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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U.S. PATENT NO. 10,478,453

PGR2020-00064

PETITIONER'S REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE

Pursuant to the Order (Paper No. 7) entered September 24, 2020, Petitioner files this reply to the Patent Owner's Preliminary Response ("POPR").[1]

I. THE PETITION MEETS THE PARTICULARITY REQUIREMENT

The claimed invention is the result of optimizing the product of the Sandoz Label using art-proven techniques for substantially preventing (1) oxidative degradation of L-Cysteine to L-cystine and pyruvic acid and (2) aluminum contamination.[2]

Patent Owner's ("PO") assertion that the Petition (Paper 1, "Pet.") lacks particularity is incorrect. The Petition relies on the four-corners of the Sandoz Label, which discloses an injectable L-Cysteine solution for use in a total parenteral

[1] The Order authorizes a 6-page reply.

[2] Shortly prior to the alleged invention, FDA began requiring substantially reduced aluminum levels as a condition for approving small volume parenteral ("SVP") products. (Pet. at 35-37; Ex. 1003, ¶¶29-30, 34-41.) Although PO asserts that those FDA communications do not qualify as prior art, they nevertheless pre-date the alleged invention, are relevant to the skill of the POSITA and demonstrate that several companies promptly and successfully reduced aluminum contamination in their respective SVPs in response to FDA pressure. (*E.g.*, Pet. at 36; Ex. 1003, ¶¶34-41.)

nutrition regimen. (Pet. at 6, 27-29; Ex. 1003, ¶¶31-32.) According to its four corners, the Sandoz Label product contains NMT 5,000 mcg/L (or ppb) aluminum[3], has a pH of 1.0-2.5, and air is replaced with nitrogen. (Pet. at 27; Ex. 1003, ¶¶31-32.)[4]

The Petition also identifies with particularity the knowledge prompting the POSITA to optimize the Sandoz Label product as claimed.

- L-Cysteine oxidation occurs at alkaline, neutral and acidic pH. (Pet. at 38-40, 42; Ex. 1003, ¶¶42-47.)[5]

[3] Even if, as PO asserts, the clinician would assume 5,000 ppb aluminum in the Sandoz Label product for dosing purposes the POSITA would nevertheless have understood that that the actual aluminum levels in the Sandoz Label product ranged from 0-5,000 ppb depending on the age of the product, which PO acknowledges increases in aluminum content over the product's shelf life. (POPR (Paper 6) at 11.)

[4] The product attributes not expressly disclosed within the four corners of the Sandoz Label are nevertheless relevant to the level of skill of the POSITA.

[5] PO's assertion that the POSITA would not be concerned with oxidation at acidic pH is belied by the plain teaching of the Sandoz Label, which discloses replacing air with nitrogen in an L-Cysteine solution having a pH of 1.0-2.5. (Ex. 1003, ¶31)

- L-cystine (which form unwanted precipitates) and pyruvic acid (which reduces efficacy) are oxidation degradation products of L-Cysteine. (Pet. at 38; Ex. 1003, ¶¶42-47.)
- Removing head space and dissolved oxygen are result-effective variables for substantially preventing degradation of oxygen sensitive drugs. (Pet. at 29-30, 39, 42, 46, 48-49; Ex. 1003, ¶¶48-51, 107-110, 112-113.)[6]
- The reasonably expected result of minimizing head space and dissolved oxygen is the substantial prevention of oxidative degradation of L-Cysteine to L-cystine and pyruvic acid. (Pet. at 38-40, 46-47; Ex. 1003, ¶¶42, 45-51, 59-60, 100-105.)
- Aluminum leaching from glass vials was a significant source of aluminum contamination (Pet. at 37-38; Ex. 1003, ¶¶33, 54-58.)
- Coated glass vials substantially prevent aluminum leaching. (Pet. at 41, 46; Ex. 1003, ¶¶56-57.)

[6] Butler, which is relied upon to show that the claimed dissolved oxygen levels were known and achievable, does not "teach away." (POPR at 35). Butler's concerns about trace oxygen when mimicking the sulfide chemistry of the ancient Earth's oxygen-free environment would not have discouraged the POSITA from using nitrogen (as taught by the Sandoz Label) to prevent oxidation of L-Cysteine.

- Heavy metals are toxic and can influence efficacy and thus should be minimized within acceptable limits. (Pet. at 40, 42, 56; Ex. 1003, ¶¶52, 158.)

The Petition demonstrates that the POSITA, armed with this knowledge, would and could have optimized the Sandoz Label product to substantially prevent oxidation of L-Cysteine to L-cystine and pyruvic acid by limiting oxygen exposure at the claimed dissolved and headspace oxygen concentrations, which are merely result-effective variables to achieve the reasonably expected result of preventing oxidation of L-Cysteine to L-cystine and pyruvic acid. (Pet. at 29-30, 40-43, 46-49; Ex. 1003, ¶¶53-70, 96, 100-113.)[7] The POSITA would also have been motivated to store the optimized Sandoz Label product in a container that substantially prevents aluminum from leaching during the product's projected shelf life. (Pet. at 38, 42, 45-46; Ex. 1003, ¶¶56-58).[8]

[7] *E.g.*, *Anacor Pharms., Inc. v. Flatwing Pharms., Inc.*, No. 2019-2264, 2020 WL 5049229, at *4 (Fed. Cir. Aug. 27, 2020) (affirming Board's obviousness finding where claims directed to routine optimization of result-effective variable).

[8] PO's assertion that the "POSITA would have had to know before attempting any optimization that L-cystine and oxygen levels were relevant to solving the aluminum problem" is incorrect. (POPR at 46.) Setting aside that PO has not demonstrated that

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