UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ETON PHARMACEUTICALS, INC.,
Petitioner

v.

EXELA PHARMA SCIENCES, LLC,
Patent Owner

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Case PGR2020-00064
Patent No. 10,478,453

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**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 | U.S. Patent No. 4,385,086 |

Patent Owner files this sur-reply pursuant to the Board's Order of September 24, 2020 (Paper 7).

## I. THE PETITION LACKS PARTICULARITY

The '453 claimed invention relates to L-cysteine parenteral compositions for treating vulnerable infants in which the compositions have very low levels of toxic aluminum that are stable over time. As a result, the claimed compositions remain safe for administration over the shelf life of the product.

Eton argues that a POSITA would know that actual aluminum levels in the Sandoz product ranged from 0-5,000 ppb because it was known that aluminum content increased over a product's shelf life. Paper 9 (Petitioner's Reply ("Reply")) at 2 n.3. This is precisely the problem with earlier L-cysteine formulations. *See* Paper 6 (Patent Owner Preliminary Response ("POPR")) at 1, 11; Ex. 2001 (Kuhn Decl.) ¶¶ 15, 21-24. It was the inventors who solved this problem. Eton's statements are an admission that the Sandoz Label describes a product no different from earlier, unsuccessful products.

The Petition suffers 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. Reply at 1–2; Paper 1 ("Petition") at 47–49. Eton relies on the "knowledge of a POSITA" to fill in the gaps. Pet. at 43. But what is this alleged "knowledge?" This is where the

lack of particularity comes in. In some instances, Eton relies on the properties of a ***product*** as measured shortly after manufacture by Allergy Labs and before it is accessible to the public. Pet. at 45–46. 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. Eton never explains how a person of ordinary skill would have been able to access Allergy Labs' data or make its own measurements within the same time frame.

In other instances, Eton relies on no fewer than 77 "additional references" to supply specific claim limitations that the Sandoz Label lacks. This is an improper "catch-all" approach that Eton does not (and cannot) defend. *See* POPR at 31–36.

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

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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

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 57–60. Eton considered none of this. Exela also highlighted that Eton provided no specifics as to why a skilled artisan would have arrived at the particularly claimed amounts of impurities in the claims. *Id.* at 54–57. Eton still has no answer.

Regarding the vial, multiple references taught using a plastic vial to reduce aluminum levels. Ex. 2011 (Mirtallo 2010) at 2; Ex. 1008 (Bohrer 2001) at 5. However, plastic vials are permeable to oxygen. Ex. 1003 (Rabinow Decl.) ¶¶ 57, 65. This is proof that the art failed to appreciate the severity of L-cysteine's oxygen sensitivity or the relationship between oxygen levels and aluminum levels. It also shows that Eton's focus on optimizing oxygen levels to solve the aluminum problem is improperly based on the inventors' own path.

Eton's "routine optimization" arguments beg the question: given the seriousness of the aluminum problem with vulnerable infants, why had the

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oxygen levels further, in the context of that pH range, let alone to the particular amounts claimed.

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