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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte HONG RYEOL JEON, DO-WOO KWON, BONG-SANG LEE, SU-JUN PARK, BONG-GEUN CHA, JUN-KI KIM, JIYEONG HAN, and MYEONGCHEOL KIL

Appeal 2019-003541
Application 14/783,670
Technology Center 1600

Before JEFFREY N. FREDMAN, DEBORAH KATZ, and JOHN G. NEW, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134(a) involving claims to a tadalafil free base-containing film. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as CTC Bio, Inc. (*see* App. Br. 3).

[2] We have considered and herein refer to the Specification of Aug. 25, 2016 ("Spec."); Final Office Action of July 3, 2018 ("Final Act."); Appeal Brief of Dec. 20, 2018 ("App. Br."); Examiner's Answer of Mar. 5, 2019 ("Ans."); and Reply Brief of Apr. 4, 2019 ("Reply Br.").

Statement of the Case

Background

"Tadalafil free base is very difficult to prepare [as] a film in an aqueous solution state due to strong hydrophobicity" (Spec. 4, 2–3). "When tadalafil is produced in . . . a dispersed or suspended state, a layer separation of a film preparing solution and non-uniformity of an active ingredient may occur due to strong water repellency. Such layer separation and non-uniformity takes place in processes of preparing the film" (Spec. 2:6–10).

"The present disclosure is based on . . . a film containing a desired content of tadalafil free base with a thickness and a size suitable for individual dose adaptation . . . obtained by dispersing (or suspending) tadalafil free base in a polymer solution based on strong hydrophobicity of tadalafil free base" (Spec. 4:4–9). "The present disclosure provides a method of producing a tadalafil free base-containing film by which a tadalafil free base-containing film is produced by drying a polymer solution having tadalafil free base dispersed therein by the addition of a vinylpyrrolidone-based polymer and/or a polyethyleneglycol-based polymer as a dispersion stabilizing agent" (Spec. 11:23–12:4).

The Claims

Claims 13, 21, 24, and 25 are on appeal. Claims 1–12 are withdrawn. Independent claim 13 is representative and reads as follows:

> 13. A method of preparing a tadalafil free base-containing film, comprising:
>
> adding a tadalafil free base, a dispersion stabilizing agent, a film-forming polymer, and optionally a surfactant, a plasticizer, or mixtures thereof to water, to prepare a polymer solution; and

> drying a polymer solution in which the tadalafil free base is dispersed and 2 wt% or less of the total tadalafil free base is dissolved,
>
> wherein the dispersion stabilizing agent is selected from a polyvinyl alcohol-polyethylene glycol copolymer, polyethylene glycol, a polyvinylpyrrolidone or a vinylpyrrolidone-vinyl acetate copolymer or mixtures thereof,
>
> wherein the film-forming polymer has a content of 20 wt% to 80 wt% based on a total weight of the dried film and comprises:
>
> a first polymer having a viscosity of 15 cp or less as measured in a 2 wt% aqueous solution, and
>
> a second polymer having a viscosity of 50 cp or more as measured in a 2 wt% aqueous solution, the second polymer having a content of 3 wt% or less based on a total weight of the dried film,
>
> wherein the tadalafil free base is stably dispersed in the tadalafil free base-containing film,
>
> wherein the film comprises 10 wt% to 30 wt% of the tadalafil free base, and 0.2 wt% to 5 wt% of the dispersion stabilizing agent, and
>
> wherein 90 wt% or more of a solvent that is used in producing the film is water.

The Rejection

The Examiner rejected the claims under 35 U.S.C. § 103 as obvious over Bangalore[3] and Andrews.[4]

[3] Bangalore, US 2009/0047330 A1, published Feb. 19, 2009.
[4] Andrews et al., US 2011/0136814 A1, published Jun. 9, 2011.

Obviousness

The Examiner finds Bangalore teaches a process to make a film dosage form containing tadalafil as an active agent (Ans. 4). The Examiner finds the film dosage form may include 0.01 to 80% by weight tadalafil, 5 to 99% by weight film-forming polymers, 0.5 to 20% by weight plasticizer, and 0.1 to 10% emulsifier (*id.*). More particularly, the Examiner finds Bangalore teaches a combination of first and second film formers, such as pullulan and xanthan gum, or Methocel hydroxypropyl methylcellulose (HPMC) and Maltodextrin, as shown in the working examples (*id.* at 20). The Examiner finds that the process includes adding a film-forming polymer to water to form a polymer solution, dispersing the bioactive agent in water, adding the bioactive agent along with additional ingredients to the mixture, and forming a film (*id.* at 4–5).

The Examiner states that "Bangalore does not expressly teach the film former comprising a first polymer having a viscosity of 15 cp or less . . . and a second polymer having a viscosity of 50 cp or more . . . the second polymer at 3 wt% or less of the total weight of dried film" (Ans. 6). However, the Examiner finds the amount of "film former is an adjustable and optimizable parameter" (*id.* at 7). The Examiner finds "although Bangalore is silent about all the functional properties instantly claimed [i.e., tadalafil is dispersed] it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure" (*id.* at 8). Therefore, the Examiner concludes that "the same tadalafil is being dispersed with the polymers . . . in the water in both the instant claims and the prior art reference" (*id.*).

The issue with respect to this rejection is:

(i) Does a preponderance of evidence of record support the Examiner's conclusion that the prior art renders the claims obvious?

(ii) If so, has Appellant presented evidence of secondary considerations, that when weighed with the evidence of obviousness, is sufficient to support a conclusion of non-obviousness?

Findings of Fact ("FF")

1. Bangalore teaches "water soluble polymer based edible films for the oral delivery of Sildenafil citrate, [] Tadalafil, or Vardenafil HCl as active agents" (Bangalore ¶ 18).

2. Bangalore teaches "the polymers include [] water soluble polymers . . . along with suitable amounts of . . . plasticizers, buffering agents, sweeteners, emulsifying agents and suitable amounts of drug substance. . . . The resultant combination . . . can be a solution, suspension or emulsion which can be spread to form films" (Bangalore ¶ 26).

3. Bangalore teaches "a film former concentration can be in the range of 5–99% of the dry weight of the films" (Bangalore ¶ 40).

4. Bangalore teaches the film forming polymers may include Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), pullulan, polyethylene glycols, polyvinylpyrrolidone (PVP), xanthan gum, and maltodextrin, used "by themselves or in combination with other polymers" (Bangalore ¶¶ 41, 42, 44).

5. Bangalore teaches:

> In a preferred embodiment, the percentage dry weight concentration of at least single ingredients incorporated in a film in each of the following categories is as follows: emulsifying agent (0.1%–10%), plasticizer(0.5–20%), active agents (0.01–80%), taste modifying agents (0.1–10%), coloring agents (0.01–5%), water soluble inert fillers (0.5–50%),

> preservatives (0.01–10%), buffering agents (0.1–10%) and stabilizers (0.01–5%)

(Bangalore ¶ 45).

6. Bangalore teaches a method in which:

> [T]he film forming polymer was dissolved in water or hydroalcoholic mixture. The bioactive agent was either dissolved or dispersed in water or hydroalcoholic mixture and added to the polymer solution under mild agitation. In addition to the active agent and the film forming polymer, any of the ingredients listed above may be added and dispersed or dissolved uniformly in to [sic] hydrocolloid solution.

7. Bangalore teaches specific formulations containing Sildenafil Citrate, Methocel E15 (HPMC), Methocel E4 M (HPMC), Plasdone K 29-32 (PVP), maltodextrin, propylene glycol, glycerol, sorbitol, sucralose, tween 80 and water (Spec. ¶ 53, Table 1, Examples 2, 3).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

Analysis

We adopt the Examiner's findings of fact and conclusion of law (Ans. 4–25; FFs 1–7) and agree that Bangalore and Andrews render the claims obvious. We address Appellant's arguments below.

Appellant contends "the Examiner provides no reason to select tadalafil rather than sildenafil citrate" (App. Br. 8). Appellant contends "Bangalore exemplifies only 0.5–5 wt% sildenafil citrate in each of the 9 working examples" (*id.*). Appellant contends sildenafil and tadalafil "are structurally distinct compounds, having different chemical properties (e.g.,

sildenafil citrate has an aqueous solubility of 3.5 mg/mL whereas tadalafil is insoluble in water)" and "there is no reason to expect that tadalafil films can be formulated as sildenafil citrate films in the absence of any additional evidence" (*id.*).

We find this argument unpersuasive. Bangalore expressly teaches tadalafil as one of three active agents to be used in the film formulations (FF 1). "A reference must be considered for everything that it teaches, not simply the described invention or a preferred embodiment." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1298 (Fed. Cir. 2012). Moreover, Bangalore teaches a method in which the active agent, e.g., tadalafil, is dispersed in water and combined with a dissolved polymer to form a film (FF 6). Because Bangalore suggests tadalafil is one of three active agents, and teaches that the active agents may be dispersed rather than dissolved in water, we are not persuaded that the Examiner erred.

Appellant contends "the method of Claim 13 is distinguished from Bangalore through the presence of the particular dispersion stabilizing agent, . . . a first polymer having a viscosity of 15 cp or less, and a second polymer having a viscosity of 50 cp or more" (App. Br. 9). Appellant argues "[n]either the cited art nor Examiner provide any rationale for selecting polyethylene glycol, pullulan, and xanthan gum from among the 109,736 three-polymer combinations of the eighty-eight film-forming polymers of Bangalore" (*id.*).

We not find Appellant's argument persuasive. The disclosure of "a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition is used for the identical purpose taught by the prior art."

Merck, 874 F.2d at 807. "[P]icking and choosing may be entirely proper in the making of a 103, obviousness rejection." *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972). Bangalore teaches that the film forming composition may include combinations of film forming polymers, plasticizers, and emulsifiers (FFs 4, 5). The film forming polymers may include combinations, such as pullulan and xanthan gum (FF 4), or Methocel E15, Methocel E4M, and Maltodextrin, along with PVP (FF 7). Within these known film forming polymers, it would have been obvious for a person of ordinary skill in the art to modify the formulations in order to prepare a tadalafil containing film. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416.

Appellant contends "neither reference reports the tadalafil free base comprising '10 wt% to 30 wt%' of the film and the second polymer comprising '3 wt% or less'" (App. Br. 10). Appellant argues "Bangalore's disclosure of an active agent comprising '0.01–80%' of the combination . . . . is so broad as to be meaningless" (*id.*). Appellant argues "[w]ithout any guidance by the art or Examiner, there is simply no suggestion that xanthan gum in particular, out of the eighty-eight polymers disclosed, should be selected and present in an amount of 3 wt% or less" (*id.* at 11). Appellant contends *Peterson* "implies that the claimed range needs to be relatively close to the cited art range, which is not the case here" (Reply Br. 2 (citing *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)).

We find Appellant's argument unpersuasive. "[A] *prima facie* case of obviousness arises when the ranges of a claimed composition overlap the ranges disclosed in the prior art." *In re Harris*, 409 F.3d 1339, 1341 (Fed.

Cir. 2005 (citing *Peterson*, 315 F.3d at 1329)). "The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims.[] These cases have consistently held that in such a situation, the applicant must show that the particular range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (citations omitted).

We address both the range of active agent and second polymer. First, as to the active agent, Bangalore discloses a broad range of active agent and a narrower range of sildenafil citrate in the working examples (FF 5, 7). A person of ordinary skill in the art would have readily optimized the amount of active agent within the range for the appropriate dosing of tadalafil. The obviousness analysis "can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. "A person of ordinary skill is also a person of ordinary creativity, not an automaton." *Id.* at 421.

Second, as to the amount of polymers, Bangalore teaches the total amount of film forming polymer ranges from 5–99% by weight (FF 4). Bangalore further teaches that combinations of polymers may be used (*id.*). In the Examples, Bangalore teaches combinations of multiple film forming polymers, e.g., Maltodextrin, Methocel E15, and Methocel E4M of specific amounts, falling with the larger range (FF 7). The Examiner has shown the prior art teaches overlapping ranges that encompass the claimed amount of polymers. Appellant has not shown that the claimed ranges of polymers are critical. For example, none of the working examples, including those described as superior by Appellant (see below), appear to contain a second

polymer separate from a dispersion stabilizing agent (*see* Spec. 15, Table 1). Therefore, we are not persuaded that the Examiner has erred.

