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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* LI-CHIEN HSU and SUN-DE TONG

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Appeal 2018-008068
Application 11/308,265
Technology Center 1600

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Before JEFFREY N. FREDMAN, JOHN G. NEW, and JAMIE T. WISZ, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134 involving claims to a method for regulating the release of one or more drugs from a drug delivery system. 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 Biotegra, Inc. (*see* App. Br. 2).

[2] We have considered and refer to the Specification of Mar. 14, 2006 ("Spec."); Final Action of June 24, 2016 ("Final Act."); Appeal Brief of Jan. 3, 2017 ("App. Br."); Examiner's Answer of Sept. 19, 2017 ("Ans."); and Reply Brief of Feb. 21, 2018 ("Reply Br.").

*Statement of the Case*

*Background*

"The ability to controllably deliver therapeutic or prophylactic agents to a specific target site within the body has been a goal in the field of drug delivery as a controlled level of drugs in the body provides the most effective prophylactic or therapeutic treatment for preventing or treating illnesses" (Spec. ¶ 2).

*The Claims*

Claims 1, 3, 4, 9–11, and 23–25 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method for regulating the release of one or more drugs from a drug delivery system, the method comprising:
>
> providing a coating composition having one or more water insoluble drugs, a water insoluble bioactive polyelectrolyte complex, and a non-ionic, water insoluble polymeric matrix, wherein the bioactive polyelectrolyte complex is anti-thrombotic and comprises heparin and an oppositely charged, non-polymeric counter ion, and wherein the counter ion is a quaternary ammonium salt, and wherein the drug delivery system is completely soluable in an organic solvent;
>
> selecting a concentration of the bioactive polyelectrolyte complex for the coating composition, wherein the concentration of the bioactive polyelectrolyte complex modulates the drug release from the drug delivery system according to an elution profile that includes an initial release rate and a subsequent release rate;
>
> implanting the drug delivery system in a patient; and
>
> eluting the one or more drugs from the drug delivery system according to the elution profile.

*The Issue*

The Examiner rejected claims 1, 3, 4, 9–11, and 23–25 under 35 U.S.C. § 103(a) as obvious over Davila,[3] Lunn,[4] Whitbourne,[5] and Pacetti[6] (Final Act. 3–7).

The Examiner finds Davila teaches "a stent that is coated with a combination of heparin complexes with a hydrophobic quaternary counterion, a hydrophobic polymer, and rapamycin, a water insoluble drug" (Final Act. 4). The Examiner finds Davila teaches the heparin complex may be benzalkonium heparin, the hydrophobic polymer may be "a combination of poly(ethylene vinyl acetate) and polybutyl methacrylate" or a "water insoluble poly(vinylidene fluoride-co-hexafluoropropene) where rapamycin is included" and the rapamycin is eluted after implantation (Final Act. 4).

The Examiner acknowledges that Davila does not teach heparin concentrations (Final Act. 4).

The Examiner finds Lunn teaches heparin coated stents where "heparin concentration is taught to result in an increase in the anti-coagulant activity it provides" and is therefore a result effective variable (Final Act. 4). The Examiner finds Whitbourne teaches "a concentration for benzalkonium heparin included in a hydrophobic polymer coating applied to a stent surface" where "[i]ncubation in blood serum yields a gradual release of heparin compound over time as assessed by heparin activity in the blood serum" (Final Act. 4–5).

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[3] Davila et al., US 2002/0111590 A1, published Aug. 15, 2002.
[4] Lunn, US 5,876,433, issued Mar. 2, 1999.
[5] Whitbourne et al., US 2002/0018795 A1, published Feb. 14, 2002.
[6] Pacetti et al., US 2004/0224001 A1, published Nov. 11, 2004.

The Examiner finds the "existence of an initial and subsequent drug release rate is an inherent feature of any drug delivery system that contains a drug" (Final Act. 6). The Examiner cites Pacetti as demonstrating "that the initial and subsequent release rate of a hydrophobic drug from a hydrophobic polymer matrix is increased by the inclusion of a hydrophilic additive that is entangled with the polymer matrix" (Final Act. 6).

The Examiner finds it obvious

> to prepare the stent of Davila et al. where a coating is composed of rapamycin, benzalkonium heparin, polybutylmethacrylate, and poly(ethylene vinyl acetate) because they explicitly teach the combination of these polymers with rapamycin and provide this heparin complex as an envisioned heparin to additionally include in the rapamycin and polymer coating. The selection of poly(vinylidene fluoride-co-hexafluoropropene) as the polymer matrix also would have been obvious since Davila et al. provide it as another desired option. Further following the guidance of Davila et al. in terms of the proportion of rapamycin to include in the coating, it would have been obvious to select a 9 wt% or 30 wt% loading level for this drug as is envisioned by Davila et al. The selection of a concentration of benzalkonium heparin as taught by Whitbourne in the coating would have also been obvious since it was previously employed in a hydrophobic polymer stent coating. This modification would have been obvious as the combination of prior art elements according to known methods to yield predictable results. Since heparin concentration is a result effective variable, it would have been obvious to one of ordinary skill to adjust the proportion of benzalkonium heparin upwards to achieve greater anti-coagulant effect.

(Final Act. 5). The Examiner also finds "it would be expected that some portion of the benzalkonium heparin complexes of Davila et al. in view of Lunn, Whitbourne et al., and Pacetti et al. would also elute from their polymer matrix when incubated in serum or saline" (Final Act. 7).

