# United States Court of Appeals for the Federal Circuit

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**IN RE: CONSTANTIN EFTHYMIOPOULOS,**
*Appellant*

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2016-1003

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Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. 08/737,141.

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Decided: October 18, 2016

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LYNNE A. BORCHERS, Myers Bigel Sibley & Sajovec, PA, Raleigh, NC, argued for appellant. Also represented by PETER DANIEL SIDDOWAY, ANTHONY P. DEROSA, SHAWNA CANNON LEMON.

FARHEENA YASMEEN RASHEED, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA, argued for appellee Michelle K. Lee. Also represented by THOMAS W. KRAUSE, SCOTT WEIDENFELLER, KAKOLI CAPRIHAN, LORA DRISCOLL.

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Before PROST, *Chief Judge*, NEWMAN and BRYSON, *Circuit Judges*.

Opinion for the court filed by *Chief Judge* PROST.

Dissenting opinion filed by *Circuit Judge* NEWMAN.

PROST, *Chief Judge*.

This appeal arises from the examination of a number of claims of U.S. Patent Application No. 08/737,141 ("'141 application"). The examiner rejected all pending claims as obvious and the United States Patent and Trademark Office, Patent Trial and Appeal Board ("Board") affirmed all of those rejections. Appellant Constantin Efthymiopoulos ("Efthymiopoulos") then requested rehearing, which the Board denied. For the following reasons, we affirm the Board's decision.

## BACKGROUND

The '141 application relates to methods of treating or preventing influenza by administering the drug zanamivir[1] by oral inhalation. On appeal, Efthymiopoulos challenges the rejection of claims 14-30, 32, 34-38, and 43-65. Independent claim 14 is representative:

> 14. A method for treating a human suffering from an infection by an influenza virus, wherein the method comprises administering to the human an effective amount of [zanamivir], wherein the [zanamivir] is administered by inhalation through the mouth alone.

J.A. 1697.

The examiner rejected the pending claims as obvious over Australian Patent No. AU-A1-27242/92 ("Von Itzstein II"), in view of WIPO Publication WO 91/16320 ("Von Itzstein I") and a number of other references. Like the '141 application, Von Itzstein I discloses that

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[1] The '141 application uses the chemical name of zanamivir: 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid. For ease of reference, we refer to the compound as zanamivir throughout the opinion.

zanamivir can be administered to treat and prevent infections by the influenza virus. Von Itzstein I only discloses intranasal administration (and not oral inhalation) of zanamivir. Von Itzstein II discloses the administration of a compound similar to zanamivir by "inhalation" for the treatment and prevention of influenza. The examiner concluded that Von Itzstein II disclosed all of the limitations of the challenged claims except that it did not teach zanamivir specifically and did not expressly teach inhalation only by mouth of its compounds. The examiner found, however, that Von Itzstein I taught zanamivir and suggested administering that compound to the respiratory tract to treat or prevent influenza. The examiner further determined that zanamivir and the compound disclosed in Von Itzstein II are "adjacent homologues" (meaning they are part of a series of compounds that differ in structure only by a single substituent) and thus concluded that using zanamivir in the method disclosed in Von Itzstein II would have been obvious.

Finally, the examiner noted that, with respect to administration, there are only two possible inhalation methods: through the mouth (oral) or through the nose (nasal). In view of the other prior art references that taught the well-known availability of inhalers, that oral inhalation delivers more drug to the lungs than nasal inhalation, and the fact that influenza infects the lungs, the examiner concluded that treating influenza by oral inhalation of zanamivir would have been obvious.

The Board agreed with and extensively cited the examiner and affirmed all of the rejections. The Board found that Von Itzstein II's disclosure of "inhalation" for treating influenza with its compounds "is reasonably understood to disclose inhalation by either the nose alone, mouth alone, or both" and thus concluded that Von Itzstein II in view of Von Itzstein I's disclosure of zanamivir rendered the claims obvious. J.A. 12-13. The Board also

considered Efthymiopoulos's evidence of secondary considerations—namely of unexpected results—but found it to be unpersuasive.

Efthymiopoulos sought rehearing, but the Board denied its request. Efthymiopoulos then timely appealed the Board's decision to us. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A) (2012).

## DISCUSSION

We review the Board's legal determinations de novo and its underlying factual determinations for substantial evidence. *Rambus Inc. v. Rea*, 731 F.3d 1248, 1251 (Fed. Cir. 2013). Obviousness is a legal question based on underlying fact findings. *In re DBC*, 545 F.3d 1373, 1377 (Fed. Cir. 2008).

Efthymiopoulos argues that the Board erred in rejecting the pending claims as obvious. Efthymiopoulos contends that none of the prior art references, alone or in combination, teach administration of zanamivir by inhalation through the mouth. Moreover, Efthymiopoulos says that a person of ordinary skill would not have expected that the administration of zanamivir through inhalation by mouth only would be effective. That is because oral inhalation delivers more drugs to the lower respiratory tract, and, at the time of the invention, it was thought that delivery of anti-influenza drugs to the upper respiratory tract was required to be effective. Finally, Efthymiopoulos faults the Board for failing to consider its evidence of unexpected results.

We conclude that the Board did not err in its obviousness determination. There is no dispute that Von Itzstein I discloses the use of zanamivir to treat and prevent influenza. There is also no dispute that Von Itzstein II discloses several pages of different administration methods for an adjacent homologue of zanamivir to achieve the same result—treating or preventing influenza. In partic-

ular, Von Itzstein II expressly discloses administration through "oral," "nasal," or other forms "suitable for administration by inhalation," among other methodologies. The Board's finding then, that a skilled artisan would be motivated to use zanamivir in the methods disclosed by Von Itzstein II, is supported by substantial evidence.

The Board also agreed with the examiner's conclusion that Von Itzstein II's disclosure of administration through "inhalation" includes oral inhalation. That finding is supported by substantial evidence. As the Board noted, "[I]nhalation can only be carried out via the nose or the mouth. Since Von Itzstein II does not limit its disclosure to nasal inhalation, it is reasonably understood to disclose inhalation by either the nose alone, the mouth alone, or both." J.A. 12-13.

The Board's conclusion is further supported by the fact that both Von Itzstein references teach that the compounds may be administered in many forms, including as a dry powder through an inhaler. And, as the Board noted, the state of the art at the time of invention established that dry-powder compositions were often used specifically for oral inhalation.

Efthymiopoulos's argument that a skilled artisan would not reasonably expect zanamivir to be effective if administered through oral inhalation is also unpersuasive. As the examiner noted, it was known in the art at the time that, although the influenza virus primarily attacks the upper respiratory tract, certain strains of the virus also attack the lower respiratory tract and that young children in particular were more susceptible to lower respiratory tract infections from the virus. And as the examiner observed, oral inhalation delivers more drugs to the lungs as compared to nasal inhalation. Thus, substantial evidence supports the determination that a skilled artisan would have a reasonable expectation of success in combining the Von Itzstein references.

Finally, Efthymiopoulos contends that the Board disregarded its evidence of unexpected results, namely the testimony of Dr. Hayden. We disagree. The record shows that the Board thoroughly considered and discussed Dr. Hayden's declaration in its decision and found that Dr. Hayden's testimony insufficient to overcome the prima facie case of obviousness. For example, the Board found that a study by Dr. Hayden did not show unexpectedly superior results between oral and intranasal inhalation. That finding is supported by substantial evidence. As the Board observed, Dr. Hayden himself conceded that the conclusion of the study he conducted was that "adding intranasal administration of zanamivir did not obviously improve" the results of using oral administration alone for the treatment of influenza. J.A. 1706. Thus, after considering Dr. Hayden's testimony and the manner in which it was conducted, the Board properly concluded that the claimed method would not necessarily yield an unexpectedly superior result.

Dr. Hayden also cited the Kaiser study which involved preventing influenza and showed that the rate of influenza was "substantially although not statistically significantly reduced" in patients treated with orally inhaled zanamivir compared to those treated with intranasal zanamivir. J.A. 1458. But, as the Board found, the Kaiser study is also unpersuasive because it did not disclose superior results, its findings were admittedly not statistically significant, and it dealt only with *prevention* of influenza, while the claims are directed to the *treatment* of influenza.

