2022 Pat. App. LEXIS 1531

Patent Trial and Appeal Board

March 17, 2022, Decided

Appeal 2021-003062 ; Application 16/072,088 ; Technology Center 1600

USPTO Bd of Patent Appeals & Interferences; Patent Trial & Appeal Bd Decs.

Reporter

2022 Pat. App. LEXIS 1531 *

Ex parte ROMAN MANETSCH, DENNIS E. KYLE, ANDRII MONASTYRSKYI, ALEXIS N. LACRUE, JORDANY R. MAIGNAN, and FABIAN MARCEL BROCKMEYER

Notice:

[*1] ROUTINE OPINION. Pursuant to the Patent Trial and Appeal Board Standard Operating Procedure 2, the opinion below has been designated a routine opinion.

Core Terms

compound, teach, optimize, prodrug, solubility, prior art, anti-malarial, experiment, temperature, synthesis, antimalarial, malaria, quinolone, aqueous, artisan, routine, resistance, long-felt, parasite, reasonable expectation, disease, invent, concentrate, synthetic, variable, profile, modify, excellent, moiety, liver

Panel: Before DONALD E. ADAMS, JEFFREY N. FREDMAN, and RACHEL H. TOWNSEND, Administrative Patent Judges.

Opinion By: JEFFREY N. FREDMAN

Opinion

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal [1] under 35 U.S.C. § 134 involving claims to an anti-malarial compound. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

"Malaria remains one of the most devastating parasitic diseases, with approximately 200 million reported infections and over 0.6 million of deaths per year . . . new drugs are urgently required to combat this deadly disease" (Spec. P 1). "Spearheaded by the Medicines for Malaria Venture, **ELQ-300 (1a)** [2] entered preclinical development in 2013. Unfortunately, the advancement of **1a** towards Phase I studies was deferred due to poor oral bioavailability, limiting preclinical safety and toxicity studies" (*id.* P 4). "DMPK studies with lead quinolone compounds suggested aqueous solubility to be the major reason for poor oral bioavailability in the series (*id.*).

The Claims

Claims 5 and 12 are on appeal and read as follows:

5. A compound or a salt thereof, wherein the compound comprises a formula:

12. A composition comprising:

a compound or a salt thereof and a pharmaceutically acceptable carrier, wherein the compound comprises a formula:

The Rejection

The Examiner rejected **[*2]** claims 5 and 12 under U.S.C. § 103 as obvious over Riscoe '904, [3] Cross, [4] and Monastyrskyi [5] (Non-Final Act. 10-14).

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as University of South Florida and Northeastern University (*see* Appeal Br. 3). We have considered the Specification of July 23, 2018 ("Spec."); Non-Final Office Action of Aug. 31, 2020 ("Non-Final Action"); Appeal Brief of Jan. 22, 2021 ("Appeal Br."); Examiner's Answer of Feb. 17, 2021 ("Ans."); and Reply Brief of April 5, 2021 ("Reply Br.").

[2] The structure of ELQ-300(1a) (Spec. P 3).

[3] Riscoe et al., US 2012/0115904 A1, published May 10, 2012.

[4] Cross et al., *Orally Bioavailable 6-Chloro-7-methoxy-4(1H)-quinolones Efficacious against Multiple Stages of Plasmodium*, 57 J. Med. Chem. 8860-79 (2014).

The Examiner finds Riscoe '904 teaches "various antimalarial compounds including the ELQ or Endochin Like Quinolone. One of the most potent was the compound ELQ-300" (Non-Final Act. 11). The Examiner finds Cross cites Riscoe '904 and "concludes that ELQ-300 along with P4Q-391 were lead compounds" (*id.*).

The Examiner finds "Monastyrskyi developed a prodrug approach to improve PK properties of these compounds" and Monastyrskyi's

> research resulted in the development of a highly soluble prodrug moiety, which can be installed in a 4(1H)-quinolone scaffold. The prodrug moiety is detached from the parent molecules via a pH-triggered mechanism *in vivo*. After some experimentation the P4Q-369 carbonate prodrug was developed. This prodrug gave the highest increases in solubility. This carbonate AOCOM analog is the same prodrug moiety in the elected species of claim 5.

(Non-Final Act. 12). The Examiner cites Monastyrskyi as providing reasons to select AOCOM analog P4Q-369 because "[C]arbonate AOCOM analogues (P4Q-369, P4Q-414) showed excellent aqueous stability-release profiles" **[*3]** and teaches a "selected set of pH-triggered prodrugs of 3-aryl-4(1H)-quinolones has been shown to possess improved in vivo antimalarial efficacy in a P. berghei infected mouse model. More importantly, the pH-regulated strategy of releasing the parent compound is easily applicable to the other classes of 4(1H)-quinolone compounds" (*id.* at 12-13 (alteration original); citing Monastyrskyi 76, 87-88).

The issue with respect to this rejection is: Does a preponderance of the evidence of record support the Examiner's conclusion that the combination of Riscoe '904, Cross, and Monastyrskyi renders claims 5 and 12 obvious?

Findings of Fact

1. Riscoe '904 teaches "the compounds disclosed herein exhibit equipotent activity against multidrug-resistant strains of *Plasmodium parasites* and may be of use in treating both the liver and blood stages of malaria as well as other infectious and/or parasitic diseases of humans and animals" (Riscoe '904 P 92).

2. Riscoe '904 teaches

> drugs active against the liver stage represent true causally prophylactic agents that can prevent all disease symptoms, including death, associated with malaria. Secondly . . . it is advantageous to strike at the liver stage where parasite numbers are low, to diminish the likelihood of selecting for a drug resistant mutant.

[*4] (Riscoe '904 P 92).

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[5] Monastyrskyi, Andrii, *Synthesis and Evaluation of 3-Aryl-4(1H)-Quinolones as Orally Active Antimalarials: Overcoming Challenges in Solubility, Metabolism, and Bioavailability*, Graduate Theses and Dissertations, http://scholarcommons.usf.edu/etd/5080, pp. 1-88 (2014).

3. Figure 4 of Riscoe '904 is reproduced, in part, below:

"FIG. 4 is a table listing compounds and their activity against Plasmodium falciparum strains in vitro" (Riscoe '904 P 26).

4. Riscoe '904 teaches a "Synthesis Scheme for ELQ-300" as reproduced below:

(Riscoe '904 P 176).

5. Riscoe '904 teaches high throughput screening for optimization, specifically teaching both "[s]imple and inexpensive fluorescence-based technique for high-throughput antimalarial drug screening" and "[e]valuation and lead optimization of anti-malarial acridones" (Riscoe '904 P 195). Riscoe '904 explains for lead optimization that "[e]xperiments were set up in triplicate in 96 well plates (Costar, Corning) with two-fold dilutions of each drug across the plate . . . Automated pipeting and dilution was carried out with the aid of a programmable Precision 2000 robotic station" (Riscoe '904 P 195).

6. Cross teaches: "Our combined efforts to further optimize the 4(1 *H*)-quinolone compound series yielded ELQ 300 **(6)** and P4Q391 **(7)**, of which the translational team from Medicines for Malaria Venture selected compound **6** to undergo preclinical development" (Cross 8861, col. 2).

7. Cross teaches:

> Both compounds **6** and **7** were highly efficacious **[*5]** against both the blood and the liver stages of the malaria parasite, as well as active against the forms critical for disease transmission. Both compounds were shown to selectively inhibit *Plasmodium* cytochrome *bc*1 complex over mammalian *bc*[1] due to the 6-chloro- **7**-methoxy substitution pattern of the 4(1 *H*)quinolone's benzenoid ring.

(Cross 8861, col. 2).

8. Cross notes that some coauthors work at the "Centre for Drug Candidate Optimisation" (Cross 8860), and describes the optimization efforts of the team, including teaching a "focus[] on the optimization of these [four] most promising 3-aryl moieties. Syntheses of these analogues were carried out in a linear fashion . . . [and] Since a broad range of Suzuki adducts was desired, myriad changes in cross-coupling conditions were employed" (Cross 8862, col. 1).

9. Monastyskyri teaches "[d]espite [an] excellent antimalarial profile ELQ-300 also lacks in aqueous solubility. Moreover, the absence of dose proportionality caused by low solubility impedes the determination of the therapeutic index and *in vivo* toxicity" (Monastyskyi 66).

10. Monastyskyri teaches "a practical and operationally simple gram scale syntheses of **ELQ-300**" (Monastyskyi 49). **[*6]**

11. Monastyskyri teaches the "development of prodrugs deliberately modified forms of the active ingredient that can undergo an enzymatic and/or chemical transformation *in vivo* - is an alternative and well-documented approach to increase aqueous solubility and bioavailability" (Monastyskyi 71).

12. Table 3.2 of Monastyskyri is reproduced, in part, below:

" **Table 3.2**: *In vitro* antimalarial activities and SPR data for **P4Q-146** prodrugs" (Monastyskyi 74).

13. Monastyskyri teaches "synthesis of Boc-protected alkyloxycarbonyloxymethyl (AOCOM) halides was accomplished as reported before in good yields (Scheme 1B). Corresponding alkyl halide was reacted with P4Q compound in presence of base to give AOCOM phenolic prodrug which upon deprotection yielded water-soluble HCl salts **P4Q-369, P4Q-414**" (Monastyskyri 76).

14. Monastyskyri teaches

> carbonate AOCOM analogues **(P4Q-369, P4Q-414)** showed excellent aqueous stability-release profiles (Figure 3.9). The stability was assessed in buffers with different pHs (2, 5,5, 6.5 and 7.4) and simulated gastric fluid (SGF) and quantified by LCMS. According to the profile received, **P4Q-414** is stable at the pH level 2 - 5 5 and start decomposing at pH~ 6.5 (35 % decomposition in 2 hours). Fast **[*7]** release (1 00% in 1 hour) of parent compound **P4Q-146** is occurring when pH is raised to 7.4. Generally, the stability of **P4Q-414** at physiological stomach pHs and its rapid release at pH> 7 is optimal for development of cyclization-activated prodrugs.

(Monastyskyri 76).

15. Monastyskyri teaches:

> Noteworthy, the deficient solubility of 3-aryl-4(1H)-quinolones is common for experimental candidates as about 40% of all drug candidates produced from high-throughput screenings are poorly soluble. A variety of techniques such as salt formation, particle size reduction and introduction of solubilizing agents have been used to overcome these barriers . . . Solubility hurdles were also conquered with a prodrug strategy especially when such a limitation is caused by compounds in which first-pass metabolism is not the main route of the systemic drug delivery.

(Monastyskyri 86-87).

16. Monastyskyri teaches optimization of synthesis conditions for desired compounds, specifically "optimization of arylation reaction conditions resulting in 2-phenyl EAA in DMF with *t*-BuOK" with variations of the "ratio of iodonium salt and EAA" as well as the later use of "modified Conrad-Limpach conditions" (Monastyskyri **[*8]** 43-45).

17. Monastyskyri teaches that other known optimizable parameters include time and temperature, stating "we were able to improve the overall yields in average by 10% by using microwave assisted conditions in toluene as a solvent and cutting the cyclization time to 3 minutes" rather than "classical high temperature thermal conditions" (Monastyskyri 45-46).

Principles of Law

A lead compound is a compound in the prior art that would be "a natural choice for further development efforts." *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014). In assessing the prior art, the PTAB also "consider[s] whether a PHOSITA would have been motivated to combine the prior art to achieve the claimed invention and whether there would have been a reasonable expectation of success in doing so." *BTG Int. Ltd. v. Amneal Pharm. LLC.*, 923 F.3d 1063, 1073 (Fed. Cir. 2019) (*citing In re Warsaw Orthopedic*, 832 F.3d 1327, 1333) (Fed. Cir. 2016).

Analysis

We adopt the Examiner's findings of fact and conclusion of law (*see* Non-Final Act. 10-14, FF 1-17) and agree that the combination of Riscoe '904, Cross, and Monastyrskyi renders the claims obvious. We address Appellant's arguments below.

Lead Compound Analysis

Riscoe '904 teaches that ELQ-300 has strong activity against malaria (FF 1-3) and teaches a scheme for the synthesis of ELQ-300 (FF 4). Cross also teaches that ELQ-300 was " highly efficacious against both the **[*9]** blood and the liver stages of the malaria parasite, as well as active against the forms critical for disease transmission" (FF 6). Monastyskyri teaches "a practical and operationally simple gram scale syntheses of **ELQ-300**" (FF 10).

Thus, ELQ-300 is reasonably identified as a natural choice for further development efforts as a highly effective anti-malarial compound. Monastyskyri explains that one weakness in ELQ-300 is that despite an "excellent antimalarial profile ELQ-300 [] lacks in aqueous solubility" (FF 9). Monastyskyri teaches a remedy for aqueous solubility issues is the development of prodrugs "is an alternative and well-documented approach to increase aqueous solubility and bioavailability" (FF 11).

Monastyskyri teaches that one of the two best solubility enhancing prodrug formulations, P4Q-414, significantly improved solubility of a similar malarial compound (FF 12), had a known synthetic route (FF 13), and that "the stability of **P4Q-414** at physiological stomach pHs and its rapid release at pH> 7 is optimal for development of

cyclization-activated prodrugs" (FF 14). Lastly, Monastyskyri teaches "[s]olubility hurdles were also conquered with a prodrug strategy" (FF 15).

We **[*10]** therefore agree with the Examiner that an ordinary artisan, interested in improving the anti-malarial activity of lead compound ELQ-300, would have reasonably selected prodrug formulations, and in particular, one of the very best prodrugs P4Q-414, in order to produce the soluble and effective anti-malarial compound recited in claims 5 and 12. As the Examiner notes: "One of ordinary skill would be motivated to make the compounds of the invention because he or she would expect the compounds to [have] improved properties including, solubility improvements and 'excellent aqueous stability-release profiles'" (Non-Final Act. 13).

Would undue experimentation in synthesis have been required?

Appellant contends

> it would not be possible to combine the teachings of *Riscoe* (also previously referred to by Appellants' as *"Riscoe 2012"* and/or *Cross* and *Monastyrskyi*, and add the prodrug moieties of *Monastyrskyi* (in particular P4Q-369 or P4Q-414) to the lead compounds ELQ-300 or P4Q-391 as asserted by the Office, based on the teachings of *Riscoe* and/or *Cross* and
>
> *Monastyrskyi*, without undue experimentation and/or with an expectation of success. Simply put, there is no reasonable expectation of success in combining the asserted prior art teachings to arrive and the compounds and compositions of Appellants' **[*11]** claims, especially without undue experimentation.

(Appeal Br. 10). Appellant cites the Manetsch [6] Declaration as teaching a need "to unexpectedly undertake significant optimization that amounts to undue experimentation in order to prepare the compounds of claims 4 and 5 (P4Q-1290 and P4Q-1291 in the declaration)" because "changes in the lead compound isolation protocol, the reaction concentrations, the reaction temperature, the reaction time, the equivalents of reagents used, all had to be modified in order to successfully produce the compounds of claims 4 and 5. The level of optimization undertaken amounts to more than undue experimentation" (*id.*). Appellant contends "the Office fails to consider the relatively large number of variables that required optimization and the undue experimentation/result of success required by the concurrent optimization of the combination of variables" (*id.* at 12).

We are not persuaded and agree with the Examiner that the

> synthetic route used in the specification is the same route used by Monastyrskyi, which is that of Thomas (Reference 39 is the same paper to Thomas, which was reference 25 in Monastyrskyi). The "undue experimentation" argued is therefore not the **[*12]** development of a new synthesis but changing the time, temperature, amount of reagents and the purification. This type of experimentation is routine for the synthetic organic chemist of ordinary skill and is not undue.

[6] Declaration of Dr. Roman Manetsch, dated Jan. 8, 2020.

(Ans. 6). The prior art itself demonstrates that time, temperature, and concentration ratios are rapid and routine optimizable parameters as Riscoe '904 teaches application of high throughput screening for optimization in the antimalarial drug space (FF 5). Cross teaches that when a broad range of syntheses were of interest to the artisan, "myriad changes in cross-coupling conditions were employed" (FF 8). And perhaps most relevant, Monastyskyri explains that when optimizing synthetic reactions, the ordinary artisan tests different reaction concentrations (FF 16) as well as reaction conditions including time and temperature (FF 17).

We recognize that one of the inventors, as Declarant, asserts that: "To succeed in the preparation of **P4Q-1290** and **P4Q-1291**, the prodrugs of **ELQ-300** or **P4Q-391**, the reaction concentrations, the reaction temperature, the reaction time, and the equivalents of reagents had to be changed" (Manetsch Decl. P 21). However, the evidence of record establishes that **[*13]** these conditions are routinely optimized, using high throughput techniques, in the synthesis of these anti-malarial compounds (FF 5, 8, 16, 17). The ordinary artisan is well aware that "discovery of an optimum value of a result effective variable . . . is ordinarily within the skill of the art." *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980).

We note that while the Manetsch Declaration recites that optimization was required, the Manetsch Declaration does not assert that the particular synthetic approach required more than optimization and does not indicate that anything other than routine optimization of the reaction conditions and isolation conditions was performed. Therefore, while we give the Manetsch Declaration some weight, we do not find it overcomes the Examiner's strong prima facie case of obviousness. *In re American Academy of Science Tech Center*, 367 F.3d 1359, 1370 (Fed. Cir. 2004) ("[T]he Board is entitled to give such weight to declarations as it deems appropriate."), *see also In re Bulina*, 362 F.2d 555, 559 (CCPA 1966) ("[A]n affidavit by an applicant or co-applicant as to the advantages of his invention is less persuasive than one made by a disinterested person.").

We have also considered Appellant's analysis of the cited routine experimentation caselaw (*see* Appeal Br. 13) and in particular, the analysis of *In re Aller*, 220 F.2d 454, 456 (CCPA 1955) where Appellant contends **[*14]** "[i]t is not enough to go down a list and simply assert individual variables (time, temp, pH, etc) can be routinely optimized without considering all of them in combination. The Office must consider that all variables must be optimized at the same time" (Appeal Br. 16).

We find this argument unpersuasive, however, because *Aller* specifically states "it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification." *In re Aller*, 220 F.2d at 456. Aller explains "[a]ny chemist reading the [prior art] could logically assume that higher yields might be obtainable, and by experimentally varying the conditions of temperature and acidity could find the most productive conditions." *Id.* at 458. And not only does the CCPA recognize that multiple variables may be optimized at the same time, but so does the cited prior art, where temperature and time of reaction were modified simultaneously (FF 17).

This is different than *In re Stepan*, 868 F.3d 1342 (Fed. Cir. 2017) where the Court found no "explanation as to *why* it would have been routine optimization to arrive at the claimed invention." *Id.* at 1346. In the present situation,

the prior art and even the Manetsch Declaration evidence that the ordinary artisan had reason to modify **[*15]** ELQ-300 to be more soluble, that the P4Q-414 had been shown to make compounds like ELQ-300 more soluble, and that reaction conditions for synthesis were ordinarily optimized for concentrations, time, and temperature and could be tested using high throughput testing (FF 1-17). Thus, the instant prior art provides both a reason to make the modification to a lead compound and provides parameters for optimization of the synthetic process.

We are unpersuaded by Appellant's argument that "the skilled artisan would have to look elsewhere for either additional methods, optimization of existing methods, or both. Such additional experimentation is necessarily undue, and there is no reasonable expectation of success" (Appeal Br. 17), because this argument presumes that the ordinary artisan in the field of chemical synthesis is entirely unaware of how to perform chemical synthesis. This is plainly inconsistent with the evidence of the prior art, which shows that ordinary artisans include those with advanced degrees working at the "Centre for Drug Candidate Optimisation" (FF 8). Such ordinary artisans would have been reasonably expected to understand how to optimize the synthesis of desired **[*16]** drug compounds.

Finally, as to the underlying issue of a reasonable expectation of success, an obviousness finding is "appropriate where the prior art 'contained *detailed enabling methodology* for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.'" *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (*citing In re O'Farrell*, 853 F.2d 894, 902 (Fed. Cir. 1988). "Obviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*." *Kubin*, 561 F.3d at 1360. The evidence of record reasonably establishes a reasonable expectation of success in performing the ordinary process of optimizing synthesis parameters in order to obtain the obvious modification of ELQ-300 with P4Q-414 to result in a more soluble anti-malarial compound.

Long-felt need

Appellant contends the "compounds and methods as recited in Appellants' present claim set meet the long-felt need at least for novel anti-malarial medications" because the "need for novel anti-malarial medications is a persistent problem recognized by those of ordinary skill in the art" and "this long-felt need has not been satisfied by others at the time of filing the application. . . . Although different therapies for malaria have been developed other than chloroquinone, resistance continues to **[*17]** develop, and large numbers of people worldwide continue to become sick and/or die" (Appeal Br. 20-21). Appellant also contends the "claims of the present application provide additional novel compounds and methods of use that satisfy the long-felt need for additional anti-malarial medicines. Physicians worldwide are in need of additional medicines to administer to patients with malaria" (*id.* at 21).

We are not persuaded and agree with the Examiner that:

> Many antimalarials existed before the invention was made including artemisinin, artesunate, artemether, dihydroartemisinin, mefloquine, amodiaquine, piperaquine, chloroquine, quinine, primaquine, lumefantrine, sulfadoxine-pyrimethamine, atovaquone, proguanil, tetracycline, doxycycline and vanous combination products sulfadoxine-pyrimethamine, artemetherlumefantrine, atovaquone-proguanil, amodiaquine and lumefantrine.

> Appellant admits that these drugs were known for treating malaria but clarifies that the long-felt need is for drugs that treat drug resistant strains of malaria (Appeal Brief at page 19). Since all known treatments have at least in part been met with resistance by the parasite, no drug in use currently meets such a need. However **[*18]** all the antimalarial drugs, at the point in time when they had not been exposed to the parasite, met the long-felt need since these were also once new. Assuming that any new antimalarial drug would satisfy long-felt need simply by being new, this would be true for almost any new drugs with a notable exception, prodrugs. Since the instantly claimed compound is a prodrug of ELQ-300, the fundamental mechanism of anti-malarial activity is the same.

(Ans. 7).

That is, the Examiner does not dispute that there is a need for anti-malarial drugs, and even drugs that do not currently have resistance. But because the active component of the drug recited in claims 5 and 12 is ELQ-300, a prior art compound, any resistance to the claimed drug would also necessarily involve resistance to ELQ-300 and so ELQ-300 would itself satisfy the need for a new drug to which malaria did not have resistance.

We also conclude that even if the long-felt need provides some evidence of a secondary consideration, the showing is insufficient to overcome the strong showing of obviousness in this case. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007) ("[W]e hold that even if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, **[*19]** this secondary consideration does not overcome the strong showing of obviousness in this case. Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed.Cir.1988)"). As we balance the evidence of long-felt need that is generic to any anti-malarial compound, and indeed to any compound that treats any infectious disease with the very strong case of obviousness, we do not find the secondary consideration controls the obviousness conclusion and find the claims obvious.

Conclusion of Law

A preponderance of the evidence of record supports the Examiner's conclusion that the combination of Riscoe '904, Cross, and Monastyrskyi renders claims 5 and 12 obvious.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
5, 12	103	Riscoe '904, Cross, Monastyrskyi	5, 12	

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

USPTO Bd of Patent Appeals & Interferences; Patent Trial & Appeal Bd Decs.

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