NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

ENDO PHARMACEUTICALS INC., STRAKAN INTERNATIONAL S.A.R.L.,
Plaintiffs-Appellees

v.

ACTAVIS LABORATORIES UT, INC.,
Defendant-Appellant

2016-1146

Appeal from the United States District Court for the Eastern District of Texas in No. 2:13-cv-00192-JRG, Judge J. Rodney Gilstrap.

Decided: October 14, 2016

BARRY P. GOLOB, Cozen O'Connor, Washington, DC, argued for plaintiffs-appellees. Also represented by KERRY BRENDAN MCTIGUE, WILLIAM BLAKE COBLENTZ, AARON S. LUKAS, DONALD R. MCPHAIL.

GEORGE C. LOMBARDI, Winston & Strawn LLP, Chicago, IL, argued for defendant-appellant. Also represented by MICHAEL KEENAN NUTTER, IVAN MICHAEL POULLAOS,

KURT A. MATHAS, JOHN REYNOLDS MCNAIR; GEOFFREY P. EATON, Washington, DC.

Before MOORE, TARANTO, and HUGHES, *Circuit Judges.*

TARANTO, *Circuit Judge.*

Strakan International S.à r.L. owns U.S. Patent Nos. 6,579,865 (issued in 2003) and 6,319,913 (issued in 2001), with priority dating to 1997. Endo Pharmaceuticals Inc. is the exclusive United States licensee of those patents. In December 2010, Endo obtained final approval from the Food and Drug Administration to market its testosterone gel product, called Fortesta®, which is used by applying it to the skin to deliver testosterone transdermally.

In 2013, Watson Laboratories filed an Abbreviated New Drug Application with the FDA, seeking to market a generic version of Fortesta. Upon receiving Watson's notification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Endo and Strakan (collectively, Endo) filed suit against Watson under 35 U.S.C. § 271(e)(2), alleging that Watson's marketing of its proposed generic product would infringe claims 1, 3, 4, 6, 11, 18, 22, and 28 of the '865 patent and claims 19 and 20 of the '913 patent. Soon after, Watson transferred its relevant interests to Actavis Laboratories UT, Inc., which was substituted for Watson in this case. For convenience, we refer to Actavis as if it, rather than Watson, had always been the named defendant and had filed the application for FDA approval of a generic version of Fortesta.

In this action, Actavis alleged that all of the Endo-asserted claims of both patents are invalid based on anticipation and obviousness. Actavis also alleged that the product described in its FDA application does not meet a limitation of claims 1, 3, 4, 6, 11, 18, and 22 of the '865 patent and, therefore, its marketing would not infringe those claims. Actavis stipulated to infringement of

the other three claims asserted by Endo. After a bench trial, the district court ruled that the asserted patent claims are not invalid for either anticipation, J.A. 30–35, or obviousness, J.A. 46–54, and that Actavis's marketing of its product would infringe all of the asserted claims, J.A. 65–68.

Actavis appeals the district court's decision regarding obviousness and infringement. We have jurisdiction under 28 U.S.C. § 1295(a)(1). We affirm.

I

The claims at issue involve combinations of testosterone (or a derivative) and penetration-enhancing systems designed to allow testosterone to enter the body through the skin. Even before the 1997 priority date for the patents here, there was interest in producing a successful transdermal delivery system for testosterone because "there had been issues with delivery of testosterone through pill form (e.g. testosterone was largely destroyed by the digestive system) and through injections (e.g. patient compliance and dosage issues)." J.A. 46; *see* J.A. 539–42. In 1993 and 1995, the FDA approved transdermal testosterone patches—Testoderm and Androderm. J.A. 507. The district court found that patients found the first problematic because of the location where the patch had to be worn and that the second "used a penetration enhancing system," in order for the testosterone to cross the outer skin barrier in less sensitive body locations, "but had significant side effects of irritation." J.A. 10–11. The '913 and '865 patents resulted from attempts to find a combination of a penetration enhancer and testosterone that was effective in delivering the testosterone while keeping irritation to acceptable levels. The claims at issue, as relevant here, claim combinations of specified penetration enhancers (sometimes in specified concentrations) with specified concentrations of testosterone or its derivatives.

The makeup of the claimed penetration enhancers differs in certain respects from claim to claim, though much remains constant. The claim-by-claim variations are significant for the obviousness analysis, but not for the usual reason that the challenger argues for invalidity on a claim-by-claim basis. Here, Actavis makes no argument that some claims are invalid even if others stand. Presumably reflecting the content of its generic-Fortesta application to the FDA, Actavis makes a single, all-or-nothing, across-the-board obviousness argument: as Actavis argues its case, if any one of the asserted claims survives, all do. As a result, the prior-art analysis called for by Actavis's approach properly considers differences between prior art and *any* of the asserted claims.

Oleic acid is required in all of the claimed penetration enhancers, as are a glycol and an alcohol, but the specific alcohol and glycol used varies in the claims. Claim 1 of the '865 patent claims a composition "consisting essentially of" (a) testosterone (or a derivative) having a concentration of about 0.1% to about 2% and (b) a penetration enhancing system consisting of oleic acid, a C_1-C_4 alcohol, and a glycol. '865 patent, col. 14, lines 34–44. C_1-C_4 alcohols include ethanol, isopropanol, and propanol. J.A. 424. The claimed composition also includes a gelling agent.

Claims 3, 4, 6, 11, 18, and 22 of the '865 patent depend on claim 1. Claim 3 limits the active agent to testosterone (rather than a derivative). Claim 4 limits the concentration of testosterone to a range of "about 1% to about 2%" (only a part of the claim 1 range). Claim 6 limits the concentration of oleic acid to a range of "about 0.1% to about 5%." Claim 11 limits the "C_1-C_4 alcohol" to a mixture of ethanol and isopropanol. Claim 18 limits the "glycol" to propylene glycol. Claim 22 limits the composition to one in which the claim 1 "glycol is present from about 30% to about 40%" of the composition's weight.

Independent claim 28 is similar to claim 1 but also requires "inert carriers."

As to the '913 patent, independent claim 19 claims a method of topically administering a composition "comprising" (a) testosterone at a concentration "of about 0.1% to about 2%" and (b) "a penetration-enhancing system comprising: (i) oleic acid; (ii) a C_3 alcohol; and (iii) propylene glycol." '913 patent, col. 15, line 31, through col. 16, line 4. C_3 alcohols include propanol and isopropanol. J.A. 434. Claim 20 depends on claim 19 and differs only in that it includes specific concentrations of testosterone. '913 patent, col. 16, lines 5–9.

II

Having decided not to appeal the district court's finding of no anticipation, Actavis no longer disputes the novelty of the claimed compositions ('865 patent) and methods ('913 patent). It argues, however, that it proved by clear and convincing evidence that the inventions defined by all of the asserted claims would have been obvious in 1997. It does so by pointing to multiple pieces of prior art.

The evidence and arguments presented to us permit findings that, for each reference, there is a gap between its teaching and at least one of the asserted claims—something in at least one claim not disclosed in the reference. That is significant because of Actavis's all-or-nothing approach to arguing obviousness. We describe examples of the gaps here, before discussing, in the next section, the findings and evidence regarding whether a relevant skilled artisan would have bridged those gaps.

Cooper '872. This reference teaches the delivery of corticosteroids, not testosterone (which is not a corticosteroid). The district court found that the reference teaches that an alcohol such as ethanol should be used, but not as part of the penetration enhancer, only as a

solvent. J.A. 32. The court relied in part on the reference's statement that the alcohol, "if used, should not significantly interfere with the penetration action of the binary combination" of "a diol and a cell-envelope disordering compound." J.A. 578, 577, quoted at J.A. 20, 22. The court also found that there is no teaching of the combination of isopropanol and ethanol required by claim 11 of the '865 patent. J.A. 32.

Cooper '934. The advance described and claimed in this reference is a penetration-enhancing vehicle containing a "binary" mixture of 1-dodecylazacycloheptan-2-one (azone) and either "a C_3-C_4 diol, such as propylene glycol, or a second N-substituted azacycloalkyl-2-one." J.A. 590. Although there was evidence that azone and oleic acid have some similar properties, it is undisputed that they are not the same compound. The points made above about Cooper '872, concerning the role of relevant alcohols and the absence of an isopropanol-ethanol combination, apply as well to Cooper '934. J.A. 34. The district court found that Cooper '934 does not specifically identify testosterone, including in any of its Examples, which discuss a significant number of differently constituted penetration vehicles. J.A. 33; J.A. 600–05. The court noted that Cooper '934 does include "male sex hormones" among the potential active ingredients listed in a multipage, unelaborated recitation of conditions and active ingredients—which the district court found "enumerates 'without limitation' a list of what appears to be every condition or ailment one might seek to apply a pharmaceutical agent to." J.A. 33; *see* J.A. 28; J.A. 505 (testifying to Cooper '934's "very long or comprehensive list of different drug classes, and . . . pretty much every known drug within those classes at the time of the invention").

Patel '970. This reference mentions testosterone among many other potential active ingredients, but Actavis has not pointed to evidence showing that it discloses the three-part penetration enhancers of all of the

asserted claims here, as required for Actavis's argument. The penetration-enhancing vehicle of the Patel '970 patent, as described in the Abstract, has three components: (i) a cell-disordering compound such as oleic acid; (ii) specific lower alkanols, namely, ethanol, propanol, isopropanol, or mixtures of them; and (iii) an optional "inert diluent." J.A. 615. But Actavis has cited to no evidence that the patent discloses a three-part penetration enhancer of oleic acid, a C_1-C_4 alcohol such as ethanol, and *propylene glycol*, as required by claim 18 of the '865 patent and claims 19 and 20 of the '913 patent.

Actavis points to certain testimony of its expert, Dr. Potts, but neither that nor other cited testimony says that Patel '970 teaches the three-part enhancer with *propylene glycol*. Thus, Dr. Potts noted that the Abstract of Patel '970 discloses a three-part composition including oleic acid and ethanol and, also, polypropylene glycol (PPG) and polyethylene glycol (PEG)—which Patel '970 identifies as among the "inert diluents" required by component (iii). J.A. 431; *see* J.A. 615, 624, 625. Dr. Potts noted that PPG and PEG are "glycols" under the '865 and '913 patents, J.A. 431, but he did not say, and Actavis has identified no testimony stating, that the disclosed PPG or PEG is "propylene glycol," as required by the above-identified claims. When Patel '970 discusses propylene glycol (PG), it is not as an "inert diluent" in the claimed compound, as with PPG and PEG, but only in comparing its own combination of oleic acid and component (ii)'s lower alkanols favorably, with respect to skin irritation, to combinations of oleic acid and PG. J.A. 621 ("[T]his combination of oleic acid and propylene glycol causes severe skin irritation. . . . [T]he combinations of 80% glycerol dioleate and/or oleic acid with 20% ethanol provide penetration enhancement similar to that obtained with propylene glycol and oleic acid and, as will subsequently be demonstrated, does not possess the skin irritation properties of propylene glycol-oleic acid combinations."); *see* J.A. 615, 617, 618, 624, 625.

Patel '190. This reference discloses a combination of testosterone, glycerin (which the '913 and '865 patents define as a glycol), oleic acid, and ethanol. J.A. 613. But Actavis points to no such combination that does not also include methyl laurate, and it neither identifies evidence, nor even argues, that Patel '190 discloses a combination "consisting essentially" of glycerin, oleic acid, and ethanol, *i.e.*, with no other material components. J.A. 612. Actavis likewise points to no evidence that Patel '190 discloses the use of propylene glycol, as required by claim 18 of the '865 patent and claims 19 and 20 of the '913 patent, or the use of an ethanol-isopropanol mixture, as required by claim 11 of the '865 patent.

