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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ANGELIQUEO E. PADILLA and
GEORGE A. BAKLAYAN

Appeal 2019-000150
Application 14/082,662
Technology Center 1600

Before ULRIKE W. JENKS, ELIZABETH A. LAVIER, and MICHAEL A. VALEK, *Administrative Patent Judges*.

VALEK, *Administrative Patent Judge.*

DECISION ON APPEAL

Appellant[1] submits this appeal under 35 U.S.C. § 134(a) involving claims to aqueous compositions containing 2-amino-3-(4-bromobenzoyal) phenylacetic acid. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42(a). Appellant identifies Bausch & Lomb Incorporated as the real party in interest. Appeal Br. 1.

STATEMENT OF THE CASE

According to the Specification, "[i]t was known that 2-amino-3-(4-bromobenzoyal)phenylacetic acid," which also goes by the name, bromfenac, "was unstable in aqueous formulations." Spec. ¶¶ 2–3. "[T]he present invention relates to a stable aqueous liquid preparation containing [bromfenac] or a pharmacologically acceptable salt thereof or a hydrate thereof." *Id*. ¶ 1.

Claims 1, 3, 6–9, 13, 15, 18, and 21–23 are on appeal and can be found in the Claims Appendix of the Appeal Brief. Claim 1 is representative of the claims on appeal. It reads as follows:

> 1. An aqueous liquid composition comprising: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof; (b) a non-ionic surfactant; (c) water; and (d) an ophthalmically acceptable preservative selected from the group consisting of polyaminopropyl biguanide ("PAPB"), polyquaterinium-1, perborate, and mixtures thereof; and wherein the non-ionic surfactant is selected from the group consisting of Poloxamer 407, Octoxynol 40, and PEG 40 hydrogenated castor oil, and at least 90 percent of the original amount of said 2-amino-3-(4-bromobenzoyl)phenylacetic acid or pharmacologically acceptable salt thereof or hydrate thereof remains in the composition after storage at 60 °C, for 4 weeks.

Appeal Br., Claims App. 1. Claim 6 additionally recites "the concentration of the non-ionic surfactant is in the range from 0.005 w/v % to 0.12 w/v %." *Id.* Claim 15 additionally recites the pH "is within a range of 7.3 to 8.5." *Id.* at 2.

Appellant seeks review of Examiner's rejection of claims 1, 3, 6–9, 13, 15, 18, and 21–23 under 35 U.S.C. § 103 as unpatentable over Desai[2] and Sawa.[3] Appeal Br. 2. Appellant does not argue any claim separately from claim 1, so claims 3, 6–9, 13, 15, 18, and 21–23 stand or fall with claim 1. 37 C.F.R. § 41.37 (c)(1)(iv).

The issue is whether the preponderance of the evidence supports Examiner's conclusion that the aqueous composition in claim 1 is obvious over the cited prior art.

Findings of Fact

FF1. Desai teaches "storage-stable preserved ophthalmic compositions containing acidic drugs in combination with polymeric quaternary ammonium compounds" such as polyquaternium-1. Desai, Abstr., 2:49–50. Desai teaches that "[s]uitable ophthalmic agents" for these compositions include those with "acidic functionality such as —COOH" and identifies "bromfenac"[4] as an example of an agent. *Id.* at 3:7–18.

FF2. Desai teaches that its compositions "may additionally include other ophthalmically acceptable components" such as "other preservatives," e.g., "biguanides," and "surfactants (e.g., poloxamers such as Pluronics®; polysorbates such as Tweens®; tyloxapol; sarcosinates such as Hamposyl®; and polyethoxylated castor oils such as Cremophor®)." Desai, 3:25–35.

FF3. In Example 1, Desai describes the addition of water and pH adjustment to "between 7 and 7.4." Desai, 4:46–48.

[2] US 5,653,972; issued Aug. 5, 1997 ("Desai").
[3] US 7,829,544 B2; issued Nov. 9, 2010 ("Sawa").
[4] Bromfenac contains a carboxylic acid group. *See* Spec. ¶ 2 (depicting chemical structure).

