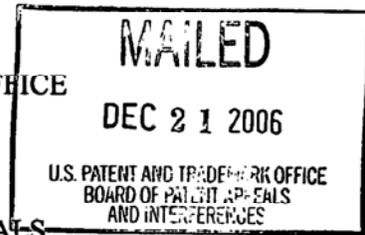


The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE



BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte CHRISTOPHER A. MULLER, JANET K. CHEETHAM, TERESA H. KUAN,
and DAVID F. POWER

Appeal No. 2006-3115
Application No. 10/856,192

ON BRIEF

Before MILLS, GREEN, and LINCK Administrative Patent Judges.

LINCK, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal from the Examiner's final rejection under 35 U.S.C. § 102(b) of pending claims 1-17 in Application No. 10/856,192 (hereafter the "'192 Application")¹ as being anticipated by Fu et al., U.S. Patent No. 5,414,011 issued May 9, 1995 ("Fu"). With the authority to adjudicate appeals from final rejections under 35 U.S.C. § 134, we reverse the Examiner's § 102 rejections, except as to claim 12, and enter a new ground of rejection under 35 U.S.C. § 103(a) in view of Fu.

¹ The present application was filed on May 28, 2004 and is assigned to Allergan, Inc.

BACKGROUND

The invention on appeal relates to topical nonsteroidal anti-inflammatory drugs (NSAIDs) and in particular, topical ophthalmic compositions comprising ketorolac tromethamine for treating or preventing ocular pain, especially in postoperative photorefractive keratectomy surgery patients. Specification at 1, 2. Assignee Allergan, Inc. (“Allergan”) provides three different types of ketorolac tromethamine ophthalmic solutions: Acular PF®, Acular®, and Acular LS™. Bob Kronemyer, *Acular reformulated to reduce ocular pain, burning, stinging: Acular LS removes the pain factor for PRK and gives enhanced patient compliance, without sacrificing potency*, Ocul. Surg. News, Sept. 15, 2003, at 48 (hereafter “Kronemyer”). Acular PF contains a concentration of 0.5% ketorolac tromethamine and no preservative. *Id.* Acular contains a concentration of 0.5% ketorolac tromethamine and preservative. *Id.* According to the specification, Acular “is a safe and effective NSAID with proven analgesic and anti-inflammatory activity” and its most common adverse event is ocular irritation. Specification at 2.

Acular LS is a reformulation of Acular and contains a reduced concentration of ketorolac tromethamine, i.e. 0.4%, and a reduced level of preservative. John Wittpenn, M.D., *Acular LS™: Reduced Discomfort Without Loss of Efficacy*, Refract. Eyecare, August 7, 2003 at 12.

The Claims at Issue

The ‘192 Application contains the following independent claims:

1. An aqueous topical ophthalmic composition comprising from 0.35% to 0.45% ketorolac tromethamine.
7. A method of treating or preventing ocular pain in a person comprising topically administering to said patient a sterile composition comprising from 0.35% to 0.45% ketorolac tromethamine.
17. An aqueous solution comprising less than 0.5% ketorolac tromethamine wherein said solution is suitable for topical ophthalmic use and wherein a therapeutically effective concentration of ketorolac tromethamine is present.

Dependent claims 2-6 and 8-16 further limit claims 1 and 7 as follows:

- (a) further limiting the amount of ketorolac tromethamine to 0.4% (claims 2 and 13);
- (b) adding certain amounts of known ophthalmic excipients (claim 3);
- (c) further limiting the amount of ketorolac tromethamine to 0.4%, adding known ophthalmic excipients and adjusting the pH from 7.2 to 7.6 (claims 4-6 and 10-12);
- (d) further narrowing ocular pain to the type resulting from photorefractive keratectomy surgery (claim 8);
- (e) further limiting the amount of ketorolac tromethamine to 0.4% and narrowing ocular pain to the type resulting from photorefractive keratectomy surgery (claim 13);
- (f) or further limiting the amount of ketorolac tromethamine to 0.4%, narrowing ocular pain to the type resulting from photorefractive keratectomy surgery, adding certain amounts of known ophthalmic excipients and adjusting the pH from 7.2 to 7.6 (claims 14-16).

The Cited Prior Art

Fu describes ophthalmic formulations containing an "ophthalmologically effective amount of an NSAID alone or in combination with an antibiotic, a quaternary ammonium preservative and a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle." Col. 2, line 66 –col. 3, line 4.

According to Fu: “Pharmaceutical ophthalmic formulations typically contain an effective amount, e.g., 0.001% to 10% wt/vol., most preferably 0.005% to 1% of an active ingredient (e.g., the NSAID of the present invention).” Col. 5, ll. 16-19. Fu also discloses exemplary pharmaceutical formulations that contain the NSAID ketorolac tromethamine in concentrations of 0.50% wt/vol. (Examples 1, 2, 3, 6, 7), 0.25% wt/vol. (Example 4), and 0.10% wt/vol. (Example 8). Col. 9, l. 3 to col. 11, l. 57.

In addition to being ophthalmologically effective, Fu’s formulations are ophthalmologically acceptable:

To be ophthalmologically acceptable, a formulation must [possess] a number of characteristics to comply with the general FDA requirements of being safe and effective. In that eyes are quite sensitive to pain, the formulation must be developed such that it causes little to no discomfort or stinging when administered. This feature is particularly important to insure user compliance and important in that such formulations are often administered in order to relieve pain or inflammation. [Col. 1, ll. 33-41(emphasis added).]

With respect to administration, Fu discloses that ophthalmic formulations are “typically administered by topical application to the eyelids or for instillation into the space (cul-de-sac) between the eyeball and the eyelids, by topically applied ophthalmic solutions, suspensions or ointments.” Col. 8, ll. 24-28. And with respect to utility, Fu’s disclosed method of use “is both curative and preventative.” Col. 8, ll. 13-14. For instance, the NSAID ophthalmic formulation can be applied pre-surgically or immediately post-traumatically to prevent inflammation. Col. 8, ll. 14-17. Or, it can be applied directly to the eye suffering from trauma caused by eye surgery or eye injury to suppress already developed inflammatory processes. Col. 8, ll. 11-12, 17-19.

DISCUSSION

The Examiner's § 102 Rejections

We initially address claims 1 and 7. The Examiner rejected these claims under § 102 as being anticipated by Fu because it teaches “the use of the claim designated compound, ketorolac tromethamine in combination with benzalkonium chloride, EDTA, Octoxynol-40, sodium hydroxide or hydrochloric acid at the claimed concentrations in a pharmaceutical formulation for the treatment of inflammation and pain.” Answer at 3 (citing col. 1, ll. 4-42; col. 5, ll. 16-18, ll. 26-50, claims 1-4 and 6-9). In particular, the Examiner directs attention to Examples 4 and 8 of Fu, which disclose pharmaceutical formulations for ophthalmic administration containing 0.25% and 0.10% concentration of ketorolac tromethamine, respectively. Final Office Action at 2. The Examiner states that the concentrations of ketorolac tromethamine disclosed in Fu are “even less than the concentrations used by the instant application.” *Id.*

Appellants counter that Fu “does not expressly or impliedly disclose the concentration range of 0.35% to 0.45% for ketorolac tromethamine, and thus does not anticipate the present application.” Brief at 3. Appellants further argue that because 0.25% and 0.1% concentrations of ketorolac tromethamine lie outside the claimed range, Fu does not teach each and every element of the claim and does not anticipate the claim. *Id.* Appellants further point out that the 0.005% to 1% range in Fu is about 10 times as broad as the claimed range. Brief at 3.

We agree with Appellants that Fu does not anticipate claims 1 and 7 of the '192 Application. Anticipation requires a showing that each limitation of a claim is found in a single reference, either expressly or inherently. *See, e.g., Atofina v. Great Lakes Chem.*

Corp., 441 F.3d 991, 999; 78 USPQ2d 1417, 1423 (Fed. Cir. 2006). Moreover, it is “well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus.” *Id.* We find no express or inherent disclosure of the claimed range of 0.35% to 0.45% ketorolac tromethamine in Fu. Thus, we reverse the Examiner’s § 102 rejection of claims 1 and 7. Further, given that claims 2-6 and 8-16 are dependent upon claims 1 and 7, we also reverse the Examiner’s § 102 rejection of these claims.

However, claim 17 is a different story in that the claimed “less than 0.5%” range is clearly anticipated by Fu. A claim covering several compositions by reciting ranges is anticipated if one of the compositions is in the prior art. *See, e.g., Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782, 227 USPQ 773, 777 (Fed. Cir. 1985). As the Examiner noted, Fu discloses exemplary ophthalmic formulations containing the NSAID ketorolac tromethamine in concentrations of 0.25% wt/vol. (Example 4) and 0.10% wt/vol. (Example 8). These disclosed aqueous solutions are representative of Fu’s general disclosure of topical ophthalmic formulations containing an effective amount of the active ingredient, i.e., ketorolac tromethamine ranging from 0.001% to 10% wt/vol. and, preferably, from 0.005% to 1% wt/vol. Col. 5, ll. 16-19. Thus we affirm the rejection of claim 17 under § 102(b).

New Grounds of Rejection under § 103(a)

While Fu fails to anticipate pending claims 1-16, we conclude at least claims 1 and 7 would have been obvious to one of ordinary skill based on Fu. A “prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness.” *In re Peterson*, 315 F.3d 1325,

1329, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). Additionally, the “discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art” and prima facie obvious. *In re Boesch*, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). More specifically, one skilled in the art “who chose to experiment with the reference process[,] would undoubtedly try the conditions defined by the claims, although he might be surprised at the extent of improvement obtained.” *In re Aller*, 220 F.2d 454, 458, 105 USPQ 233, 237 (CCPA 1955) (citations omitted). Thus, no invention is involved in “discovering optimum ranges of a process by routine experimentation,” where the general conditions of a claim are disclosed in the prior art. *Id.* at 456, 458, 105 USPQ at 235, 237 (citations omitted).

Here, Fu’s disclosure of a preferred range of 0.005% to 1% encompasses the claimed narrower range of 0.35% to 0.45% ketorolac tromethamine. A prima facie case of obviousness is reinforced by Fu’s example formulations with 0.25% and 0.50% concentrations of the active ingredient ketorolac tromethamine. These formulations lie very close to each end of Appellants’ range and, in effect, set the boundaries of the 0.35% to 0.45% range for ketorolac tromethamine. One skilled in the art experimenting with ophthalmic formulations would discover Appellants’ claimed range of ketorolac tromethamine through routine optimization of Fu’s ophthalmic formulations with ketorolac tromethamine such that “it causes little to no discomfort or stinging when administered.” Col. 1, ll. 36-38. In fact, Appellants concede in their specification that the claimed “compositions have a concentration of ketorolac tromethamine which is *optimized* to reduce side effects and improve ease of formulation, while maintaining

clinical efficacy in treating ocular pain.” Specification at 3 (emphasis added). We conclude that the claimed range would have been prima facie obvious in view of Fu.

The burden now shifts to the Appellants to rebut. *E.g.*, *In re Harris*, 409 F.3d 1339, 1343, 74 USPQ2d 1951, 1954. “When an applicant seeks to overcome a prima facie case of obviousness by showing improved performance in a range that is within or overlaps with a range disclosed in the prior art, the applicant must ‘show that the [claimed] range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range.’” *In re Geisler*, 116 F.3d 1465, 1471-72, 43 USPQ2d 1362, 1365 (quoting *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995)).

Apparently in anticipation of an obviousness rejection, Appellants cite to a declaration made by Calvin W. Roberts, M.D., August 26, 2005 and three supplemental articles to demonstrate that the claimed composition “provides an unexpected improvement in the tolerability of the product, while maintaining efficacy.” Brief at 5. Dr. Roberts conducted a “comfort study”² “to compare the ocular comfort of ketorolac tromethamine solution 0.4% (Acular LS) with that of a 0.5% ketorolac tromethamine composition (Acular PF) in [45] healthy volunteers.” Declaration at 1. Dr. Roberts concluded from the study that 0.4% ketorolac tromethamine is more comfortable than 0.5% ketorolac tromethamine. *Id.* at 2. In particular, Dr. Roberts stated:

² The subjects were “randomized to receive a single drop of the Acular LS in one eye and Acular PF in the contralateral eye at two evaluations on a single day. Before and after receiving their first set of drops, subjects were asked to rate their ocular discomfort on a scale of 0-4, where 0 = no discomfort and 4 = a definite continuous burning/stinging that last[s] more than 30 seconds. The procedure was repeated 5 minutes after the first set of drops were instilled.” Declaration at 2.

Acular LS is at least as comfortable upon instillation as Acular PF, and more comfortable on the second administration. This data suggests that the lower concentration of ketorolac tromethamine improves the comfort of the formulation to such an extent that Acular LS is more comfortable *despite the fact that it contains benzalkonium chloride*, while Acular PF does not. [*Id.* (emphasis added).]

Acular LS contains less ketorolac tromethamine than Acular PF, and Acular LS also contains benzalkonium chloride while Acular PF does not. Kronemyer at 48. *See also* Brief at 4. Appellants state that benzalkonium chloride “is known to be irritating to the eye, so it was . . . expected that the benzalkonium chloride would adversely affect the comfort of Acular LS.” Brief at 4. Thus, according to Appellants, “it is also surprising that Acular LS could have *preservative* and be more comfortable than the preservative free formulation.” *Id.* (emphasis added).

Dr. Roberts’ Declaration does not establish that the claimed range of 0.35% to 0.45% ketorolac tromethamine unexpectedly provides more comfort than a formulation containing 0.5%. Rather, due to failure to control other variables they have merely provided some evidence that a ketorolac tromethamine solution could contain preservative and be more comfortable than a ketorolac tromethamine solution without preservative. Appellants have not compared their claimed invention to the closest prior art, i.e., Fu’s “ophthalmologically acceptable” formulations containing ketorolac tromethamine at concentrations of 0.25 and 0.10%. Thus, the Declaration does not overcome the prima facie case of obviousness for claims 1 and 7.

Appellants also cite the following supplemental articles to demonstrate that “those skilled in the art now recognize that the presently claimed composition (Acular LS) is more comfortable [than] and as efficacious as the commercial ketorolac.” Brief at 4.

- John Wittpenn, M.D., *Acular LS: Reduced Discomfort Without Loss of Efficacy*, Refact. Eyecare, Aug. 7, 2003 (hereafter “Wittpenn”); and
- Linda Charter, *Lower-concentration NSAID reduces pain after*, Ophthalmol. Times, Aug 15, 2003 (hereafter “Charter”); and
- Kronemyer, *see supra* at 2.

All three articles praise the benefits of the product Acular LS when compared to a “vehicle” without ketorolac tromethamine. Wittpenn at 12; Kronemyer at 48; Charter at 22-23. However, contrary to Appellants’ position, we find that these articles do not provide evidence that the claimed range is critical, or provides unexpected results. There is no evidence in the articles that Acular LS was compared to the closest prior art, i.e., Fu’s ophthalmologically effective and acceptable formulations containing 0.25 and 0.10% ketorolac tromethamine.

There is no evidence in the record showing it would have been surprising that reduced concentrations of the active ingredient ketorolac tromethamine would maintain clinical efficacy, or reduce pain, in comparison to the placebo. According to Kronemyer, Dr Francis W. Price, MD, said ketorolac tromethamine “is one of the most *potent* pain relievers, especially in regard to nonsteroidal anti-inflammatory drugs (NSAIDs) So I expected significant pain reduction [compared to the placebo].” Kronemyer at 48 (emphasis added).

Furthermore: those skilled in the art noted: “Preservatives often create discomfort,” Wittpenn at 14, and “stinging can come either from preservatives or from

the active ingredient.” Dr. Price, *quoted in* Kronemyer at 48. Thus, reducing the levels of either the active ingredient or the preservative, or both, would *predictably* reduce burning and stinging side effects.

Appellants have not yet provided sufficient evidence to overcome *prima facie* obviousness of claims 1 and 7. Thus, we conclude these claims would have been obvious to one of ordinary skill in the art at the time the invention was made.

The Dependent Claims Are Prima Facie Obvious Over Fu

Dependent claims 2-6 and 8-16 further limit claims 1 and 7 by:

- (g) further limiting the amount of ketorolac tromethamine to 0.4% (claims 2 and 13);
- (h) adding certain amounts of known ophthalmic excipients (claim 3);
- (i) further limiting the amount of ketorolac tromethamine to 0.4%, adding known ophthalmic excipients and adjusting the pH from 7.2 to 7.6 (claims 4-6 and 10-12);
- (j) further narrowing ocular pain to the type resulting from photorefractive keratectomy surgery (claim 8);
- (k) further limiting the amount of ketorolac tromethamine to 0.4% and narrowing ocular pain to the type resulting from photorefractive keratectomy surgery (claim 13);
- (l) or further limiting the amount of ketorolac tromethamine to 0.4%, narrowing ocular pain to the type resulting from photorefractive keratectomy surgery, adding certain amounts of known ophthalmic excipients and adjusting the pH from 7.2 to 7.6 (claims 14-16).

We recognize that some claims are limited by the language “consisting of” or “consisting essentially of” and have taken this language into consideration in making our determinations.

With respect to (a), the 0.4% limitation, we apply the same analysis as we did previously in considering the 0.35% to 0.45% range of ketorolac tromethamine. *Supra* at

7-9. For the same reasons we concluded it would have been obvious to reach the claimed range through routine experimentation, we also conclude the 0.4% amount (a slight variation) would have been obvious. At this time, we find no evidence in the record of unexpected results to alter our opinion.

The addition of known ophthalmic excipients (b) would also have been well within the ordinary skill in the art. Evidencing this level of skill are the teachings of Fu. Fu discloses each and every claimed excipient as a preferred ingredient in the disclosed ophthalmic NSAID solutions and the approximate ranges for each excipient. Col. 4, ll. 61-68; col. 5, ll. 26-50; col. 6, ll. 23-44, 51-54; col. 7, ll. 20-27. Thus, we further conclude the addition of these excipients does not render them patentable over the prior art.

Moreover, treating ocular pain caused by photorefractive keratectomy surgery (c) is clearly suggested by the prior art. *See* Fu, col. 8, ll. 5-19 (stating that the disclosed formulations are useful to treat or prevent pain resulting from eye surgery). One skilled in the art would have been motivated to use such ophthalmic formulations to treat pain caused by surgery, including photorefractive keratectomy surgery.

Furthermore, the adjustment of pH, from 7.2 to 7.6, required by some of the dependent claims would also have been routine. Fu teaches how to do so and “most preferably” teaches adjusting the pH to 7.4. Col. 6, l. 63-col. 7, l. 2.

Combining two or more of the above obvious variations, as has been done for example in claims 4-6 and 10-16, does not render patentability to these claims, absent some showing of unexpected results. We find none, based on the submissions now

before us. Thus, we conclude all of the dependent claims would have been obvious to one of ordinary skill in the art in view of Fu's teachings.

Summary

We reverse the rejection of claims 1-16 under 35 U.S.C. § 102 and affirm the rejection of claim 17 under this section.

We enter a new ground of rejection of claims 1-16 under 35 U.S.C. § 103(a).

This decision contains new grounds of rejection pursuant to 37 CFR § 41.50(b) (2005). 37 CFR § 41.40(b) provides that "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 CFR § 41.40(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new grounds of rejection to avoid termination of the appeal as to the rejected claims:

(1) Reopen prosecution. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . .

(2) Request rehearing. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . .

• Appeal No. 2006-3115
Application No. 10/856,192

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