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. 10,583,155

PGR2020-00068

PETITIONER'S REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE

Petitioner files this reply to Patent Owner's Preliminary Response ("POPR").[1]

I. THE PETITION MEETS THE PARTICULARITY REQUIREMENT

The challenged claims are the result of optimizing the Sandoz Label product using known techniques for substantially preventing (1) oxidative degradation of L-Cysteine to L-cystine and pyruvic acid and (2) aluminum contamination.[2]

The Petition's two grounds rely on the four-corners of the Sandoz Label, which discloses an injectable L-Cysteine solution for use in a total parenteral nutrition regimen. (Pet. at 31-34; Ex. 1003, ¶¶33-35.)[3] The Sandoz Label product

[1] The Board authorized a 6-page reply (Paper No. 7).

[2] Shortly prior to the alleged invention, FDA demanded substantially reduced aluminum levels in small volume parenteral ("SVP") products. (Pet. at 36-39; Ex. 1003, ¶¶29-32, 36-43.) Even if not statutory prior art, these FDA communications pre-date the alleged invention, are relevant to the skill of the POSITA and demonstrate that companies promptly and concurrently reduced aluminum contamination in response to FDA pressure. (*E.g.*, Pet. at 38-39; Ex. 1003, ¶¶36-43.)

[3] The attributes not expressly disclosed by the Sandoz Label are nevertheless relevant to the state of the art and were readily ascertainable through routine testing of the commercially available product.

contains NMT 5,000 mcg/L (or ppb) aluminum,[4] has a pH of 1.0-2.5, and air is replaced with nitrogen.[5] (Pet. at 31-32; Ex. 1003, ¶¶33-34.)

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

- L-Cysteine oxidation occurs at alkaline, neutral and acidic pH. (Pet. at 40-42; Ex. 1003, ¶¶44-46.)
- L-cystine (which forms unwanted precipitates) and pyruvic acid (which reduces efficacy) are oxidation degradation products of L-Cysteine. (Pet. at 40, 43; Ex. 1003, ¶¶44, 47-49.)

[4] Contrary to the PO's assertions, the Sandoz Label product contained substantially less than 5,000 ppb (*less* than 375 ppb aluminum) as demonstrated by the Geissler Declaration submitted in the PO's related applications discussed below. (Ex. 1116 at 2-8, 45, 49). Thus, even if the pharmacist would *assume* 5,000 ppb aluminum for dosing purposes (as PO asserts), the POSITA would have understood (and could have confirmed by routine testing) that the *actual* level was between 0-5,000 ppb.

[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. (Pet. at 31-32.)

- Removing head space and dissolved oxygen are result-effective variables for substantially preventing degradation of oxygen-sensitive drugs. (Pet. at 41-43; Ex. 1003, ¶¶50-52.)
- 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 44-45; Ex. 1003, ¶¶61-62.)
- Aluminum leaching from glass vials was a significant source of aluminum contamination (Pet. at 39-40, 42-43; Ex. 1003, ¶¶35, 58-59.)
- Coated Schott glass vials substantially prevent aluminum leaching. (Pet. at 41-43; Ex. 1003, ¶¶58-62.)

The Petition also demonstrates with particularity that the POSITA, armed with this knowledge, would and could have optimized the Sandoz Label product to minimize oxygen exposure (a result-effective variable) during manufacture and storage to achieve the reasonably expected result of substantially preventing oxidation of L-Cysteine to L-cystine and pyruvic acid. (Pet. at 44-45; Ex. 1003, ¶60-62.)[6] The POSITA would also have been motivated to manufacture the optimized

[6] *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).

Sandoz Label product in a substantially aluminum-free environment and store the product in a Schott coated glass container that is not only oxygen impermeable but also substantially prevents aluminum from leaching into the product during its projected shelf life. (Pet. at 44-45; Ex. 1003, ¶¶58-62.)[7]

[7] PO's assertion that solving the "high-aluminum problem" requires optimization of cystine levels (and associated dissolved oxygen and head space oxygen levels) (POPR at 39) not only lacks evidentiary support but also, even if true, does not make the alleged invention patentable. The POSITA addressing the aluminum problem would have also understood that L-Cysteine is oxygen-sensitive. As such, the POSITA would have taken known steps to prevent oxidation while also eliminating the sources for aluminum contamination. Thus, for example, the POSITA would have selected a Schott coated glass container, which is both oxygen impermeable and does not leach aluminum. (Pet. at 42-45; Ex. 1003, ¶¶58-62.) The '155 patentee's alleged discovery of the purported benefit of preventing oxidation to minimizing aluminum contamination (even ***if*** true) is merely the discovery of an additional benefit of optimizing the Sandoz Label product to prevent oxidation as taught by the prior art. *See In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) ("It is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable.").

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