

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JOEL E. BERNSTEIN¹

Appeal 2014-007316
Application 13/197,581
Technology Center 1600

Before DONALD E. ADAMS, ROBERT A. POLLOCK, and
JACQUELINE T. HARLOW, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellant appeals under 35 U.S.C. § 134(a) from the final rejection of claims 30–37, and 40 as obvious.² We have jurisdiction under 35 U.S.C. § 6(b).

We affirm-in-part.

STATEMENT OF THE CASE

The invention concerns methods of mitigating hepatotoxicity. Claim 30, the sole independent claim on appeal, reads as follows (formatted for clarity):

¹ Appellant identifies the Real Party in Interest as Winston Laboratories, Inc. App. Br. 2.

² The rejections under 35 U.S.C. § 112, second paragraph have been withdrawn. Ans. 5.

30. A method of mitigating the hepatotoxicity of a hepatotoxic compound, the method comprising formulating a composition containing a combination of

a quantity of the hepatotoxic compound,
a quantity of nicotinamide,
and a quantity of methionine,

wherein the combination of the hepatotoxic compound, nicotinamide and methionine is administered contained together in the same individual dosage form selected from the group consisting of capsules, tablets and oral solutions.

Claims 30–37, and 40 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Kröger,³ Ogata,⁴ and Murdock.⁵

FACTUAL FINDINGS

We have reviewed Appellant’s contentions that the Examiner erred in rejecting claims 30–37, and 40 as unpatentable over the cited art. App. Br. 4–13; Reply 2–8. With respect to the rejection of claims 30–33, 37, and 40, we disagree with Appellant’s contentions and adopt as our own the factual findings concerning the scope and content of the prior art set forth in the Examiner’s Answer. Our opinions with respect to the rejection of claims 34–36 are set forth below. For emphasis, we highlight and address the following:

³ H. Kröger et al., *Protection from Acetaminophen-Induced Liver Damage by the Synergistic Action of Low Doses of the Poly(ADP-ribose) Polymerase-Inhibitor Nicotinamide and the Antioxidant N-Acetylcysteine or the Amino Acid L-Methionine*, 28 GEN. PHARMAC., 257–263 (1997).

⁴ Ogata et al., US Patent No. 5,478,815, issued Dec. 26, 1995.

⁵ Murdock et al., US Patent No. 4,526,788, issued July 2, 1985.

FF1. Kröger teaches that the combination of nicotinamide and L-methionine (methionine) are synergistic for ameliorating acetaminophen-induced hepatotoxicity in mice. Kröger 261–262 (Discussion section). In particular, Kröger discloses that male NMRI mice were orally administered 500 mg/kg acetaminophen to induce liver damage, as evidenced by increased glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) activity. *Id.*, *see e.g.*, Abstract, 259–260 (Materials and Methods), Fig. 2. Where mice were also injected intraperitoneally with increasing amounts of either nicotinamide (from 25 mg/kg to 100 mg/kg IP) or methionine (from 50 mg/kg to 300 mg/kg IP) “acetaminophen-induced release of both GOT and GPT from injured liver cells could be inhibited in a dose-dependent manner.” *Id.* Abstract, *see* Fig. 1. Moreover, “[a] combination of both L-methionine and . . . nicotinamide (at the low dose of 12.5 mg/kg IP each) resulted also in complete protection from acetaminophen-induced release of GOT and GPT.” *Id.* Abstract, *see* Fig. 2; Ans. 2; *see also id.* at 7 (Kröger “constitutes a proof of principle paper documenting evidence of the efficacy of administering nicotinamide and L-methionine as liver protectants to mitigate acetaminophen toxicity.”). Kröger concludes that “[t]reatment with combinations of the drugs exhibited a synergistic effect.” *Id.* at 262.

FF2. The Examiner finds that Kröger “does not explicitly teach [] a single dosage form comprising acetaminophen, nicotinamide and methionine that is a tablet, capsule or oral solution” or the specific amounts of nicotinamide, methionine, or acetaminophen set forth in dependent claims 31–33, and 40. Ans. 3.

FF3. Ogata discloses the use of a tocophery-ascorbyl-phosphate compound (L-ascorbyl DL- α -tocopheryl phosphate potassium or “EPC-K”) as an oral or parenteral liver protectant useful in treating liver damage associated with alcohol intake and hepatic impairment due to acetaminophen and other drugs. Ogata, Abstract, 2:26–37. Ogata discloses four working examples in which EPC-K was tested in rat models of chronic liver disorder (Ex. 1), fulminant liver disorder (Ex. 2), acute liver disorder associated with vitamin E deficiency (Ex. 3), and acute intrahepatic cholestasis (Ex. 4). *See id.* at 3:60–5:35. In these examples, EPC-K was administered intraperitoneally at 5 mg/kg (Ex. 1, 2, and 4) or orally at 141 mg/kg (Ex. 3, Table 3). *See id.* at 3:60–5:35.

FF4. With respect to clinical application, Ogata states that:

The dosage of [EPC-K] as a liver protectant depends on the species of compound, the patient's body weight and age, indication, dosage form and treatment protocol but may for example be about 1–100 mg/day/adult man in the case of an injectable preparation or about 10–1000 mg/dose/adult man, which is to be administered a few times daily, in the case of an oral preparation.

Id. at 2:45–51. Applicable dosage forms include “solid preparations as tablets, granules and powders, capsules, etc. and such liquid preparations as injections.” *Id.* at 2:38–40; *see also* 5:35–57 (representative formulations for EPCK tablets and injectable solution); Ans. 3.

FF5. The Examiner finds that Murdock “documents the routine knowledge available in the pharmaceutical arts regarding the calculation of human dosages based upon the interrelationship of dosages for animals of various sizes and species as described by Freireich E.J., et al. (*Cancer*

Chemotherap. Rep., 50(4); 1966:219-244; col.5, 1.45-51).”⁶ Ans. 3; *see* 10–13; Murdock 5:45–51.

FF6. Murdock discloses the testing of anti-cancer agents by intraperitoneal administration using mouse models of lymphocytic leukemia and melanotic melanoma. Murdock 2:40–5:34. Murdock teaches that the disclosed compounds may be “administered in amounts ranging from one mg to about 1.2 gm per square meter of body surface area per day,” which can be calculated based on the size and species to be treated. *Id.* 5:39–45. In particular,

The interrelationship of dosages for animals of various sizes and species and humans (based on mg/m² of surface area) is described by Freireich, E. J., et. al., Quantitative Comparison of Toxicity of Anticancer Agents in Mouse, Rat, Hamster, Dog, Monkey and Man. *Cancer Chemother. Rep.*, 50, No. 4, 50 219-244, May 1966. A preferred dosage regimen for optimum results would be from about 3 mg/m²/day to about 200 mg/m²/day, and such dosage units are employed that a total of from about 5 mg. to about 360 mg. of the active compound for a subject of 70 kg. of body weight are administered in a 24 hour period. This dosage regimen may be adjusted to provide the optimum therapeutic response.

Id. at 5:45–58.

FF7. The Examiner finds that it would have been obvious to combine hepatotoxic compound acetaminophen with the hematoprotective combination of methionine and nicotinamide in a single dosage form “to provide maximal liver protection by administering the liver protectants

⁶ Appellant points to Exhibit E of Appellant’s Evidence Appendix as documenting the knowledge of Freireich. App. Br. 11; *see* Ans. 11. Exhibit E appears to be an excerpt from a 2007 NIH Guidance document employing Freireich’s dosage conversion data.

simultaneously with the hepatotoxic drug acetaminophen . . . [and] because a single dosage form eliminates the need to administer multiple formulations of each of the three components, which would have been reasonably expected to improve patient compliance by providing a single effective and well-tolerated dosage form.” Ans. 3–4; *see also*, 9 (“[a] person of ordinary skill in the art would have unequivocally appreciated the benefit of formulating a single oral dosage form of the three components to eliminate the need to administer multiple formulations.”)

FF8. With respect to the specific amounts of nicotinamide, methionine, and acetaminophen set forth in dependent claims 31–33, and 40, the Examiner finds that determining the optimal or workable ranges is a matter of routine experimentation. *See id.* at 5. In particular,

the determination of the optimum amounts of liver protectants nicotinamide and L-methionine per amount of acetaminophen would have been a matter well within the purview and experience of one of ordinary skill in the art as evidenced by Murdock et al. and further as determined by good clinical practice, the clinical condition of the individual patient and the desire of the artisan to administer the minimum amount necessary to achieve the desired therapeutic effect. Regardless of the manner of administration, such a determination would have been made in accordance with a variety of factors, such as the age, weight, body surface area, organ size, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination.

Id. at 4–5. The Examiner further finds that Murdock “documents that it was routine practice [to] . . . calculate a reasonable human dosage from a mouse dosage based on the interrelationship of dosages for animals of various sizes and species.” *Id.* at 11. Applying the Freirich conversion factor, the Examiner finds Kröger’s dosage of 12.5 mg/kg each of methionine and nicotinamide in mice is equivalent to 1.04 mg/kg of each compound in a human, amounts that “clearly fall within the dosage ranges” of claims 31–33. *Id.*

ANALYSIS

Claims 30–33, 37 and 40

Appellant contends that the Examiner errs because Kröger and Ogata are directed to intraperitoneal, rather than oral administration (App. Br. 7–9); that Ogata is directed to rats, rather than to the treatment of human subjects, and fails to suggest using IP injection in animals to determine the effects of drugs administered systemically or orally to a human patient (*id.* at 10); that Kröger employs dosages in mice that are “very substantially greater than those” set forth in the specification⁷ or claims (*id.* at 8); and that Murdock does not demonstrate that it was routine to calculate a human dosage based on the interrelationship of human and animal doses (*id.* at 11).

For the reasons set forth at pages 6–14 of the Examiner’s Answer, we do not find Appellant’s arguments persuasive. Briefly, we agree with the Examiner that Kröger “constitutes a proof of principle paper documenting

⁷ We understand Appellant’s references to the “‘760 application” as referring to US Pat. App. 10/813,760, which is the parent of the instant (divisional) application. *See* Reply Br. 5.

evidence of the efficacy of administering nicotinamide and L-methionine as liver protectants to mitigate acetaminophen toxicity.” FF 1. Although Kröger employs intraperitoneal administration of the nicotinamide and methionine, we agree with the Examiner that one of ordinary skill in the art would recognize from Ogata that “IP injection was a route of administration routinely used for experimental animal testing to determine the effect of drugs intended to be administered orally to a patient,” and which could be “in the form of, e.g., a tablet, capsule or oral liquid.” *Id.* at 7–8; 12; *see* FF 4.

With respect to the calculation of dosage ranges set forth in claims 31–33, and 40, we credit the Examiner’s finding that one of ordinary skill in the art would have found it routine to calculate a reasonable human dosage based on and mouse dosage, and would further have found guidance in Murdock’s discussion of the Freireich’s work, which takes into account the interrelationship of animal size and species. FF5–8; *see also* Ans. 13 (Noting that Appellant’s Exhibit F “only further documents the routine nature of dose optimization considering the species to be treated, body surface area and the desire of the skilled artisan to administer the minimal amount necessary to achieve the desired effect when faced with the proof of principle study described in Kröger.”). Applying the Freireich conversions, the Examiner reasonably determines that the amounts of nicotinamide and methionine used in Kröger are within the dosage ranges claimed. *See* FF 8.

We are also not persuaded by Appellant’s argument that “a very different route of administration [i.e., intraperitoneal] does not predict the results of the combination when administered in other ways [i.e., orally].” Reply Br. 3. “Obviousness does not require absolute predictability of

success . . . *all that is required is a reasonable expectation of success.*” *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (citing *In re O’Farrell*, 853 F.2d 894, 903–904 (Fed. Cir. 1988)). Given the Examiner’s findings regarding the knowledge of those of ordinary skill in the art, including the guidance set forth in Murdock regarding translating animal data into workable clinical ranges, we find that the Examiner has made this showing.

Appellant further contends that the Examiner errs in failing to take into account evidence of longstanding public need for the present invention. *See* App. Br. 5 and Reply Br. 2–3. Appellant’s argument, however, focuses on unsupported statements regarding companies allegedly responsible for “over 95% of the OTC acetaminophen in the world,” “Confidentiality Agreements” with “global pain management companies,” and “conferences to address acetaminophen liver toxicity.” *Id.* For the reasons set forth at pages 14–16 of the Examiner’s Answer, we do not find Appellant’s argument persuasive. Attorney argument is not evidence. *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974). And mere lawyer’s arguments and conclusory statements that are unsupported by factual evidence are entitled to little probative value. *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997). Appellant’s arguments do not overcome the Examiner’s strong prima facie case of obviousness, particularly in view of Kröger’s demonstration of the synergistic effect of nicotinamide and methionine in ameliorating acetaminophen-induced hepatotoxicity. *See, e.g., Pfizer, Inc. v. Apotex, Inc.* 480 F.3d 1348, 1372 (Fed. Cir. 2007). (“Here, the record establishes such a strong case of obviousness that Pfizer’s alleged unexpectedly superior results are ultimately insufficient.”); *see also, Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 719 (Fed. Cir. 1991) (holding on summary judgment

that the claimed invention was obvious because “secondary considerations did not carry sufficient weight to override a determination of obviousness based on primary considerations”).

Claims 34–36

Claim 34, depending from claim 30, further requires that the composition comprise “a quantity of folic acid.” Claims 35 and 36 similarly specify folic acid “in the amount of 50 mcg–5 mg” and “in the amount of 500 mcg–1 mg,” respectively. In each case, the Examiner contends that claims 34–36 read on the *absence* of folic acid (“i.e. 0 mg of folic acid”) as taught by Kröger. Ans. 2–3. Applying the broadest reasonable interpretation in light of the Specification, we do not find the Examiner’s position reasonable. Whether a composition comprises “a quantity of folic acid” or “50 mcg” of folic acid, it has by definition, some measurable amount that compound.

In order to establish a *prima facie* case of obviousness, the Examiner must show that each and every limitation of the claim is described or suggested by the combination of prior art references or would have been obvious based on the knowledge of those of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). Because the Examiner has not shown that Kröger, or any of the art of record, teaches or suggests the use of folic acid, we reverse the rejection of claims 34–36.

SUMMARY

- I. We *affirm* the rejection of claims 30–33, 37, and 40 under § 35 U.S.C. 103(a) as unpatentable over the combination of Kröger, Ogata, and Murdock.

- II. We *reverse* the rejection of claims 34–36 under § 35 U.S.C. 103(a) as unpatentable over the combination of Kröger, Ogata, and Murdock.

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-IN-PART

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