No. 12-182

In the
Supreme Court of the United States

HUGH EDWARD MONTGOMERY, JOHN FRANCIS MARTIN AND JORGE DANIEL ERUSALIMSKY,

Petitioners

-against-

The HONORABLE DAVID KAPPOS, in his official capacity as Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office,

Respondent

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Petitioner's Reply Brief

J. MARK POHL
Counsel of Record
PHARMACEUTICAL PATENT ATTORNEYS, LLC
55 Madison Avenue, 4th fl.
Morristown, New Jersey 07960
(973) 984-6159

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Attorneys for Petitioner

Question Presented

Undisputed facts produce either of two contradictory outcomes at The Court of Appeals for the Federal Circuit because different judges apply conflicting rules for "inherent anticipation." The Circuit acknowledges this intra-Circuit conflict, yet has rebuffed every request to resolve the conflict *en banc*. Petitioner thus asks this Court to do so. The question presented is:

> Whether a research proposal which was never in fact performed can, as a matter of law, inherently anticipate a patent claim under *Tilghman v. Proctor*, 102 U.S. 707 (1880)?

Rule 14(b) Statement

A list of all parties to the proceeding in the court whose judgment is sought to be reviewed:

Hugh Edward Montgomery, John Francis Martin, M.D., and Jorge Daniel Erusalimsky, *Petitioners*. The real party in interest is the assignee of the instant patent application, Ark Therapeutics Limited.

The Honorable David Kappos, in his official capacity as Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, *Respondent*.

Corporate Disclosure Statement

Petitioner Ark Therapeutics Limited hereby identifies Ark Therapeutics Group plc, a publicly held company as its parent company owning 100% of Petitioner's stock.

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Statement of the Case

Respondent's brief misrepresents a critical fact, apparently because Respondent fails to understand that ramipril is fat soluble. Respondent also newly-raises a host of legal issues which are irrelevant to this case. Petitioner respectfully submits this *Reply* to correct Respondent's factual misrepresentation, and to respond to its newly-raised issues.

The Circuit Correctly Found That HOPE Administered "Screening" Doses

Respondent (at 13:4-6) alleges that "when the HOPE reference was published, all of the patients in the HOPE study had been given therapeutic doses of ramipril." Respondent is mistaken: the Circuit court found (correctly) that those patients had merely been given low, short-term doses. The Circuit court correctly found those low, short-term doses were used for screening, i.e., identifying patients potentially allergic or unduly sensitive to ramipril.

Dose duration is critical here because ramipril is fat soluble. *See Petition* at 11:13-14. It thus accumulates in fat tissue over time. The Circuit court thus correctly noted that even a low dose could eventually treat mild hypertension, Pet. App. 14a n. 12, *if given for "a minimum of six months and an average of fifteen months*."[1]

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[1] The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators, *Effect of Ramipril On Mortality and Morbidity of Survivors of Acute Myocardial Infarction…*, 342 LANCET 821, 821 (1993), summarized in Frampton, James E. *et al., Ramipril:*

Thus, the Circuit below correctly found that while "HOPE does expressly disclose an actual administration of a low dose of ramipril for a short period of time as part of an initial 'randomization' step[,] [] there is no evidence in the record to prove that HOPE discloses administration sufficient to inevitably treat or prevent stroke, and the PTO does not argue otherwise." *Pet. App. at* 23a.

Furthermore, HOPE's patients were "generally not hypertensive," *see Petition* at 12 n. 4, so HOPE's screening doses could not have inherently treated hypertension because the patients were not even hypertensive to begin with.

Respondent (at 13 n. 1) now alleges the Circuit court had a "factbound disagreement" over whether HOPE's screening in fact involved a dose large enough, for a long enough time, to inherently prevent hypertension. Respondent is again mistaken: the Circuit below unanimously recognized they faced an evidentiary void. No evidence indicates that HOPE's screening was effective to treat hypertension. Indeed, this evidentiary void is precisely the reason the Circuit majority based its decision not on what HOPE actually did, but on what HOPE proposed to do in the future.

The Circuit Correctly Found that HOPE Only Gave Low, Short-Term "Screening" Doses

Certain anti-hypertensive drugs make cerebral blood vessels more brittle. *Petition* 9 n. 3. They thus paradoxically decrease hypertension yet increase stroke risk. *Id*. For example, the *Acute Infarction*

An Updated Review (1995) (Abstract only), cited in Pet. App. 14a n. 12.

Ramapril Efficacy ("AIRE") study found that using ramipril in patients with a history of acute myocardial infarction increased stroke risk by an eye-popping *43%*. *Id.* at 8:26-28, 10:3-4. Government-approved warning labels for these drugs thus uniformly warned against use in patients at risk of stroke. *Id.* at 9:1-7. Respondent does not dispute any of this.

Respondent (at 3 ¶3.b) correctly notes that some years after the AIRE study, the *Heart Outcomes Prevention Evaluation* ("HOPE") study proposed a new study of ramipril combined with vitamin E. Given the notorious fact that ramipril increased stroke risk in the AIRE study, the HOPE study was designed to specifically avoid hypertensive patients. *See Petition* 12 n. 4.

Respondent now alleges, "when the HOPE reference was published, all of the patients in the HOPE study had been given therapeutic doses of ramipril." *See Brief for Respondent* at 13:4-6.

Respondent is mistaken: contrary to Respondent's representation to this Court, when the HOPE reference was published, the patients had been given only low, short-term doses of ramipril – too little, to briefly, to do anything therapeutic, particularly in light of the fact that those patients didn't even have hypertension.

The HOPE study was supposed to be four years long and use a 10 mg / day dose. Before that study even began, however, the study had to first find suitable patients. Thus, potential patients were first screened using a low dose (2.5 mg) for a short time (7-10 days). Pet. App. 5a n. 7. This was not a "therapeutic" dose. Rather, this was merely to

identify patients who might have some kind of adverse reaction to ramipril. No evidence indicates that 2.5 mg for 10 days would have any effect on hypertension. Further, the patients were not even hypertensive.

Patients passing that initial screen were then "randomized" and again screened for sensitivity to a larger dose. Here, the patients were tested to assure that they could tolerate something approaching the full 10 mg / day dose. Thus, these patients were started (again) at 2.5 mg, and then increased to 5 mg. *Id*. Contrary to Respondent's representation, this was not a "therapeutic" dose. Rather, this was merely to identify patients who might who might have some kind of adverse reaction to somewhat grater exposure to ramipril. No evidence indicates that this dose / time would have any effect on hypertension. Further, the patients were not even hypertensive.

And that is the sum total of HOPE's prior art testing.

Thus, after studying HOPE, the Federal Circuit correctly found, "HOPE does expressly disclose an actual administration of a low dose of ramipril for a short period of time as part of an initial 'randomization' step. But there is no evidence in the record to prove that HOPE discloses administration sufficient to inevitably treat or prevent stroke, and the PTO does not argue otherwise." *Pet. App. at* 23a.

Respondent (at 13 n. 1) now alleges the Circuit court had a "factbound disagreement" over whether HOPE's screening was effective to prevent hypertension. Respondent misrepresents the factual record because Respondent ignores the fact hat ramipril is fat-soluble, so Respondent assumes

(incorrectly) that *short-term* administration is the same as *long-term* administration.

Ramipril is fat soluble. *See Petition* at 11:13-14. It thus accumulates in fat tissue over time. Thus, even a low dose can produce a mild antihypertensive effect if given for *"a minimum of six months and an average of fifteen months*." *Supra* n. 1.

Contrary to Respondent's allegation, the Circuit did not find HOPE's screening effective to prevent hypertension. Rather, the circuit found that long-term use (at least six months, as taught by AIRE and Frampton) treated mild hypertension (which did not occur in the HOPE patients). Further, HOPE specifically selected its patients to be *normotensive*, not hypertensive. *See Petition* 12 n. 4. Thus, contrary to Respondent's allegation, HOPE's screening could not possibly have been "therapeutic" for the simple fact that the patients did not even have hypertension.

These undisputed facts left the Circuit court with an evidentiary void: HOPE does not say whether its screening affected stroke risk, and the only other relevant evidence of record - AIRE - says that ramipril can *increase* stroke risk.

This evidentiary void is precisely why the Circuit majority rested its decision not on HOPE's short-term screening, but on HOPE's proposed future four year trial. The Circuit majority did not rule based on what actually happened, but on what would have happened, or what could have happened, or should have happened, had the HOPE investigators in fact performed their proposed four-year study. "Should have, would have, could have," however, is not the law.

HOPE Failed To Put The Artisan In Possession Of The Claimed Invention

Respondent raises a number of new legal arguments. Those arguments, however, are simply not relevant to this case.

For a patent case, this one is unusually simple. This case hinges on whether HOPE's proposal for future research enabled cardiologists to practice the inventors' invention, and to do so predictably and reliably, without requiring further experimentation to see whether they'd accidentally *cause* stroke like they did in the AIRE study.