FF4. Sawa describes "[s]table and clear aqueous solution preparations comprising an aminoglycoside antibiotic or a pharmacologically acceptable salt thereof and bromfenac being a nonsteroidal anti-inflammatory agent or a pharmacologically acceptable salt thereof." Sawa, Abstr, 3:40–43. Sawa teaches the addition of a nonionic surfactant such as "polyoxyethylene (40) hydrogenated castor oil" or "poloxamer" in an amount that is "about 0.01 w/v %, preferably about 0.05 w/v%, to a maximum concentration of about 10.0 w/v %, preferably about 1.0 w/v %" to such solutions. *Id.* at 4:52–5:1, 6:53–59.

FF5. Sawa teaches adjusting the pH of the aqueous solution to a pH "not less than 6.0, preferably 7.5 to 8.5." Sawa, 7:24–26.

FF6. Sawa teaches that additional additives, including "preservatives (e.g., benzalkonium chloride, benzetonium chloride, chlorhexidine gluconate, chlorobutanol, benzyl alcohol, sodium dehydroacetate, p-oxybenzoic acid esters, sodium edetate, boric acid, etc.)," may be included in the aqueous solution. Sawa, 7:33–36.

Analysis

Examiner finds Desai teaches a storage stable solution including polyquaternium-1, bromfenac, water, and non-ionic surfactants such as poloaxmers and polyethoxylated castor oil. Final 3. Examiner determines Desai also teaches the use of "additional preservatives, such as biguanides." *Id.* Examiner finds that Sawa teaches bromfenac in an aqueous formulation along with one or more of the recited non-ionic surfactants in concentrations that overlap with that recited in the dependent claims. Examiner determines it would have been obvious to "use the non-ionic surfactants at the claimed concentration range, considering that Sawa teaches such concentrations in

combination with bromfenac is considered to be old and well known." *Id.* at 4. Examiner finds that the combination is expected to have "at least 90% of the original amount" of bromfenac "after storage at 60 °C, for 4 weeks," as recited in claim 1, because "all the components are the same as the composition of the claimed invention and the concentrations of non-ionic surfactants can be incorporated from the teachings of Sawa et al." *Id.*

We adopt the Examiner's findings and reasoning regarding the scope and content of the prior art (Final 3–6; FF1–FF6) and agree that the claims are rendered obvious by Desai and Sawa. We address Appellant's arguments below.

We are not persuaded by Appellant's argument that a prima facie case has not been established because there is no specific identification of a composition having all of the recited components in the cited prior art. *See* Appeal Br. 4. Desai teaches aqueous pharmaceutical compositions comprising all of the ingredients recited in claim 1. FF1–FF2. The fact that Desai lists bromfenac as one of approximately ten specific drugs that can be used in such compositions does not make the use of bromfenac in such formulations any less obvious. *See Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (explaining that a reference's disclosure of "a multitude of effective combinations does not render any particular formulation less obvious"). To the contrary, Desai teaches that "storage stable" compositions are formed by the combination of any of listed drugs, including bromfenac, with polyquaternium-1 and other listed ingredients, such as biguanides, poloaxmers, and polyethoxylated castor oils. *See* FF1–FF2.

Appellant argues that Examiner's determination that the composition of Desai is "expected" to exhibit the recited stability is not supported by the record. *See* Appeal Br. 4–5. We disagree. As Examiner determined, Desai, in combination with the non-ionic surfactant concentrations described in Sawa, teaches a composition containing the same ingredients at the same pH and surfactant concentration recited in Appellant's claims. *See* FF1–FF6. Although neither reference expressly teaches that at least 90% of the bromfenac in such a composition will remain after storage at 60 °C, for 4 weeks, there is a presumption that the prior art composition containing the same ingredients will exhibit the same storage stability property. *See, e.g., In re Dillon*, 919 F.2d 688, 692–93 (Fed. Cir. 1990) (en banc) ("[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness and that the burden (and opportunity) then falls on an applicant to rebut that prima facie.") (emphases omitted). Thus, Examiner has met the burden to establish a prima facie case of unpatentability.

Appellant further argues that Examiner's prima facie showing is rebutted by evidence of unexpected results in Tables 3, 3R, 4, 4R, 5, 5R of the Specification. *See* Appeal Br. 5–7. These tables report the percentage of bromfenac remaining in formulations comprising the three preservatives recited in claim 1 and various claimed and unclaimed non-ionic surfactants after one month of storage at 60 °C. *See* Spec., Table 3R, 4R, 5R. According to these data, the percentage of bromfenac remaining after one month was above 90% for each of the combinations of preservative and surfactant recited in claim 1, whereas it sometimes fell slightly below 90%,

i.e., to a range between 85-87%, when an unclaimed surfactant was used. *Compare id.* (Examples containing recited surfactants: NGB-10, 12, 13, 15, 17, 18, 20, 22 and 23) to *id.* (Examples containing unrecited surfactants: NGB-11, 14, 21, and 24). According to Appellant, these results are unexpected and probative of non-obviousness because

> each specific claimed combination has been shown to enable the specific claimed high level of bromfenac stability, while other possible combinations of various preservatives and surfactants also based on possible selections from the combined disclosures of Desai and Sawa have been shown to result in significantly lower levels of stability than that required for the present claimed invention (see, e.g., Examples NGB-11 and NGB-14 in Table 3R, and NGB-21 and NGB-24 in Table 5R), and that the claimed stability requirement has thus been demonstrated for each such specific claimed combination.

Reply Br. 3–4.

We are not persuaded by Appellant's unexpected results argument for several reasons. First, as explained above, Desai teaches compositions comprising all of the ingredients of claim 1. FF1–FF2. Such compositions are closer prior art than the formulations comprising unrecited surfactants in Tables 3, 4, and 5. Thus, Appellant's results do not demonstrate unexpected results as compared to the closest prior art. *See Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) ("To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained ant host of the closest prior art.") (citations omitted).

Second, even for those examples containing unrecited surfactants, Appellant has not shown that the difference in the percentage of bromfenac remaining after one month is a difference in "kind and not merely in

degree." *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) ("Unexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art.") (internal quotations omitted). For example, the percentage of bromfenac remaining after one month for Examples NGB-11 and NGB-14 (containing unrecited surfactants) are about 86%, which is only 7% lower than the percentage reported for NGB-12 and NGB-13 (containing recited surfactants). Our reviewing court has explained that "[r]esults which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time." *Galderma*, 737 F.3d at 739. Appellant has not presented sufficient evidence to show that the differences observed in the data here would have been beyond the capability of a skilled artisan such that they are more than mere differences in degree. Appellant's assertion that the results for NGB-11, 14, 21 and 24 represent "significantly lower levels of stability" is unsupported attorney argument. *See* Appeal Br. 7; Reply Br. 3–4; *see also See In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984) (explaining that arguments and conclusions unsupported by factual evidence carry no evidentiary weight).

Third, the data for Examples NGB-16 and 19 in Table 4R and NGB-25 in Table 5R suggest that the use of the recited surfactants is not critical to achieving the degree of stability recited in Appellant's claims. For each of these examples, the percentage of bromfenac remaining after one month was above 90% even though those formulations are outside the scope of claim 1 because they contain unrecited surfactants (NGB-16 and 19) or no surfactant at all (NGB-25). *See* Spec., Table 4R, 5R. Accordingly, and contrary to

Appellant's suggestion, the data do not show that the specific combination of preservatives and surfactants in claim 1 is necessary to provide the recited degree of stability.

Given the above-noted shortcomings, we determine that Appellant's evidence is insufficient to overcome the strong prima facie showing of obviousness. As explained above, both Desai and Sawa teach aqueous compositions comprising bromofenac and the recited non-ionic surfactants and Desai specifically teaches the use of polyquaternium-1 and biguanides as preservatives to enhance the storage stability of such. *See* FF1–FF6. Weighing that evidence together with Appellant's unexpected results evidence, which on balance is weak, we determine that the preponderance of the evidence supports Examiner's obviousness rejection. *See, e.g.*, *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1329 (Fed. Cir. 2017) (weighing evidence of unexpected results and copying together with other evidence, including "strong evidence of a motivation to make the claimed combination" in the cited prior art, to conclude that combination was obvious); *Bayer Healthcare*, 713 F.3d at 1377 (finding that secondary indicia evidence did not "overcome[] the plain disclosures and express motivation to combine those disclosures in the prior art").

For these reasons, we determine the preponderance of the evidence supports Examiner's rejection and therefore affirm.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 3, 6–9, 13, 15, 18, 21–23	103	Desai, Sawa	1, 3, 6–9, 13, 15, 18, 21–23	

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED