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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JU HEE KIM and MIN SUNG KIM

Appeal 2024-000508
Application 17/832,229
Technology Center 1600

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and TAWEN CHANG, *Administrative Patent Judges.*

CHANG, *Administrative Patent Judge.*

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 1–7. *See* Final Act. 1. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

STATEMENT OF THE CASE

"Luteinizing hormone releasing hormone (LHRH), also known as gonadotropin releasing hormone (GnRH), . . . controls the reproductive

[1] "Appellant" refers to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as INVENTAGE LAB INC. Appeal Br. 3.

system of vertebrates," acting on the gonadal stimulated target cells to "induce[] the biosynthesis and release of the gonadotropin FSH (follicle-stimulating hormone) and LH (luteinizing hormone)." Spec. ¶¶ 2–4. LHRH agonists and antagonists have been found to be effective for the treatment of a variety of diseases. *Id.* ¶ 4.

The Specification states that "LHRH agonists are drugs for chronic diseases that should be taken for a long period of time," and further states that "[o]ne of the LHRH agonists, leuprolide acetate, has a drawback in that it has a short half-life upon conventional subcutaneous or intramuscular injection" and, thus, "has the inconvenience of having to be administered every day in order to maintain the medicinal effect thereof." Spec. ¶¶ 6–7.

According to the Specification, although sustained release formulations of leuprolide acetate have been developed and sold, "all products currently distributed in the market show excessive release of leuprolide at an initial stage . . . after administration by injection," but "when excessive release of leuprolide at the initial stage does not appear, the effect of leuprolide is not exhibited." Spec. ¶¶ 8, 10. Further according to the Specification,

> [an] object of the present invention is to provide microparticles containing leuprolide, which, when administered by injection, may lower pain due to their small size, control the release rate of leuprolide at a target site, prevent excessive release at an initial stage, enable exposure to a sufficient amount of the drug to exhibit the effect of leuprolide, and exhibit the effect of leuprolide for 1 month or more.

Spec. 15.

CLAIMED SUBJECT MATTER

The claims are directed to microparticles containing leuprolide and a biodegradable polymer, and method for producing the same. Claims 1 and 4, reproduced below, illustrates the claimed subject matter:

> 1. Microparticles containing leuprolide and a biodegradable polymer and having an average diameter of 40 to 100 μm and a value of 0.5 to 2 as determined by the following Equation 1:
>
> [Equation 1]
>
> $$\frac{D90-D50}{D50-D10}$$
>
> wherein D10 is a particle diameter corresponding to 10% cumulative (from 0 to 100%) undersize particle size distribution,
> D50 is a particle diameter corresponding to 50% cumulative (from 0 to 100%) undersize particle size distribution, and
> D90 is a particle diameter corresponding to 90% cumulative (from 0 to 100%) undersize particle size distribution,
> wherein the leuprolide and the biodegradable polymer are contained in a weight ratio of 1:2 to 1:10.
>
> 4. A method for producing microparticles containing leuprolide, the method comprising steps of:
> 1) preparing a first mixture by mixing leuprolide and a biodegradable polymer;
> 2) preparing a second mixture by dissolving a surfactant in a solvent;
> 3) injecting the first mixture and the second mixture into a first microchannel and a second microchannel, respectively, which have an intersection formed therebetween, and allowing the first mixture and

the second mixture to flow, thereby producing microparticles at the intersection;

4) collecting the microparticles in a bath containing the second mixture;

5) removing an organic solvent from the collected microparticles; and

6) washing the microparticles, from which the organic solvent has been removed, with purified water, followed by freeze drying,

wherein the microparticles have a value of 0.5 to 2 as determined by the following Equation 1:

[Equation 1]

$$\frac{D90-D50}{D50-D10}$$

wherein D10 is a particle diameter corresponding to 10% cumulative (from 0 to 100%) undersize particle size distribution,

D50 is a particle diameter corresponding to 50% cumulative (from 0 to 100%) undersize particle size distribution, and

D90 is a particle diameter corresponding to 90% cumulative (from 0 to 100%) undersize particle size distribution.

Appeal Br. 26, 27–28 (Claims App.).

REJECTIONS

A. Claims 1–7 are rejected under 35 U.S.C. § 102(a)(1) as being anticipated by Thanoo.[2]

[2] Thanoo et al., WO 01/10414 A1, published Feb. 15, 2001.

B. Claims 1–7 are rejected under 35 U.S.C. § 103 as being unpatentable over Thanoo and Schwach.[3]

OPINION

A. Anticipation over Thanoo

1. Issue

The Examiner finds that "Thanoo teaches a slow release microsphere having average particle size between 10-40 μm," including microparticles comprising leuprolide and biodegradable polymer, the two required components of claims 1 and 4. Final Act. 2. The Examiner finds that, "given the D_{10}, D_{50} and D_{90} particle size" disclosed, "[t]he span value calculated from Table 1 [of Thanoo] is 1.8."[4] *Id.* The Examiner also finds that Thanoo teaches a process wherein "leuprolide and polymer are dissolved in solvent to obtain a dispersed phase to be introduced into a continuous phase comprising a surfactant dissolved in solvent" and wherein the resulting microparticles are collected, washed, and freeze dried. *Id.* The Examiner further points to "Example 6 in Thanoo, where Thanoo teaches 50% (average) of the particles diameter is 48.4 μm or less, and 80% has a diameter between 23-69.7 μm." *Id.* at 7. The Examiner asserts that Example 6 shows that "Thanoo clearly teaches a diameter that is not just touching the claimed range, but also falls within the claimed range." *Id.*

Appellant contends that, with respect to claim 1, neither Thanoo's disclosure of "average particle size . . . between 10-40 μm" nor its Example

[3] Schwach et al., US 2016/0228494 A1, published Aug. 11, 2016.
[4] We understand that by "span value" the Examiner refers to the value determined from Equation 1 recited in the claims on appeal.

6 anticipate the claimed average diameter range of 40 to 100 μm, which Appellant further contends was "critical for the effective administration and sustained release of leuprolide from microparticles." Appeal Br. 8–13 (emphases omitted). Appellant further contends the Examiner has not articulated how Thanoo anticipates the limitation that "the leuprolide and the biodegradable polymer are contained in a weight ratio of 1:2 to 1:10," which is similarly "critical for the effective and sustained release of leuprolide over a long period of time." *Id.* at 13–14.

With respect to independent claim 4, which recites a method for producing microparticles containing leuprolide, Appellant contends that the Examiner has not met "the initial burden of showing that the prior art teaches all the claimed limitations," for example because the Examiner fails to articulate how Thanoo "teaches the first microchannel and the second microchannel" in step 3) of the claim. Appeal Br. 14–16. With respect to claims 5–7, which depends from claim 4, Appellant further contends that the Examiner fails to articulate how Thanoo teaches the additional limitations on "pressure ranges (in claims 5-6) and stirring conditions (rpm and temperature ranges in claim 7)" to be used in the claimed method of producing microparticles containing leuprolide. *Id.* at 16–17.

The issue with respect to this rejection is whether a preponderance of evidence supports the Examiner's determination that Thanoo teaches each of the limitations of the claims arranged in the manner recited in the claims.

2. Analysis

We agree with Appellant that the Examiner has not established a prima facie case that the claims are anticipated by Thanoo. As an initial matter, we note that to anticipate "it is not enough that the prior art reference

discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). Instead,

> unless a prior art reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102.

Id. Furthermore, "disclosure of a range is no more a disclosure of the end points of the range than it is of the intermediate points," *Atofina v. Great Lakes Chemical Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006), and anticipation of a claimed range by an overlapping range disclosed in the prior art requires that the overlap in the prior art "describes the entire claimed range with sufficient specificity" such that a skilled artisan would conclude that "there is no reasonable difference in how the invention operates over the ranges." *Id.*; *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015).

Claims 1–3

Claims 1–3 recites "[m]icroparticles containing leuprolide and a biodegradable polymer . . . having an average diameter of 40 to 100 μm." Appeal Br. 26 (Claims App.). The Examiner asserts that Thanoo's disclosure of leuprolide containing microspheres "hav[ing] an average particle size of from about 10 μm to about 40 μm" anticipates the claimed average diameter range, given that Thanoo teaches "a microsphere for the same use and having the same advantageous result desired by the present inventor, namely, a microsphere useful for the delivery of leuprolide in a

continuous slow release over a period of about 30 days." Final Act. 7. The Examiner further asserts that "drug release rate is not based on . . . particle size alone," and, "[h]ere, Thanoo teaches: i) the particle size that falls within the claimed range, or at least touches the claimed range; ii) the claimed polymer ratio; iii) a release rate of up to 120 days (up to 17 weeks); and iv) the process for preparing the claimed microparticle." Ans. 4–5.

We are not persuaded. The Specification states that having "small sustained-release particles with a diameter of less than 40 μm . . . may affect the release and *in vivo* absorption of the effective drug." Spec. ¶ 97. The Examiner does not appear to dispute Appellant's assertion that particle size affects the operation of the microspheres but only contends that other parameters, such as the "physiochemical properties of drugs, excipients, dosage form design, and manufacturing process," may be adjusted to achieve the desired release rate and duration for microparticles. Ans. 4.

There is no indication, however, that a skilled artisan would understand, for instance, that microparticles having an average diameter in the prior art range would have the same release profile (rather than simply duration)[5] as the claimed microparticles, or that adjustment of other microparticle properties to achieve a particular desired release profile, while retaining the average particle size within the prior art range, would result in microparticles that meet the other limitations of the claims. Furthermore, as

[5] Appellant asserts the diameter of the particle affects the amount and timing of the drug release (i.e., the release profile), not only the duration of the release. Appeal Br. 11–12. In particular, citing to the comparison of Production Example 2 and Comparative Example 1 disclosed in the Specification, Appellant contends that the diameters of the drug particles affect whether a large initial drug release, i.e., an "initial burst," occurs. *Id.*

noted above, in order to anticipate it is not enough that a skilled artisan may be able to combine the various teachings in Thanoo, supplemented with knowledge in the art as to how to adjust other microparticle parameters to arrive at a desired release profile, to achieve the claimed invention. *Net MoneyIN, Inc.*, 545 F.3d at 1371.

The Examiner also cites Example 6 of Thanoo, which teaches microspheres comprising human serum albumin and polymer, wherein "particle size distribution analysis showed that 50% of the particles were below 48.4 μm, and 80% were between 23.0 and 69.7 μm." Final Act. 7; Thanoo 16:16–17:1 (Example 6). The Examiner contends that, "[a]s such, Thanoo clearly teaches a diameter that is not just touching the claimed range, but also falls within the claimed range" and that, "[t]herefore, the claims are anticipated by Thanoo. *Id.*

We are not persuaded. The Examiner appears to take the position that the teaching, "50% of the particles were below 48.4 μm" is a teaching that the average diameter of the particles is 48.4 μm. Final Act. 7 (stating "Thanoo teaches 50% (average) of the particles diameter is 48.4 μm or less"). We agree with Appellant, however, that the cited teaching from Thanoo relates to particle size distribution and is not an inherent disclosure of a particular average particle diameter. Appeal Br. 9. Furthermore, as Appellant also points out, Example 6 teaches a particle comprising human serum albumin. *Id.*; Thanoo 16:16–17:1 (Example 6). Thus, even if Example 6 disclosed an average particle diameter of 48.4 μm, Thanoo does not anticipate the claims, which relate to microparticles containing leuprolide. *Net MoneyIN, Inc.*, 545 F.3d at 1371 (explaining that to anticipate "it is not enough that the prior art reference . . . includes multiple,

distinct teachings that the artisan might somehow combine to achieve the claimed invention").

Accordingly, for the reasons set forth above, we find that the Examiner has not established a prima facie case that Thanoo anticipates claims 1–3 on appeal.

Claims 4–7

Independent claim 4 and claims 5–7, which depend from claim 4, recite a method for producing microparticles containing leuprolide. Appeal Br. 27–29 (Claims App.). Unlike claim 1, these claims do not recite a limitation regarding average particle diameter.

In the Final Rejection, the Examiner states that "[t]he claimed process is disclosed in pages 9-11[of Thanoo], wherein leuprolide and polymer are dissolved in solvent to obtain a dispersed phase to be introduced into a continuous phase comprising a surfactant dissolved in solvent, collecting the microsphere, washing, and freeze drying." Final Act. 2.

As Appellant points out, however, the claims on appeal recite specific structural limitations for introducing the first mixture of leuprolide and biodegradable polymer with the second mixture of surfactant and solvent, namely step 3), "injecting the first mixture and the second mixture into a first microchannel and a second microchannel, respectively, which have an intersection formed therebetween, and allowing the first mixture and the second mixture to flow, thereby producing microparticles at the intersection." Appeal Br. 15–16. We agree with Appellant that the Examiner has not explained how Thanoo teaches or suggests the above limitations relating to the first and second microchannels and the

arrangement thereof.[6] Accordingly, because "anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference," *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991), we find that the Examiner has not established a prima facie case that Thanoo anticipates claims 4–7 on appeal.

B. Obviousness over Thanoo and Schwach

1. Issue

The Examiner finds that Schwach teaches "microparticles having a mean particle diameter from 30-60 μm," including "[m]icroparticles comprising GnRH receptor and biodegradable polymer in the claimed ratio." Final Act. 3–4. The Examiner finds that Schwach teaches "D_{10}, D_{50}, and D_{90} values which is calculated from the claimed equation to obtain a value of 1.8 that falls within the claimed range." *Id.*

The Examiner acknowledges that "Schwach while disclos[ing] the microparticle is useful for the delivery of hormones such as goserelin, does not specifically disclose microparticle comprising leuprolide." Final Act. 4.

[6] We note that Thanoo teaches the use of a Silverson unit in preparing the microparticles of a polymer (poly(lactide-co-glycolide)) and leuprolide. Spec. 12:10–17, wherein a dispersed phase (DP) of a mixture of leuprolide dissolved in methanol and the polymer dissolved in dichloromethane is connected to an inlet of the Silverson unit through a micrometer Teflon needle valve and a continuous phase (CP) of a surfactant (polyvinyl alcohol, or PVA) dissolved in water is connected to the Silverson unit through a CP addition tube from the CP tank using a peristaltic pump for flow control. The Examiner does not appear to rely on the method disclosed in Thanoo's Example 1 for its anticipation rejection; neither has the Examiner explained how such a method would meet the limitations regarding microchannels in step 3) of claims 4–7 on appeal. We decline to consider in the first instance whether the Silverson unit disclosed in Thanoo meets the microchannel limitations of claims 4–7.

However, the Examiner finds "Thanoo teaches a slow release microsphere having average particle size between 10-40 μm" and further teaches "[m]icroparticles compris[ing] leuprolide and biodegradable polymer." *Id.* The Examiner finds that, based on the values of D_{10}, D_{50}, and D_{90} given in Thanoo's Table 1, Thanoo teaches microparticles having the span value of 1.8, which falls within the claimed range. *Id.* Finally, the Examiner finds that Thanoo teaches the claimed process of producing the microparticles. *Id.*

The Examiner determines that, based on the above, it would have been prima facie obvious to an ordinarily skilled artisan at the time of the invention "to optimize the composition of Schwach to include leuprolide with the expectation of at least similar result," because "Thanoo teaches using sustained release microparticle for the delivery of hormone such as leuprolide is known in the art." *Id.*

Appellant contends that "[i]f a skilled person in the art used both leuprolide and the manufacturing method of Thanoo in Schwach, the person would also have followed the teaching of Thanoo regarding the diameter of the particles." Appeal Br. 18. Appellant contends that the Examiner has not shown how the cited references suggest the limitation that "the leuprolide and biodegradable polymer are contained **in a weight ratio of 1:2 to 1:10**," which Appellant asserts is "critical for the effective and sustained release of leuprolide over a long period of time." *Id.* at 20. Appellant contends that, similarly, "[t]he claimed size range, with other limitations, is critical for the effective administration and sustained release of leuprolide from microparticles." *Id.* at 18 (emphasis omitted). Appellant contends that, furthermore, the Examiner has not addressed Appellant's arguments

regarding the unexpected results achieved by the claimed invention. *Id.* at 20.

With respect to claims 4–7, which are directed to a "method for producing microparticles containing leuprolide," Appellant contends that the Examiner has not specified "how the cited reference[s] teach[] each and every one of the claimed steps, conditions, and limitations," such as for instance the use of a first and a second microchannel. Appeal Br. 22–23. With respect to dependent claims 5–7, Appellant further contends that the Examiner has not shown "how the cited references teach the . . . limitations on pressure ranges (in claims 5-6) and stirring conditions (rpm and temperature ranges in claim 7)." *Id.* at 23.

