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EXAMINER

ZUCKER, PAUL A

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte XIANQI KONG, DAVID MIGNEAULT, and XINFU WU¹

Appeal 2015-001486
Application 12/842,990
Technology Center 1600

Before JACQUELINE WRIGHT BONILLA, ULRIKE W. JENKS, and
DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving a claim to a purity-enhanced pharmaceutical drug candidate free of bromide. The Examiner has entered final rejections of anticipation and obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

The Specification discloses “[t]his invention pertains to methods of preparation of sulfonate derivatized compounds, *e.g.*, 3-amino-1-propanesulfonic acid and 1,3-propanedisulfonic acid disodium salt with increased purity, with reduced potential for toxic by-products, and that are

¹ Appellants identify the Real Party in Interest as Kiácta Sarl. App. Br. 3.

pharmaceutically useful, *e.g.*, for the treatment of amyloidosis. Spec. 11:32–35. “[An] aspect [of] the invention is directed to a purity-enhanced pharmaceutical drug candidate comprising: 1,3-propanedisulfonic acid or a salt thereof, wherein the pharmaceutical drug candidate is free of bromide.” *Id.* at 11:3–6.

The following issues are before us on review (Ans. 3–5):

A. Claim 185 is rejected under 35 U.S.C. § 102(b) as anticipated by Zuffanti² or Kisilevsky.³

B. Claim 185 is rejected under 35 U.S.C. § 103(a) as obvious over Zuffanti or Kisilevsky.

Claim 185 is the sole claim on appeal and reads as follows:

185. A purity-enhanced pharmaceutical drug candidate comprising:
1,3-propanedisulfonic acid or a salt thereof,
wherein the pharmaceutical drug candidate is free of bromide.

App. Br. Claims Appendix 15.

ANTICIPATION

Issue

The issue is: Does the preponderance of evidence of record support the Examiner’s finding that Zuffanti or Kisilevsky teach the composition of claim 185?

² Saverio Zuffanti and Rudolf Hendrickson, *The Preparation of Some Alkane- α , ω -disulfonic Acids*, 63 JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, 2999-3000 (1941) (“Zuffanti”)

³ Robert Kisilevsky *et al.*, WO 96/28187 A1, published Sept. 19, 1996 (“Kisilevsky”)

Findings of Fact

FF 1. The Specification states:

The language “free of” is used herein, in reference to a final product of a sulfonate derivatized compound, *e.g.*, a pharmaceutical drug candidate, *i.e.*, derived from a crude or purified reaction mixture, which is completely lacking a referenced item, for example, a byproduct (such as bromide), which has been introduced into the reaction through the synthetic process. For example, in certain embodiments, the language “free of” is not intended to encompass impurities, for example, residual sodium, which has been introduced through environmental factors rather than through the synthetic process.

Spec. 17:14–20.

FF 2. The Specification states:

The language “purity-enhanced” is used in reference to a final product of a sulfonate derivatized compound, *e.g.*, a pharmaceutical drug candidate, *i.e.*, derived from a crude or purified reaction mixture, *e.g.*, including, but not limited to the sulfonate derivatized compounds produced by the methods of the invention, which is significantly free of byproducts, *e.g.*, toxic by-products (*i.e.*, by-products that are side-products of the reaction or residual starting material that would be considered unsuitable for administration to a subject, *e.g.*, a human, or preferentially omitted by a skilled artisan from a pharmaceutical composition prepared for administration to a subject). It should be noted that purity-enhanced compounds of the invention are not intended to be limited by scale of the reaction that produces the compounds.

Id. at 15: 14–23.

FF 2. Zuffanti discloses purification of anhydrous α,ω -Decamethylene-disulfonic acid as follows:

The acids were purified by redissolving them in a minimum of absolute methanol and saturating the solutions with dry

hydrogen chloride. This procedure carried the reaction further to completion as evidenced by the precipitation of sodium chloride. After filtration, the acids were recovered as previously indicated and recrystallized several times from absolute methanol.

Zuffanti col. 2, ¶ 2.

FF 3. Kisilevsky discloses that sodium 1,3-propanedisulfonate is prepared by a modification of the method described in Stone, . . . 1,3-Dibromopropane (40.4 g, 0.20 mol) was treated with sodium sulfite (60.3 g, 0.50 mol) in water at reflux temperature for 48 h. Inorganic salts (sodium bromide and sodium sulfite) were removed by successive treatment of the resultant reaction mixture with barium hydroxide and silver(I)oxide. The solution was then neutralized with Amberlite-120 (acid form) and decolorized with Norit-A. Barium ions were removed by treatment of the aqueous solution with Amberlite-120 (sodium form) ion exchange resin. The solvent was removed on a rotary evaporator, and the crude product was recrystallized from water-ethanol several times to give the title compound (42.5 g). The small amount of trapped ethanol was removed by dissolving the crystals in a minimum amount of water and then concentrating the solution to dryness. The pure product was further dried under high vacuum at 56 °C for 24 h

Kisilevsky 33:1–15.

FF 4. Kisilevsky discloses

A method for inhibiting amyloid deposition in a subject comprising administering to the subject an effective amount of a therapeutic compound, the therapeutic compound comprising at least one sulfonate group covalently attached to a carrier molecule, or a pharmaceutically acceptable salt thereof . . . wherein the therapeutic compound is . . . 1,3-propanedisulfonic acid.

Id. at 34:1–13.

FF 5. The Barriault Declaration⁴ reflects the results of chromatogram analysis of 1,3-propanedisulphonic acid, disodium salt that was prepared by Appellants using the method of Kisilevsky. Barriault Decl. 1–2.

FF 6. The Barriault Declaration explains that “[t]he peak on both chromatograms labeled C990 is bromide.” *Id.* at 4.

Principles of Law

“A single prior art reference that discloses, either expressly or inherently, each limitation of a claim invalidates that claim by anticipation.” *Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368, 1375 (Fed. Cir. 2005).

Analysis

The Examiner finds that the definition of “free of” in the Specification (*see* FF 1)

does not mean that an impurity is absent but only that it has not been introduced by the synthesis of 1, 3-propanedisulfonic acid. Any amount of any arbitrary impurity (including bromide) is permitted as long as it has not been introduced in the synthesis of 1, 3-propanedisulfonic acid. Claim 185 therefore must be treated as a product-by-process claim and the examiner considers that any impurities, regardless of the amounts, in the products of either Zuffanti or Kisilevsky are permitted by the language “free of” when given its broadest reasonable interpretation in light of the specification. Patentability for a product-by-process claim is determined on the basis of the product and not its method of formation. Claim 185 is therefore anticipated by Zuffanti or Kisilevsky.

⁴ Declaration under 37 C.F.R. § 1.132 by Nancy Barriault, signed Nov. 1, 2012 (“Barriault Decl.”).

Ans. 4.

Appellants argue neither Zuffanti or Kisilevsky “disclose any preparation of 1,3-propanedisulfonic acid (or a salt thereof) that meets the specific purity requirements of the present claims.” App. Br. 10. Appellants argue the Examiner incorrectly interprets “free of bromide” and that

[a] component such as bromide is clearly identified as an unavoidable by-product of the synthesis process. In contrast, other components which may inadvertently (and acceptably) be present in (or added to) invention compositions are identified as “environmental factors.” Those of skill in the art readily appreciate the difference between a reaction by-product (which is produced as a direct consequence of the synthetic protocol employed) as opposed to “environmental factors” (which may vary depending on the purity of the reagents employed, the reaction vessels employed, the methodology employed, and the like).

Id. at 5–6.

According to Appellants, the Examiner’s interpretation of the claims is unreasonable and “[t]he purity of the claimed compositions is based on the presence or absence of certain defined components, and not by the method used to prepare the claimed compositions.” *Id.* at 6.

Rejection based on Zuffanti

We find the Examiner correctly interpreted “free of” based on the language in the Specification (FF 1), but do not agree with the Examiner’s position that claim 185 is a product-by-process claim. We find that claim 185 recites a composition “free of bromide” wherein “free of” means that any bromide introduced in the synthesis process must be completely removed. FF 1. The language “purity-enhanced” is likewise defined by the Specification in reference to the final product, and establishes what the

product is “free of,” e.g., bromide. FF 2. With respect to the composition of Zuffanti, Appellants have not identified bromide as a source in the synthesis process or otherwise established that bromide is present in Zuffanti. Instead, the Examiner sufficiently establishes that the composition of Zuffanti meets the limitation of “completely lacking” bromide according to the language of the Specification because no bromide is introduced in the synthesis process. Ans. 4, FF 1–2. Accordingly, we find Zuffanti teaches “purity-enhanced” 1,3-propanedisulfonic acid “free of bromide” and affirm the rejection of anticipation based on Zuffanti.

Rejection based on Kisilevsky

Kisilevsky discloses the use of 1,3-Dibromopropane (a source of bromide) to synthesize sodium 1,3-propanedisulfonate sodium bromide. FF 3. While sodium bromide is removed from the synthetic milieu, the Barriault Declaration confirms that bromide is present as detected by chromatography. FF 5–6. Accordingly, we are persuaded that Kisilevsky does not teach “purity-enhanced” 1,3-propanedisulfonic acid “free of bromide” and reverse the rejection of anticipation based on Kisilevsky.

Conclusion of Law

A preponderance of the evidence of record supports the Examiner’s finding that Zuffanti teaches the composition of claim 185. However, a preponderance of the evidence of record does not support the Examiner’s finding that Kisilevsky teaches the composition of claim 185.

OBVIOUSNESS

Issue

The issue is: Does the preponderance of evidence of record support the Examiner's finding that Zuffanti or Kisilevsky teaches the composition of claim 185?

The Examiner finds that:

The difference between the instantly claimed 1, 3-propanedisulfonic acid and that taught by Zuffanti or Kisilevsky is that Zuffanti is that a purer 1, 3-propanedisulfonic acid is claimed . . . Appellants have not demonstrated any unexpected result or new utility for the purer form of the compound they claim. Thus, the instantly claimed purity-enhanced 1, 3-propanedisulfonic acid would have been obvious to one of ordinary skill in the art.

Ans. 6–7.

Appellants argue that neither “Zuffanti nor Kisilevsky disclose or suggest methods to produce 1,3-disulfonic acid which meet the purity requirements of the present claims, i.e., that is free of bromide [or] provide any motivation to produce 1,3-disulfonic acid meeting such purity requirements. Only the present Appellants describe such methods, and reason to do so.” App. Br. 13. Appellants’ cited reason for increasing purity is “to produce preparations of 1,3-propanedisulfonic acid or a salt thereof that met purity or quality standards sufficient for drug development purposes; i.e., that met GMP standards or were sufficient for, e.g., the United States FDA regulatory standards.” *Id.*, citing Garceau⁵ Decl., ¶ 6.

⁵ Declaration under 37 C.F.R. § 1.132 by Denis Garceau, signed Apr. 15, 2011 (“Garceau Decl.”).

Appellants further argue that prior preparations of 1,3-disulfonic acid, which they acknowledge has been “reported and known in the art for at least 65 years prior to 2003/2004” were “not suitable for clinical administration due to the presence of synthetic by-products and other impurities.” *Id.*, citing Garceau Decl., ¶ 7.

Rejection based on Zuffanti

For the reasons given above regarding Zuffanti (FF 1–3), we find Zuffanti anticipates and likewise also renders claim 185 obvious because it teaches every limitation of claim 185. *See In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (citations omitted) (“It is well settled that ‘anticipation is the epitome of obviousness’”). Accordingly, we affirm the finding of obviousness over Zuffanti.

Rejection based on Kisilevsky

Kisilevsky discloses a method of treating amyloid deposition in a subject comprising administering an effective therapeutic amount of 1,3-propanedisulfonic acid or its salt. FF 4. The Examiner states “sufficient motivation to produce pure material is found in Kisilevsky who teaches pharmaceutical administration of 1, 3- propanedisulfonic acid as set forth in the rejection of record. Kisilevsky also teaches 1, 3- propanedisulfonic acid of suitable purity for administration as well as a method for producing it as set forth in the rejection of record.” Ans. 11.

While Kisilevsky teaches purification of 1,3- propanedisulfonic acid to remove bromide, not all of the bromide used in the synthetic process is removed as shown in the Barriault Declaration (FF 5–6). We acknowledge that the Examiner interprets Kisilvesky’s teaching of “a pharmaceutically acceptable salt [] . . . wherein the therapeutic compound is . . . 1,3-

propanedisulfonic acid” and the Examiner’s interpretation of the chromatogram in the Barriault Declaration to mean that the 1,3-propanedisulfonic acid of Kisilevsky is sufficiently pure for pharmaceutical administration. (FF 4–6) But to establish a prima facie case of obviousness, the Examiner must articulate that the teachings of Kisilevsky would have motivated one of skill in the art to further modify its 1,3- propanedisulfonic acid to remove any remaining bromide, thereby arriving at the composition of claim 185. We agree with Appellants that the Examiner has not met this burden. Reply Br. 7–8. Accordingly, we reverse this rejection.

Conclusion of Law

A preponderance of the evidence of record does not support the Examiner’s findings that Zuffanti and Kisilevsky suggest the composition of claim 185.

SUMMARY

We affirm the rejection of claim 185 35 U.S.C. § 102(b) as anticipated by Zuffanti.

We reverse the rejection of claim 185 35 U.S.C. § 102(b) as anticipated by Kisilevsky.

We affirm the rejection of claim 185 under 35 U.S.C. § 103(a) as obvious over Zuffanti.

We reverse the rejection of claim 185 under 35 U.S.C. § 103(a) as obvious over Kisilevsky.

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TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED