

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte CYNTHIA B. ROBINSON and JONATHAN W. NYCE

Appeal 2007-4455
Application 10/461,563
Technology Center 1600

Decided: February 26, 2008

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and
FRANCISCO C. PRATS, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a composition for treating a respiratory disease. The Examiner has provisionally rejected the claims for obviousness-type double patenting, and

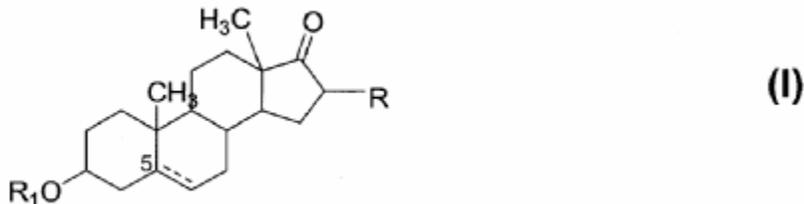
also rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.¹

STATEMENT OF THE CASE

The Specification discloses “a composition, formulations and a method for treating respiratory and lung diseases and conditions regardless of their mechanism” (Spec. 6).

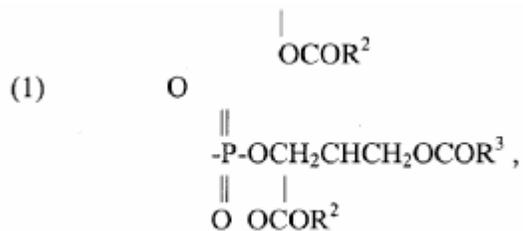
Claim 1 is representative of the appealed subject matter and reads as follows:

1. A pharmaceutical composition, comprising a pharmaceutically or veterinarily acceptable carrier and amounts of the first and second active agents effective to treat a respiratory disease,
 - (a) the first active agent being selected from a non-glucocorticoid steroid having the chemical formula

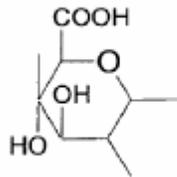


wherein the broken line represents a single or a double bond; R is hydrogen or a halogen; the H at position 5 is present in the alpha or beta configuration or the compound of chemical formula I comprises a racemic mixture of both configurations; and R¹ is hydrogen or SO₂OM, wherein M is selected from the group consisting of H, Na, sulfatide – -SO₂O-CH₂CHCH₂OCOR³; and phosphatide

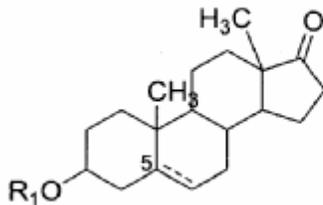
¹ In this decision we consider only those arguments actually made by Appellants. Arguments that Appellants could have made but chose not to make in the Briefs have not been considered and are deemed to be waived. See 37 C.F.R. § 41.37(c)(1)(vii).



wherein R² and R³, which may be the same or different, are straight or branched (C₁-C₁₄) alkyl or glucuronide



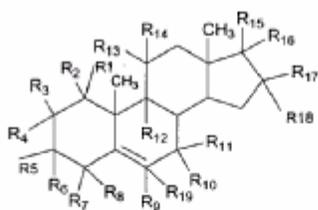
or a compound salt of the chemical formula (V)



(V)

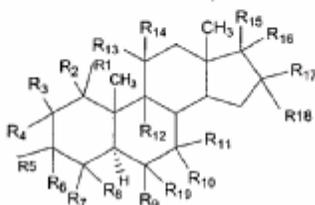
or pharmaceutically or veterinarily acceptable salts [sic] thereof; wherein R₁ is A-CH(OH)-C(O)-, and A is H or (C₁-C₂₂) alkyl, alkenyl, or alkynyl, each of which may be substituted with one or more (C₁-C₄) alkyl, halogen, HO, or phenyl which may be substituted with one or more halogen, HO, CH₃, or CH₃O;

or a non-glucocorticoid steroid of the chemical formula



(III)

, OR



(IV)

wherein R1[,] R2, R3, R4[,] R5, R7, R8, R9, R10, R12, R13, R14 and R19 are independently H, OR, halogen, (C1-C10) alkyl or (C1-C10) alkoxy, R5 and R11 are independently OH, SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane, --OSO₂R₂₀,

--OPOR₂₀R₂₁ or (C1-C10) alky[l], R5 and R6 taken together are =O, R10 and R11 taken together are =O; R15 is (1) H, halogen, (C1-C10) alkyl, or (C1-C10) alkoxy when R16 is --C(O)OR₂₂, (2) H, halogen, OH or (C1-C10) alkyl when R16 is halogen, OH or (C1-C10) alkyl, (3) H, halogen, (C1-C10) alkyl, (C1-C10) alkenyl, (C1-C10) alkynyl, formyl, (C1-C10) alkanoyl or epoxy when R16 is OH, (4) OR, SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane, --OSO₂R₂₀ or --OPOR₂₀R₂₁ when R16 is H, or R15 and R16 taken together are =O; R17 and R18 are independently (1) H, --OH, halogen, (C1-C10) alkyl or --(C1-C10) alkoxy when R6 is H OR, halogen[,] (C1-C10) alkyl or --C(O)OR₂₂, (2) H, (C1-C10) alkyl).amino, ((C1-C10) alkyl)ⁿ amino-(C1-C10) alkyl,

(C1-C10) alkoxy, hydroxy-(C1-C10) alkyl, (C1-C10) alkoxy-(C1-C10) alkyl, (halogen)_m (C1-C10) alkyl, (C1-C10) alkanoyl, formyl, (C1-C10) carbalkoxy or (C1-C10) alkanoyloxy when R15 and R16 taken together are =O, (3) R17 and R18 taken together are =O; (4) R17 or R18 taken together with the carbon to which they are attached form a 3-6 member ring containing 0 or 1 oxygen atom; or (5) R15 and R17 taken together with the carbons to which they are attached form an epoxide ring; R20 and R21 are independently OH, pharmaceutically acceptable ester or pharmaceutically acceptable ether; R22 is H, (halogen)_m (C1-C10) alkyl or (C1-C10) alkyl; n is 0, 1 or 2; and m is 1, 2 or 3; or pharmaceutically or veterinarily acceptable salts thereof; and
(b) the second active agent comprising an anti-muscarinic receptor agent and/or pharmaceutically or veterinarily acceptable salts thereof.

Claims 1-19, 21-23, 26, 27, 41-47, 59-63, 66-81, and 83-90 are pending (*see* App. Br. 2). Claims 14-17 have been withdrawn from consideration by the Examiner (*see id.*). Claims 1-13, 18, 19, 21-23, 26, 27, 41-47, 59-63, 66-81, and 83-90 are on appeal (*id.*).

The following rejections are before us for review:

Claims 1-13, 18, 19, 21-23, 26, 27, 41-47, 59-63, 66-81, and 83-90, all of the claims on appeal, stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of Application No. 10/923,556 (Ans. 3).

Claims 1-13, 18, 19, 21-23, 26, 27, 41-47, 59-63, 66-81, and 83-90 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Nyce (U.S. Patent No. 6,087,351 (filed May 22, 1997)) and McNamara (U.S. Patent No. 5,603,918 (filed Jun. 9, 1995)) (Ans. 4-5).

OBVIOUSNESS-TYPE DOUBLE PATENTING

The Examiner states that claims 1-13, 18, 19, 21-23, 26, 27, 41-47, 59-63, 66-81, and 83-90, are not patentably distinguishable from claims 1-19 of Application No. 10/923,556 “because the claimed compositions and methods are within the scope of the compositions and methods claimed in the copending application” (Ans. 3). Appellants do not contend that the Examiner erred in making this rejection, stating instead that they “have agreed to provide the requisite terminal disclaimer upon indication of allowable claims” (App. Br. 2; *see* Reply Br. 2).

Because Appellants do not contest the merits of the rejection, and because our review of the record reveals no defect in the Examiner’s reasoning, we affirm the Examiner’s provisional obviousness-type double patenting rejection.

OBVIOUSNESS

ISSUE

The Examiner cites Nyce as disclosing “compounds of formula (I) useful for treating asthma,” and McNamara as disclosing “the use of ipratropium bromide as bronchodilator and for the treatment of chronic obstructive airway disease” (Ans. 4). The Examiner notes that “the use of ipratropium for the treatment of acute asthma was known in the art at the time of the present invention as stated by [A]ppellants on page 8 of the specification, lines 16-19” (*id.*). The Examiner concludes that a “person having ordinary skill in the art at the time the claimed invention was made would have been motivated to combine two agents which are known for the treatment of asthma in order to address the need of an asthma patient for a bronchodilator and for the treatment of adenosine depletion” (*id.* at 4-5).

Appellants contend that the Examiner failed to establish a prima facie case of obviousness, erred in improperly taking official notice of facts that are not well known, failed to adequately consider evidence of unexpected results, and failed to recognize that the claimed invention “fulfills a long felt but unresolved need for the effective treatment of asthma and related respiratory diseases” (App. Br. 5).

The issue, therefore, is whether the Examiner erred in concluding that a person of ordinary skill in the art would have considered claims 1-13, 18, 19, 21- 23, 26, 27, 41-47, 59-63, 66-81, and 83-90 obvious in view of Nyce and McNamara.

PRINCIPLES OF LAW

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. “[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.”

In re Fritch, 972 F.2d 1260, 1265 (Fed. Cir. 1992) (citations omitted, bracketed material in original).

Thus, as the Supreme Court recently pointed out, “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR Int’l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The Court also indicated, however, that the analysis under 35 U.S.C. § 103 “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *Id.* The Supreme Court thus

implicitly endorsed the principle, stated in *In re Kerkhoven*, 626 F.2d 846, 850 (CCPA 1980) (citations omitted), that:

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. . . . [T]he idea of combining them flows logically from their having been individually taught in the prior art.

It is well settled that evidence of unexpected results may rebut an examiner's prima facie case of obviousness. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998); *see also KSR*, 127 S. Ct. at 1740 (“The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams’s design was not obvious to those skilled in the art.”) (discussing *United States v. Adams*, 383 U.S. 39 (1966)).

However, it is also “well settled that unexpected results must be established by factual evidence. ‘Mere argument or conclusory statements in the specification does not suffice.’” *In re Geisler*, 116 F.3d 1465, 1470, (Fed. Cir. 1997) (quoting *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984)). Also, “[m]ere improvement in properties does not always suffice to show unexpected results. . . . [W]hen an applicant demonstrates *substantially* improved results . . . and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary.” *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995).

FINDINGS OF FACT

1. Claim 1 recites a composition containing a pharmaceutical or veterinary carrier in combination with two ingredients that are effective in

treating a respiratory disease. The two active ingredients are (a) a compound of formula (I),² and (b) an anti-muscarinic receptor agent.

2. The Specification discloses that “[c]ompounds illustrative of chemical formula I . . . are DHEA [(dehydroepiandrosterone)] [P]referred compounds [include] DHEA and DHEA salts, such as the sulfate salt (DHEA-S)” (Spec. 13).

3. The Specification discloses that “[e]xamples of anti-muscarinic agents are ipratropium bromide” (Spec. 15). The Specification also discloses that “[a]lthough ipratropium is not usually employed as a first-line bronchodilator to treat chronic asthma, it has been used extensively in hospital emergency departments as adjunctive therapy for the emergency treatment of acute asthma exacerbation” (Spec. 8).

4. Nyce discloses “a method of reducing adenosine levels, particularly in the lung, liver and brain . . . , and, therefore for treating asthma, particularly non-steroid dependent asthma, by administering to a subject in need of such treatment dehydroepiandrosterone (DHEA), an analog thereof, or a pharmaceutically acceptable salt thereof” (Nyce, col. 4, ll. 40-46). As “[e]xamples of DHEA and analogs thereof that may be used to carry out this method,” Nyce sets forth a version of formula (I) that is virtually identical to that recited in appealed claim 1 (*see* Nyce, col. 4, l. 50 through col. 5, l. 29).

² The Examiner states that “[c]laims 1-13, 18, 19, 21-23, 26, 27, 41-47, 59-63, 66-81 and 83-90 have been examined only insofar as the elected compound of formula (I) is concerned” (Final Rejection 2 (May 9, 2006); *see also* App. Br. 2-3)). We therefore limit our consideration of the appealed rejection to the examined subject matter. *See Ex parte Ohsaka*, 2 USPQ2d 1461 (BPAI 1987).

5. McNamara discloses that “ipratropium bromide and albuterol (base) have been administered concomitantly from separate aerosol containers for bronchodilation” and that “an aqueous mixture of nebulized ipratropium bromide and albuterol (salbutamol) in treatment of chronic obstructive airway disease” has been reported (McNamara, col. 2, ll. 18-23).

6. On April 10, 2006, Appellants submitted a Declaration by Dr. Cynthia B. Robinson, M.D., pursuant to 37 C.F.R. § 1.132. At the time of the Declaration Dr. Robinson had over six years of drug development experience and had been working in the area of pulmonary/critical care, including the treatment of asthma and other pulmonary diseases, since 1989 (Declaration 1).

The Declaration presents data regarding the effects of various treatments on the proliferation of tracheal-derived ASM cells in culture (Declaration 2-3). The Declaration presents the following data:

When ASM cells are untreated, a cell count of about 200³ is obtained (*see* Declaration 3 (Table)). When ASM cells are treated with “EGF,” presumably epidermal growth factor, a cell count of about 1200 is obtained (*see id.*). When ASM cells are treated with EGF and methylcholine (Mch), a cell count of about 1750 is obtained (*id.*). Methylcholine therefore appears to potentiate the proliferative response induced by EGF alone by about 500 cells.

³ The Declaration does not provided the actual cell counts for each experiment, but rather presents the data in bar graph form. We estimated the cell count numbers from the bar graph in order to more clearly articulate the differences between each condition; however, we recognize that the values assigned by us are approximate.

When ASM cells are treated with EGF, methylcholine, and atropine, an anti-muscarinic receptor agent, the cell count appears to be about 1300 (*id.*). Atropine therefore appears to reduce the EGF/methylcholine-induced proliferative response by about 450 cells (i.e., about 1750 minus 1300).

When ASM cells are treated with EGF, methylcholine, DHEAS, and atropine, a cell count of about 800 is obtained (*id.*). Thus, the combination of atropine and DHEAS appears to reduce the EGF/methylcholine-induced proliferative response by about 950 cells (i.e., 1750 minus 800).

The Declaration does not present data regarding the effect of DHEAS on the EGF/methylcholine-induced proliferative response of ASM cells. That is, the Declaration does not present the results of an experiment in which ASM cells are treated with EGF, methylcholine, and DHEAS.

However, when ASM cells are treated with EGF and DHEAS, the cell count is reduced to a little under 1000 (*id.*). DHEAS therefore appears to reduce the proliferation induced by EGF by about 200 to 250 cells (i.e., 1200 minus 1000).

7. From the data presented in the Declaration, Dr. Robinson concludes that “this experiment shows that a combination of DHEA-S and the muscarinic antagonist, atropine, is a successful combination” (Declaration 3). Dr. Robinson does not state that the data show unexpected results. Dr. Robinson does not state that the data demonstrate synergy.

8. In the Declaration, Dr. Robinson states:

[A] combination of a bronchodilator drug, such as an antimuscarinic agent, which dilates the airways, facilitates the delivery of the non-glucocorticoid to the distal peripheral airways, when this agent is used as an inhalant. Use of the combination thus provides an improved sustained pharmacologic effect that translates to improved disease

management. As the mechanism of action of both the agents are different, it is my opinion that the combination of a non-glucocorticoid, such as DHEA or its derivatives, and an antimuscarinic agent as inhalants to treat asthma would not be obvious to one skilled in the art.

(Declaration 4).

Dr. Robinson also states that other DHEA analogs and anti-muscarinic would be expected to have similar properties, and that therefore “it is my opinion that similar combination effects would be observed with other non-glucocorticoid compounds in combination with other muscarinic antagonists” (*id.*).

ANALYSIS

We agree with the Examiner that a person of ordinary skill in the art would have considered it obvious to combine a compound of formula (I) with an anti-muscarinic receptor agent. Specifically, a person of ordinary skill treating asthma with a compound of formula (I) according to Nyce’s teachings would have been prompted to include ipratropium in the administered compositions because of McNamara’s disclosure that ipratropium was a useful bronchodilator (*see* Ans. 4-5).

Thus, a person of ordinary skill advised by Nyce and McNamara that compounds of formula (I), such as DHEA (*see* Findings of Fact (“FF”) FF 4, above), and anti-muscarinic receptor agents, such as ipratropium (FF 5), both had properties making them desirable in compositions used for treating asthma, would have considered it obvious to combine those ingredients so that they could be used together to treat asthma. *See In re Kerkhoven*, 626 F.2d at 850. We therefore agree with the Examiner that claim 1 would have been obvious to a person of ordinary skill in the art.

Appellants argue that the Examiner has failed to make out a prima facie case of obviousness because Nyce does not suggest combining the compounds of formula (I) with anti-muscarinic agents, and because McNamara has a very specific teaching of a combination of ipratropium bromide and albuterol, and therefore does not suggest combining the ipratropium with any active ingredients other than albuterol, much less the compounds of formula (I) (App. Br. 5-6). Appellants argue that the Examiner has provided no specific prior art-based explanation as to why a person of ordinary skill would have combined the claimed ingredients, which therefore leads to an inference of hindsight reasoning (*id.* at 6). Appellants conclude “the Examiner's unsupported assertion of the expectations of one skilled in the art does not constitute a convincing line of reasoning sufficient to establish the prima facie case of obviousness” (*id.* at 7).

We are not persuaded by this argument that the Examiner erred. As noted above, in emphasizing a flexible approach to the obviousness question, the Supreme Court stressed that the analysis under 35 U.S.C. § 103 “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The Court also emphasized that “[a] person of ordinary skill is . . . a person of ordinary creativity, not an automaton.” *Id.* at 1742. Regarding hindsight reasoning, the Court stated that “[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. Rigid preventative rules that deny factfinders

recourse to common sense, however, are neither necessary under our case law nor consistent with it.” *Id.* at 1742-1743 (citations omitted).

Thus, we agree with the reasonableness of the Examiner’s conclusion that one of ordinary skill in the art practicing Nyce’s method of treating asthma, being a person of ordinary creativity and common sense, would have inferred from McNamara’s disclosure of ipratropium’s bronchodilating properties that ipratropium would have been useful in Nyce’s asthma-treating compositions. The reason for combining the claimed ingredients therefore would have come solely from the prior art’s disclosure that those ingredients were useful in treating symptoms common to single disorder, asthma, and not from an after-the-fact viewing of Appellants’ disclosure.

Appellants argue, as evidenced by a list reproduced from Genarro (Remington’s Pharmaceutical Sciences, 18th Ed., 1990), that hundreds of prior art compounds capable of treating respiratory diseases were known in the art, and that therefore literally thousands of potential combinations were available in the art (App. Br. 7). Appellants argue that “the fact that a compound is on this list does not make its combination with another compound on the list obvious” (*id.*). Appellants also point out that Genarro contains recommended combinations of medicaments, therefore suggesting that finding a suitable combination is not a trivial matter (*id.*).

We are not persuaded by this argument. The issue with respect to this rejection is not whether the prior art availability of hundreds of respiratory disease-treating drugs leads, in the abstract, to a conclusion that every possible combination of two of those drugs would have been obvious. Rather, the issue is whether one of ordinary skill in the art would have considered claim 1’s combination of a compound of formula (I) and anti-

muscarinic receptor agent obvious. For the reasons discussed above, we agree with the Examiner that one of ordinary skill viewing only the prior art, being a person of ordinary creativity and common sense, would have considered the claimed combination of ingredients *prima facie* obvious.

Even assuming for argument's sake that a medical doctor, as a person of ordinary skill, would have recognized certain combinations of drugs to be undesirable and/or contraindicated (*see* App. Br. 7-8; Reply Br. 4-5), Appellants do not provide, nor do we see, any evidence on the current record suggesting that that person of ordinary skill would have considered it undesirable to combine the claimed ingredients. Rather, in the instant case the cited prior art teaches that the claimed compounds are useful in treating two known aspects of asthma -- Nyce teaches that compounds of formula (I) are useful in reducing adenosine levels and McNamara teaches that ipratropium addresses the problem of bronchodilation (*see* FF 4 and 5). Thus, because Appellants do not provide any specific evidence suggesting that a person of ordinary skill would have considered it undesirable to combine the two claimed ingredients, despite their different structures and specific activities, we do not agree that a person of ordinary skill would have been dissuaded from making the claimed combination.

Also, while Appellants urge that "this area is highly unpredictable" (App. Br. 8), Appellants do not provide, nor do we see, any evidence of record suggesting that a person of ordinary skill in the art viewing Nyce and McNamara would have been dissuaded from combining the disclosed ingredients based on the unpredictable behavior of those compounds. Moreover, it is well settled that "[o]bviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is

required is a reasonable expectation of success.” *In re O’Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). Given the direct disclosures in Nyce and McNamara regarding the efficacy of their respectively disclosed compounds, we agree with the Examiner that a person of ordinary skill viewing those references would have had the required expectation of success.

Appellants argue that the Examiner’s rationale for combining the claimed ingredients is at best “obvious to try,” which is not the standard of obviousness (App. Br. 9 (citing *O’Farrell*, 853 F.2d at 903)). Appellants urge that the Examiner’s prima facie case of obviousness similarly fails under *KSR Int’l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), because the Examiner did not identify “a design need or market pressure to move from administering DHEA and an antimuscarinic agent alone as described in Nyce and McNamara to a pharmaceutical composition comprising a DHEA compound and an antimuscarinic agent,” and because, “[u]nlike in the mechanical arts, there are not a finite number of identified predictable solutions to this unstated problem” (Reply Br. 6).

We are not persuaded by this argument. Regarding the “obvious to try” standard, the Supreme Court stated:

When 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. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 127 S. Ct. at 1742.

However, when taken in context, it is clear that in making this statement the Court did not intend to *require* the Examiner to identify a specific design need or market pressure as a *prerequisite* for a conclusion of obviousness. Rather, the Court rejected a “rigid approach” to the obviousness question, and instead emphasized that “[t]hroughout this Court's engagement with the question of obviousness, our cases have set forth an expansive and flexible approach” *Id.* at 1739. The Court also rejected the use of “rigid and mandatory formulas” as being “incompatible with our precedents.” *Id.* at 1741; *see also* 1742-43 (“Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it.”).

Therefore, while the Court stressed that the Examiner's rationale for practicing the claimed subject matter “should be made explicit,” the Court also recognized that the Examiner's reasoning need not be based on express disclosures in the prior art. *Id.* at 1741 (“[T]he analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.”).

In the instant case, the Examiner states that a “person having ordinary skill in the art at the time the claimed invention was made would have been motivated to combine two agents which are known for the treatment of asthma in order to address the need of an asthma patient for a bronchodilator and for the treatment of adenosine depletion” (Answer 4-5). As stated above, we agree with the reasonableness of the Examiner's conclusion that one of ordinary skill in the art practicing Nyce's method of treating asthma with compounds of formula (I), being a person of ordinary creativity and

common sense, would have inferred from McNamara's disclosure of ipratropium's bronchodilating properties that ipratropium would have been useful in Nyce's asthma-treating compositions.

We therefore agree with the Examiner that the combination of ingredients recited in claim 1 would have prima facie obvious to a person of ordinary skill. Moreover, because a person of ordinary skill in the art would have inferred from the references that the two claimed active ingredients would have been useful for the common purpose of treating asthma, we do not agree with Appellants (*see* Reply Br. 6-7) that the Examiner erred in applying *In re Kerkhoven*, 626 F.2d 846 (CCPA 1980), to the instant fact situation.

Appellants argue that "the field of pharmaceutical treatment of respiratory diseases is not an area that is of general common knowledge" as evidenced by the various respiratory diseases' different symptoms and treatments (App. Br. 10). Therefore, Appellants argue, because the Examiner made a conclusion of obviousness without citing "some reference work . . . recognized as standard in the pertinent art," the Examiner erroneously took "official notice" of facts that are not well known (*id.*).

We are not persuaded by this argument. The Examiner cited two pieces of prior art and explained why a person of ordinary skill in that art would have combined their disclosures (*see* Ans. 4-5). We do not see, and Appellants do not point to, where in the record the Examiner relied on official notice.

Appellants argue that the Examiner "failed to adequately consider evidence of unexpected results presented during prosecution" (App. Br. 10; *see also* Reply Br. 7-8). Appellants urge that in the Declaration filed April

Appellants point out that the Declaration shows that growing ASM cells in culture in the presence of epidermal growth factor (EGF) and methylcholine yields a rapid growth response of 1746 cells, whereas when the anti-muscarinic agent atropine is added with EGF and methylcholine, a modulated growth of 1333 cells results (*id.*). Appellants further point out that when DHEA-S and atropine were both added along with EGF and methylcholine, “there was an even greater modulation of growth, resulting in only 829 cells. These data show that the combination of the compound of formula (I) and an anti-muscarinic agent are more effective in modulating rapid cell growth than the anti-muscarinic agent alone” (*id.*). Appellants contend that, contrary to the Examiner’s position, the data presented in the Declaration “does, in fact, indicate synergy” (*id.* at 12; *see also* Reply Br. 7-8).

The Examiner contends that “the data presented shows the effect of EGF + DHEAS; the effect of EGF + Atropine and the effect of EGH [sic, EGF], DHEAS, Mch and Atropine but fails to show the effect of EGF + DHEAS + Atropine” (Ans. 7). Therefore, the Examiner concludes, “the synergistic effect of the combination of DHEAS and Atropine on EGF elicited ASM proliferation cannot be ascertained from the data presented” (*id.*).

We agree with the Examiner that Appellants have not made a sufficient showing of unexpected results to overcome the prima facie case of obviousness. We note that the combination of DHEA-S and atropine appears to reduce the EGF/methylcholine-induced proliferative response by about 950 cells, whereas atropine by itself appears to reduce the EGF/methylcholine-induced proliferative response by about 450 cells (*see* FF 6).

However, DHEA-S by itself has a significant effect on ASM cells' proliferative response to EGF, apparently reducing the proliferation induced by EGF by about 200 to 250 cells (*see* FF 6). Thus, because the Declaration shows that both DHEA-S and atropine have an inhibitory effect on induced ASM cell proliferation, a person of ordinary skill would not have considered it unexpected that a combination of the two ingredients would have a greater inhibitory effect than either ingredient alone.

Also, the Declaration does not present data regarding the effect of DHEA-S alone on the EGF/methylcholine-induced proliferative response of ASM cells. It is therefore not clear from the Declaration whether the disclosed amount of inhibition by the DHEA-S/atropine combination on the EGF/methylcholine-induced proliferative response is anything beyond the mere additive effect one would expect, given the demonstrated capacity of both compounds to inhibit proliferation.

Moreover, the Declaration does not state that the data present unexpected or synergistic results. Rather, the Declaration states only that "this experiment shows that a combination of DHEA-S and the muscarinic antagonist, atropine, is a successful combination" (Declaration 3).

As pointed out above, “[m]ere improvement in properties does not always suffice to show unexpected results.” *See In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995). Thus, given the disclosures in Nyce and McNamara that these classes of compounds are effective in treating symptoms of asthma, the Declaration’s conclusion that DHEA-S and atropine is a successful asthma-treating combination does not appear to present a result that a person of ordinary skill would consider unexpected.

We note Dr. Robinson’s statement that, given the different mechanisms of action of a non-glucocorticoid such as DHEA, and an anti-muscarinic receptor agent, “it is my opinion that the combination of a non-glucocorticoid, such as DHEA or its derivatives, and an antimuscarinic agent as inhalants to treat asthma would not be obvious to one skilled in the art” (Declaration 4). We also note that while “Appellant’s opinion on the ultimate legal issue is not evidence in the case[,] . . . some weight ought to be given to a persuasively supported statement of one skilled in the art on what was not obvious to him.” *In re Lindell*, 385 F.2d 453, 456 (CCPA 1967) (citation omitted). However, given the cited prior art’s suggestion for combining the claimed ingredients, discussed above, combined with the absence of evidence that the combination produces an unexpected result, we do not agree that the claimed combination would have been unobvious to a person of ordinary skill in the art.

Appellants argue that “the non-obviousness of the invention is supported by the fact that the combination fulfills a long felt but unresolved need for the effective treatment of asthma” (App. Br. 12).

We are not persuaded by this argument. Establishing nonobviousness from the failure of others to invent the claimed subject matter requires

“evidence that, notwithstanding knowledge of the references, the art tried and failed to solve the problem.” *In re Wright*, 569 F.2d 1124, 1127 (CCPA 1977). *See also, In re Kahn*, 441 F. 3d 977, 990 (Fed. Cir. 2006) (“Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness.” (quoting *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004))).

As Appellants point out, the Nyce patent issued in 1997. Appellants do not point to, and we do not see, evidence that others tried and failed to obtain a therapeutic effect when combining Nyce’s compounds of formula (I) with other asthma treatments. Appellants therefore have not met the burden required to demonstrate nonobviousness based on the failure of others.

In sum, as discussed above, we agree with the Examiner that one of ordinary skill in the art practicing Nyce’s method of treating asthma with compounds of formula (I), being a person of ordinary creativity and common sense, would have inferred from McNamara’s disclosure of ipratropium’s bronchodilating properties that ipratropium would have been useful in Nyce’s asthma-treating compositions. We therefore agree with the Examiner that claim 1 would have been prima facie obvious to a person of ordinary skill in the art.

Because we find that Appellants have not shown unexpected results sufficient to rebut the Examiner’s prima facie case, we affirm the Examiner’s obviousness rejection of claim 1. Because claims 2-13, 18, 19, 21- 23, 26, 27, 41-47, 59-63, 66-81, and 83-90, were not argued separately

Appeal 2007-4455
Application 10/461,563

from claim 1, we also affirm the Examiner's obviousness rejection of those claims. *See* 37 C.F.R. § 41.37(c)(1)(vii).

SUMMARY

We affirm the Examiner's provisional obviousness-type double patenting rejection of claims 1-13, 18, 19, 21- 23, 26, 27, 41-47, 59-63, 66-81, and 83-90 over claims 1-19 of Application No. 10/923,556.

We affirm the Examiner's rejection of claims 1-13, 18, 19, 21- 23, 26, 27, 41-47, 59-63, 66-81, and 83-90 under 35 U.S.C. § 103(a) as obvious in view of Nyce and McNamara.

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

Ssc:

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