Even Respondent (at 10:30-31) concedes that HOPE on its face says further experimentation is needed. And, an astonishing amount of it: finding over 9,000 volunteers without hypertension, getting them to agree to take a hypertension drug, and having them each commit to do so for a full four years, and having physicians closely monitor the entire process.

In teaching that further experimentation was needed, HOPE itself confirms that as a matter of law, it *could not have* enabled the artisan to practice the claimed invention. This rule is simple, common-sense and fair. It was perhaps most artfully summarized by Judge Learned Hand:

> No doctrine of the patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated. If the earlier

> disclosure offers no more than a starting point for further experiments, if its teaching will sometimes succeed and sometimes fail, if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation.

Dewey & Almy Chemical Co. v. Mimex Co., 124 F.2d 986, 989 (2nd Cir. 1942) (Learned Hand, J.).

Respondent does not allege that HOPE enabled the artisan to reduce stroke risk. Indeed, Respondent does not dispute that after reading HOPE, the artisan might still inadvertently *increase* stroke risk, as happened in the AIRE study. Rather, Respondent now raises a number of new - but irrelevant - arguments.

Whether The Artisan Would Have "Recognized" The Invention Is Irrelevant

Respondent stridently argues (at e.g., 7 ¶1.a) that a critical factual issue is whether the artisan "recognized" the allegedly-inherent feature. No. "Recognition" is irrelevant. This appeal is not about whether an artisan reading HOPE would "recognize" the inventors' invention. This appeal is about whether that artisan would have been able to *practice* the inventors' invention: to use it, and do so safely, without inadvertently *increasing* stroke risk as the AIRE study did.

The HOPE Investigators' Subjective Intent is Irrelevant

Respondent (at e.g. 9-10) argues that a critical factual issue is whether the HOPE screening was "accidental" or intentional. No. Mental intent is immaterial to anticipation.

Patent examiners are not mind readers. Neither the patent office, nor any Federal court, can reliably say what the mental "intent" was of the several hundred physicians slated to participate in HOPE. The critical legal issue is not their subjective mental intent(s), but whether their publication taught enough so that other cardiologists, reading that article, would be able to confidently and predictably practice the inventors' invention without inadvertently *increasing* stroke risk as the AIRE study did.

Regulatory Approval is Irrelevant

Respondent (at e.g. 10:29-31) argues that a critical factual issue is whether the HOPE proposal was "designed to secure regulatory approval." No. HOPE was not "designed to secure regulatory approval": regulatory approval had already been secured years before, by the time HOPE was planned, King Pharmaceutical Inc.'s ALTACE® brand ramipril was widely available.

This Case Is Not An "Interference" Case

Respondent (at 6:27-32) argues that the HOPE investigators could have used their proposal to apply for a patent on their proposed work. This is correct, but irrelevant.

When two competing groups of inventors pursue the same patent, the Patent Office adjudicates an

"interference" proceeding to identify which group first conceived the invention and reduced it to practice. *See* 35 U.S.C. § 135(a).

The instant appeal, however, is not an appeal of an interference. The instant appeal centers on whether the HOPE paper taught cardiologists enough so they could know how to use ramipril safely, without inadvertently causing stroke as the AIRE study did.

"Would have, could have, should have" is not the law: whether the HOPE investigators could have applied for a patent, or should have applied for a patent, is simply not relevant here.

This Case Exemplifies Precisely The Kind Of Appellate Conflict Which Cries Out For *Certiorari*

Respondent (at 16) argues that "individual judges' disagreement" with over applicable legal standards "does not create the sort of conflict … that warrants this court's review." Respondent is mistaken: *this sort of conflict is exactly why we need you*. If a decade-long, vocal dispute between two clearly-defined factions of appellate judges on a fundamental issue of patent law with far-reaching economic implications does not warrant review, what does?

Summary

In *Tilghman*, this Court mandated that a prior art reference cannot anticipate unless it teaches the artisan enough to actually practice the invention. The majority below refuses to follow *Tilghman*. This is a fundamental issue of patent law; as such, it is extremely important economically, far too important to be left unsettled.

The Circuit below having repeatedly avoided resolving the dispute *en banc* below, Petitioner respectfully asks this Court to grant *certiorari* to resolve the Circuit conflict.

Respectfully submitted,

J. MARK POHL
Counsel of Record
PHARMACEUTICAL PATENT ATTORNEYS, LLC
55 Madison Avenue, 4th floor
Morristown, New Jersey 07960
(973) 984-6159

Attorneys for Petitioner