminum problem, which is not "merely the discovery of an additional benefit of optimizing the Sandoz Label product to prevent oxidation

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[1] Eton points out that the Sandoz Label recites a pH of 1.0 to 2.5 and that air was replaced with nitrogen. Reply at 2 n.5. Yet Eton fails to explain in the Petition or Reply why a skilled artisan would have been concerned with addressing oxygen levels further, in the context of that pH range.

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