The issues with respect to this rejection are (1) whether the Examiner has provided sufficient articulated reasoning, with rational underpinning, to support the determination that claims 1–3 are obvious over Schwach and Thanoo, and 2) whether a preponderance of evidence supports the determination that claims 4–7 are obvious over the combination of Schwach and Thanoo.

2. Analysis

Claims 1–3

Assuming that the Examiner has made out a prima facie case of obviousness, we nevertheless agree with Appellant that the Examiner has not established that claims 1–3 are obvious over Thanoo and Schwach. In particular, after a prima facie case obviousness has been established, "the burden (and opportunity) then falls on an applicant to rebut that *prima facie* case," including, for instance, by "showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art

does not have." *In re Dillon*, 919 F.2d 688, 692–693 (Fed. Cir. 1990). Once Appellant submitted evidence in rebuttal, however,

> the decision-maker must start over. Though the burden of going forward to rebut the prima facie case remains with the applicant, the question of whether that burden has been successfully carried requires that the entire path to decision be retraced. An earlier decision should not, as it was here, be considered as set in concrete, and applicant's rebuttal evidence then be evaluated only on its knockdown ability. . . . Prima facie obviousness is a legal conclusion, not a fact. Facts [established] by rebuttal evidence must be evaluated along with the facts on which the earlier conclusion was reached, not against the conclusion itself.

In re Rinehart, 531 F.2d 1048, 1052 (CCPA 1976).

In this case, Appellant alleges the criticality of the claimed average diameter range and the presence of "unexpected and unique effects" of microparticles having an average diameter of 40 to 100 μm, citing among other things to paragraph 97 and the comparison of Production Example 2 and Comparative Example 1 in the Specification. Reply to Non-Final Office Act. 9 (Dec. 26, 2022); Appeal Br. 18–19, 20–21; Reply Br. 7. The Examiner does not appear to have substantively addressed this rebuttal. As we are not persuaded the Examiner has re-weighed the totality of the evidence with Appellant's rebuttal in mind, and because we decline to conduct this re-weighing in the first instance,[7] we reverse the Examiner's

[7] Because we decline to conduct the evaluation of Appellant's assertions regarding the criticality and/or unexpected results of microparticles having an average diameter within the claimed range, we take no position as to whether the alleged evidence of unexpected results, when taken together with the evidence of obviousness, show claims 1–3 to be non-obvious. *See, e.g., Rinehart*, 531 F.2d at 1052 (explaining that, "[t]hough the tribunal must

rejection of claims 1–3 as obvious over Thanoo and Schwach. *See also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.").

Claims 4–7

As noted above, claims 4–7 recite a method for producing microparticles containing leuprolide. As with the anticipation rejection, the Examiner relies on Thanoo for disclosure of the claimed process, asserting that the "claimed process is disclosed in pages 9-11 [of Thanoo], wherein leuprolide and polymer are dissolved in solvent to obtain a dispersed phase to be introduced into a continuous phase comprising a surfactant dissolved in solvent, collecting the microsphere, washing, and freeze drying." Ans. 4. For the same reasons we discuss above with respect to the anticipation rejection — namely that the Examiner has not explained how Thanoo teaches or suggests the limitations regarding microchannels in step 3) of claims 4–7 on appeal, we reverse the rejection of claims 4–7 as obvious over Thanoo and Schwach.

begin anew [once rebuttal evidence has been submitted], a final finding of obviousness may of course be reached, but such finding will rest upon evaluation of all facts in evidence, uninfluenced by any earlier conclusion . . . upon a different record").

CONCLUSION

The Examiner's rejection of claims 1–7 as anticipated by Thanoo is reversed. The Examiner's rejection of claims 1–7 as obvious over Thanoo and Schwach is reversed.

DECISION SUMMARY

The following table summarizes our decision:

Claim(s) Rejected	35 U.S.C. §	Reference(s)/ Basis	Affirmed	Reversed
1–7	102(a)(1)	Thanoo		1–7
1–7	103	Thanoo, Schwach		1–7
Overall Outcome				1–7

REVERSED