Appellant contends the "Examiner has no basis for asserting that the inherency conclusion is 'reasonable'" (App. Br. 13). Appellant contends Bangalore teaches "a solution, suspension, or emulsion" rather than a dispersion (*id*.). Appellant further contends "inherency by itself is not sufficient to establish obviousness . . . as unexpected properties may cause what may appear to be an obvious composition to be nonobvious" (*id.* at 14, citing *Honeywell Int'l., Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1355 (Fed. Cir. 2017)). Appellant contends the "Examiner has not shown that tadalafil would be expected to be dispersed in a pullulan/xanthan gum/polyethylene glycol mixture" (Appeal Br. 14).

We do not find Appellant's argument persuasive. Bangalore teaches the compositions may be formed by preparing a solution or dispersion of active agent in water which is combined with a dissolved polymer (FF 6). We do not agree with Appellant's argument that forming a suspension suggests a solution rather than a dispersion. Given tadalafil's known properties as a water insoluble drug, it would not have been unexpected by the artisan that tadalafil would be dispersed, rather than dissolved, in an aqueous solvent and water soluble polymer as suggested by Bangalore. After a *prima facie* case is made out, the burden shifts to the Appellant to show an unobvious difference between the prior art compounds and the claimed compound because the PTO lacks the resources to do such comparisons. *In re Best*, 562 F.2d 1252, 1254–1255 (CCPA 1977). Accordingly, we are not persuaded that the Examiner erred. Because Appellant does not argue the dependent claims separately, we agree with the

Examiner that claims 21, 24, and 25 are *prima facie* obvious over the prior art.

Appellant contends the "Examiner has not considered unexpected results" (App. Br. 14) (emphasis omitted). Appellant contends "films prepared by the method of Claim 13 have a dispersion stability relative standard deviation (RSD%) of 0.5–1.1 (Examples 4, 6, 7, and 13[]). In contrast, compositions prepared by a method utilizing compounds not recited in Claim 13 but disclosed in Bangalore (Examples 5, 8, 19–12, and 14) have an inferior dispersion stability . . . hav[ing] RSD% of 2.9 and above" (App. Br. 14–15).

We are not persuaded by Appellant's evidence for a number of reasons. First, we begin with Appellant's submission of the wrong table in the Appeal Brief, which was corrected in the Reply Brief (Reply Br. 4–5). Due to Appellant's submission, the Examiner did not have the opportunity make the proper comparison and we do not have the Examiner's expert opinion before us. Second, Appellant has not submitted evidence in the Specification or by affidavit that the results are unexpected. "It is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements . . . [do] not suffice." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Third, the results are not commensurate with the scope of the claims. "It is well established that the objective evidence of nonobviousness must be commensurate in scope with the claims." *In re Lindner*, 457 F.2d 506, 508 (CCPA 1972). "Commensurate in scope" means that the evidence provides a reasonable basis for concluding that the untested embodiments encompassed by the claims would behave in the same manner as the tested embodiment(s). *See id.* at 508. The claims

recite broad ranges encompassing numerous formulations, particularly as to the film-forming polymers. However, all of the examples are limited to hydroxypropyl cellulose as the first polymer (*see* Spec. 15, Table 1). Moreover, there is no indication that the exemplary formulations include a second polymer separate from a dispersion stabilizing agent as claimed (*see id.*).

Conclusion of Law

A preponderance of the evidence of record supports the Examiner's conclusion that the prior art renders the claims obvious. Appellant has not presented evidence of secondary considerations, that when weighed with the evidence of obviousness, is sufficient to support a conclusion of non-obviousness.

CONCLUSION

In summary:

Claims Rejected	Basis	Affirmed	Reversed
13, 21, 24, 25	§ 103 Bangalore, Andrews	13, 21, 24, 25	

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