Aungst. Both the 1989 and 1995 Aungst references teach the combination of fatty acids, such as oleic acid, with propylene glycol, but Actavis does not show that they disclose the combination of those ingredients with an alcohol. *See* J.A. 50. And while the 1995 Aungst reference mentions testosterone with a different fatty acid and propylene glycol, Actavis does not show that either reference discusses the use of testosterone with an oleic-acid penetration-enhancing system. *See* J.A. 1333–34, 1357.

Other References. The Santus reference, not specifically addressed by the district court, discusses the use of oleic acid, propylene glycol, and "ethyl alcohol," another name for ethanol, as one example among many different penetration enhancers shown in patents. J.A. 750. Actavis identifies in Santus no mention of testosterone, for this or any other enhancer, or of a mixture of ethanol and isopropanol. The district court found, and it is not disputed, that the Francoeur and Touitou references do not disclose the use of testosterone. J.A. 51. Cormier teaches the use of cytotoxic agents such as 5-flourouracil as the active ingredient, and the district court found no evidence that testosterone is a cytotoxic agent or substantially similar to one. J.A. 51. And Actavis does not demonstrate, or even clearly argue, that any of those

references discloses the subject matter of all of the Endo-asserted claims—not just some claimed combinations, not just elements of claimed combinations, but all the specific combinations claimed, together with "consisting essentially of" for the '865 patent. In particular, the Actavis-cited testimony of Endo's expert is fairly read as making only more limited points than that. *See* J.A. 519–20, 522–25.

III

The district court concluded that a relevant skilled artisan would not have considered it obvious to bridge the gaps that separate the prior art from (at least one of) the claimed compositions and methods. The only relevant problem identified in the record was balancing delivery effectiveness with acceptable irritation for testosterone. J.A. 36. And while it would have been obvious to pursue a transdermal delivery mechanism for testosterone, and to consider using a penetration enhancer, the district court determined, it would not have been "obvious how to select and configure a particular penetration enhancer to combine with a particular level of testosterone." J.A. 47–48. Actavis "has not established that it was obvious that a person of ordinary skill in the art, which in this case is a highly and specifically educated person, would have, considering the art of the time, including the art presented to the Court, found the inventions of the patents-in-suit to be obvious either alone or in combinations of the numerous various references [Actavis] puts forward in the specific way that would yield the inventions of the patents-in-suit." J.A. 52–53.

Actavis has not presented a persuasive showing of prejudicial factual or legal error in the district court's determination. Notably, sufficient evidence supports the finding that "there were tremendous numbers of penetration enhancers that were known in the relevant time period and that one of ordinary skill, in this case, could have combined with testosterone." J.A. 52; *see*, *e.g.*, J.A.

40, 47; J.A. 441–43, 739–58, 1606–10.[1] So too for the finding that the desired balance of effects varies "unpredictabl[y]" according to the "specific" makeup of the particular enhancer and the choice of active ingredient with which it was to be combined. J.A. 33; *see*, *e.g.*, J.A. 501 (quoted at J.A. 16) ("quite difficult to predict"), 31, 33 (noting "the extensive record describing how specific and unpredictable mixtures are in the context of transdermal agents"), 36, 47, 52, 1292–96, 1333. And it is relevant, too, in determining what specific course a relevant skilled artisan would have had reason to pursue, among a large number of possibilities, that some prior art taught that a combination of oleic acid and propylene glycol could cause "severe skin irritation" whereas certain other enhancers would not. J.A. 621, 1355–57.[2]

That evidence is sufficient to uphold the district court's determination against the arguments Actavis has presented for reversal, and we need not go on to review

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[1] Just as to what is reflected in patents (not other publications), the Santus article, from 1993, reviews more than 150 enhancer patents, categorizing them into twelve groups of different types of enhancers, each type covering different individual enhancers—"(a) alcohol enhancers; (b) amide enhancers; (c) amino acid enhancers; (d) azone and azone-like enhancers; (e) essential oil enhancers; (f) fatty acid and fatty acid ester enhancers; (g) Macrocyclic enhancers; (h) phospholipid and phosphate enhancers; (i) 2-pyrrolidone derivatives; (j) soft penetration enhancers; (k) sulphoxide enhancers; (l) miscellaneous enhancers." J.A. 741; *see* J.A. 839–51.

[2] When Actavis argues that the irritability of the claimed composition is irrelevant because Fortesta is the most irritating product on the market, it is impermissibly comparing the composition's irritability to that of products that entered the market after the priority date.

certain other determinations made by the district court that, if sound, could only further weaken, not aid, Actavis's argument for obviousness. Thus, we need not consider whether the prior art's discussion of irritation effects of certain enhancer compositions, beyond supporting the finding of insufficient reason of a relevant skilled artisan to pursue the combinations at issue here, actually "teach away" from a path such an artisan otherwise would pursue with the required expectation of success. Nor need we consider whether any otherwise-persuasive showing of obviousness could be overcome in this case by objective indicia such as unexpected results, long-felt need, or others' failure to arrive at the inventions.

Finally, we see no basis for reversing the district court's judgment in the court's statement that "the effectiveness and side effects of using a combination of a particular penetration enhancer to deliver a particular compound were not readily predictable." J.A. 47. Unlike Actavis, we do not read that statement as applying an improperly high threshold for proving obviousness—ready predictability rather than a reasonable expectation of success—where the requisite motivation to combine is otherwise proved. Here, we read the district court's opinion as finding no such motivation to combine, a question to which the sheer number of possible combinations and degree of uncertainty are both relevant.

Moreover, the district court recited the expert testimony that the relevant effects are "quite difficult to predict," J.A. 18 (internal quotation marks omitted), and that "a person of ordinary skill would not have expected success using the penetration enhancing system," J.A. 36. And far from requiring ready predictability, the passage Actavis quotes immediately goes on to explain that "experiments were depended upon for the characterization of the properties of such a combination" and to credit the evidence "that extensive work, including a progression of studies, was generally required to characterize such a

combination on human subjects." J.A. 47. In the end, we do not read the district court's passage as raising the threshold for proof of obviousness the way Actavis alleges. We read the passage as addressing and rejecting one of Actavis's contentions in the very terms of "predictable results" and "predictable use" from *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416, 417 (2007), that Actavis itself invoked. Watson's Proposed Findings of Fact and Conclusions of Law 74–75, ECF No. 130.

IV

Actavis also argues that the district court's finding of infringement was clearly erroneous as to all of the asserted claims of the '865 patent except claim 28. Its theory is that in its accused product water plays a material role as part of the enhancer, so that its penetration enhancer does not "consist[] essentially" of the claim-listed components. Actavis agreed at oral argument in this court that the infringement issue need not be decided if we affirm the district court's validity determination, because Actavis stipulated to infringement of claim 28 of the '865 patent and claims 19 and 20 of the '913 patent, and it needs to succeed on all claims to be permitted to market its generic product. Oral Arg. at 2:00–2:55. In any event, we do not see clear error in the district court's finding that Endo proved infringement. Actavis, in its filings with the FDA, listed only one function for water in its product—serving as a solvent—even while it listed dual solvent/enhancer functions for other components. It is a legitimate inference in the circumstances here that water in Actavis's product does not play a material role in the penetration enhancer. *See* J.A. 17, 66–67. Therefore, we refuse to disturb the court's infringement finding.

CONCLUSION

For the foregoing reasons, we affirm the judgment of the district court.

AFFIRMED