The Board therefore properly considered Efthymiopoulos's evidence of unexpected results and simply found it lacking. That finding is supported by substantial evidence. We thus conclude that the Board correctly affirmed the examiner's rejection of all pending claims as obvious.

## CONCLUSION

For the foregoing reasons, we affirm the Board's decision.

**AFFIRMED**

# United States Court of Appeals for the Federal Circuit

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NEWMAN, *Circuit Judge*, dissenting.

This litigation concerns the influenza drug zanamivir, marketed under the trademark Relenza®. The PTAB and now this court rule that it was obvious to administer this drug by oral inhalation, although there is no reference, no prior art, no suggestion, proposing that this mode of application might succeed, or that it should be tried. There was evidence of skepticism even as oral inhalation was evaluated. There was no contrary evidence. The evidence on which the Board and now this court rely is the evidence in the patent application itself, describing oral inhalation, its benefits, and its effectiveness. Upon learning this information from this inventor's disclosure, the Board found that it was obvious, and my colleagues agree that it is obvious to them.

Zanamivir was a known drug for treatment of influenza, administered by nasal inhalation, for the influenza virus was believed to infect the upper respiratory tract. The PTAB recognized that "the Examiner acknowledges that Von Itzstein II does not specifically teach inhalation

of the compound through the mouth." PTAB Op. 7. Nor does any other reference teach or suggest treatment of influenza by oral inhalation of this compound or any related compound. My colleagues nonetheless deem this treatment of influenza obvious on the ground that inhalation occurs only through the nose or the mouth. Thus the court rules that the discovery of effective treatment by oral inhalation is obvious to the court, although not obvious to experts, and not suggested in the prior art.

The applicant provided the expert opinion of Dr. Hayden, who discussed a large international study in which he participated, and concluded that the "effectiveness of orally inhaled zanamivir as compared with nasal administration . . . could be considered an unexpected result":

> In part because uncertainties existed regarding the transmission and pathogenesis of influenza as of the effective filing date of the present application, it was unclear whether oral inhalation of zanamivir with the dry powder inhaler device utilized in the studies would be clinically effective alone for prevention or treatment of naturally occurring uncomplicated influenza. In view of this uncertainty, the clinical effectiveness of orally inhaled zanamivir as compared to nasal administration for prevention of naturally occurring uncomplicated influenza above could be considered an unexpected result. Similarly, the effectiveness of orally inhaled zanamivir without intranasal zanamivir for treatment of naturally occurring uncomplicated influenza alone could be considered an unexpected result.

Decl. of Frederick G. Hayden, M.D. at 7 (filed in U.S. Patent Application No. 08/737,141 Mar. 12, 2013). Both the Board and the court discount Dr. Hayden's opinion because these experiments were not conducted for patent purposes but for scientific purposes, and were not direct

comparisons with the Board's view of the closest prior art. Dr. Hayden explained that:

> Although this study was not designed to compare directly the effects of zanamivir administration by oral inhalation alone to the effects of zanamivir administration by intranasal administration alone, it nonetheless found that the oral inhalation route alone provided unexpectedly significant activity without requiring intranasal administration for effective treatment of influenza virus illness . . . .

*Id.* at 3. Dr. Hayden explained that it was unexpected that this study "demonstrated the therapeutic value of drug delivery by the oral inhalation route to the posterior oropharynx (throat) and lower respiratory tract to treat naturally occurring influenza virus infection." *Id.* at 4.

Dr. Hayden also discussed a study that showed that the rate of influenza infection during 5 days of prophylaxis treatment was 6% for nasal inhalation alone – the same as for the placebo group – but was 2-3% for the group that received zanamivir "both by oral inhalation and intranasally." *Id.* at 4, citing Kaiser et al. *Short-Term Treatment with Zanamivir to Prevent Influenza: Results of a Placebo-Controlled Study*, 30 CLINICAL INFECTIOUS DISEASES 587–89 (2000). Dr. Hayden concluded that "[t]he results of this study supported a difference in protection between intranasal zanamivir and orally inhaled zanamivir" and "suggest the importance of delivering zanamivir to the posterior oropharynx and/or lower respiratory tract for the prevention of naturally acquired influenza virus illness." *Id.* at 4–5. As quoted *supra*, Dr. Hayden stated that this result was unpredictable and unexpected. *Id.* at 7.

As stated in *In re Dihrendra Ranchhoddas Merchant*, 575 F.2d 865, 868 (CCPA 1978), "The Board's basic error resides in its determination that Pring was the closest

prior art and that absent comparative tests vis-à-vis Pring, there was no rebuttal of what the Board considered a prima facie case." The Board erred in refusing to consider Dr. Hayden's results and in criticizing his tests as not in accordance with the Board's design of patent-oriented directly comparable experiments. The Board disregarded that Von Itzstein I only evaluated administration by nasal administration of a solution. *See* International Patent Application No. WO91/16320 at 54 (Oct. 31, 1991) ("Von Itzstein I") (describing intranasal administration of aqueous solution). The fact that scientific studies did not compare oral inhalation to liquid nasal administration does not mean the comparative evidence can be disregarded entirely. Dr. Hayden explained his conclusions; the Board should have considered them.

The Board did not hold that the result here was expected. However, the Board held that the claimed subject matter was obvious, on a rationale akin to "obvious to try." However, in the unpredictable arts such as medicinal treatment, for a method to be obvious to try, there must be some suggestion in the prior art that the method would have a reasonable likelihood of success.

There is no suggestion in the prior art to pursue oral inhalation, for the teachings of Von Itzstein II must be taken in context. It is noteworthy that there is extensive discussion in Von Itzstein II directed to all of the known forms of oral administration of this product—plus parenteral, topical, rectal, vaginal, and intranasal administration—but Von Itzstein II lacks any mention of oral inhalation. The Von Itzstein II reference, which is the primary reference relied on by the Board, states:

> Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical, (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for

> administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.
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> Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixers, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.[1]

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[1] This is the text on which the panel majority appears to rely for the statement that "Von Itzstein II expressly discloses administration through 'oral,' 'nasal,' or other forms 'suitable for administration by inhalation.'" Maj. Op. at 5.

Australian Patent No. AU-A-27242/92 at 8–9 (April 4, 1993). The description of suitable formulations continues for almost three more pages, but does not mention or suggest oral inhalation. No disclosure of administration of zanamivir by oral inhalation can be found here or anywhere else in the prior art. One wonders how it can nonetheless be obvious, particularly in view of the specific teaching in Von Itzstein I that nasal administration is the mode for administering zanamivir. To make a *prima facie* case, the prior art must provide, and the Board must identify, a reason or motivation to depart from the prior art; no reference or combination of references has been so identified—even in hindsight.

It cannot be "obvious to try" the only form of oral administration that is absent from the Von Itzstein recitations. In *KSR v. Teleflex* the Court explained that "obvious to try" may arise "where there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." 550 U.S. 398, 416 (2007). The Board's conclusion relies on a general finding that "inhalation can only be carried out via the nose or the mouth." PTAB Op. 11. But this is a flawed rationale, for Von Itzstein II teaches a totality of "oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation." Von Itzstein II at 8. The omission of oral inhalation from this compilation of all the "known options" for this drug makes conspicuously clear that oral inhalation was not an "identified predictable solution." The Board's ruling that oral inhalation was nonetheless obvious is not supported by substantial evidence. *See In re Huai-Hung Kao*, 639 F.3d 1057, 1067 (Fed. Cir. 2011) ("The Board's own conjecture

does not supply the requisite substantial *evidence* to support the rejections . . . .").

It was undisputed that, at the time of this invention, it was believed that the influenza virus infected primarily the upper respiratory tract, that is, the nasal passages. It was undisputed that there was not a reasonable expectation that administration to the lower respiratory tract by oral inhalation would be effective. The Von Itzstein references do not show or suggest oral inhalation, either for zanamivir or for any related compounds. The Board's statement that inhalation is "reasonably understood" to include oral inhalation, PTAB Op. 12, is without authority. There was no record showing or supporting such an understanding. There was no suggestion or hint in any reference that treatment by oral inhalation would have a reasonable expectation of success.

This mode of therapy is taught only by this inventor. There was not substantial evidence to support the Board's ruling of obviousness. From the court's flawed analysis and unsupported conclusion, I respectfully dissent.