The issue with respect to this rejection is: Does a preponderance of the evidence of record support the Examiner's conclusion that Davila, Lunn, Whitbourne, and Pacetti render the claims obvious?

*Findings of Fact*

1. Davila teaches "a stent may be utilized in combination with rapamycin and heparin to treat vascular disease" (Davila ¶ 134).

2. Davila teaches that "a rapamycin coating may be applied to stents . . . Various polymers may be utilized. For example, as described above, poly(ethylene-co-vinyl acetate) and polybutyl methacrylate blends may be utilized. Other polymers may also be utilized, but not limited to, for example, polyvinylidene fluoride-cohexafluoropropylene" (Davila ¶ 137).

3. Davila teaches "heparin may be complexed with hydrophobic quaternary ammonium salts, rendering the molecule soluble in organic solvents (e.g. benzalkonium heparinate, troidodecylmethylammonium heparinate). Such a formulation of heparin may be compatible with the hydrophobic rapamycin coating" (Davila ¶ 138).

4. Davila teaches "the rapamycin is directly incorporated into a polymeric matrix and sprayed onto the outer surface of the stent. The rapamycin elutes from the polymeric matrix over time and enters the surrounding tissue" (Davila ¶ 85).

5. Davila teaches

> a top coating may be applied to delay release of the pharmaceutical agent, or they could be used as the matrix for the delivery of a different pharmaceutically active material. Layering of coatings may be used to stage release of the drug or to control release of different agents placed in different layers.

(Davila ¶ 102).

6. Lunn teaches that "heparin coatings appear highly effective in inhibiting thrombus formation in this highly thrombotic model of the stent placed in the ex vivo AV shunt" (Lunn 5:8–11).

7. Lunn teaches "there is indeed a relationship between the amount and activity of heparin initially coated on the stent, and the reduction of thrombus at the lesion sites. . . . the more heparin coated, the less thrombogenic the stent when emplaced at a lesion and expanded beyond its elastic limit" (Lunn 5:12–18).

8. Whitbourne teaches stent coatings that comprise 2% benzalkonium heparinate and teaches "[e]ach of the coatings was applied to a tube substrate to approximate the loading on a stent and the resulting devices were tested for drug release by placing them in serum and incubating them at 37° C" (Whitbourne ¶¶ 82–83).

9. Table V of Whitbourne is reproduced below:

TABLE V

(Data indicate estimated USP heparin units released into the serum per cm of the substrate.)

| | Device Coating | | |
|---|---|---|---|
| Day | A | B | C |
| 1 | 0.275 | 1.58 | 0.68 |
| 2 | 0.275 | 1.75 | 0.65 |
| 4 | 0.02 | 1.8 | 0.4 |
| 7 | 0.02 | 0.9 | 0.55 |
| 11 | 0.02 | 0.7 | 0.38 |
| 14 | 0.02 | 0.8 | 0.35 |
| 18 | 0.02 | 0.5 | 0.13 |
| 21 | 0.02 | 0.5 | 0.1 |
| 25 | 0.01 | 0.5 | 0.08 |

Table V shows "that samples C provided a longer and more uniform release of the drug than did either of the other two samples" (Whitbourne ¶ 84).

10. Figure 4 of Pacetti is reproduced below:

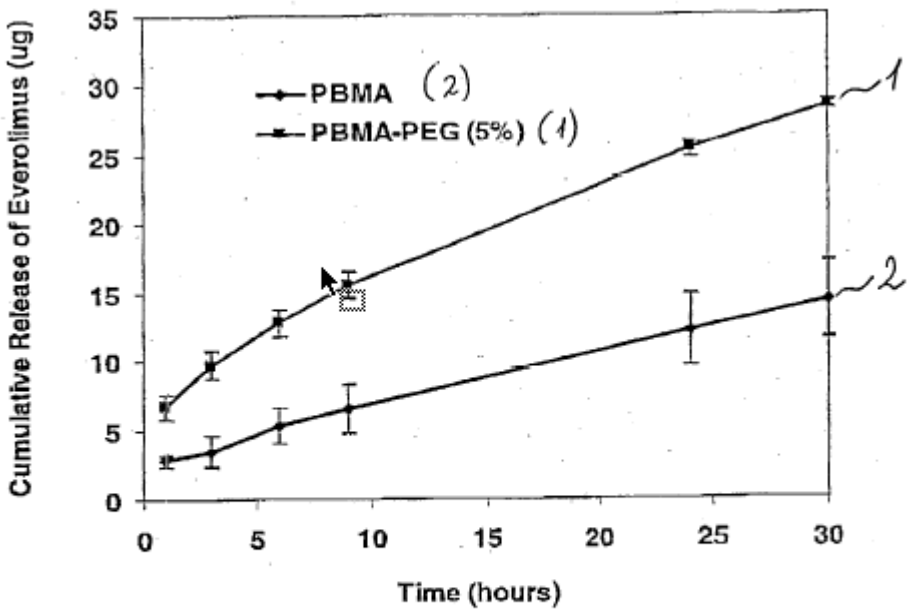


FIG. 4

"As seen from **FIG. 4**, the rate of release of EVEROLIMUS through the PBMAPEG topcoat is about twice the rate of release through the PBMA topcoat" (Pacetti ¶ 73).

11. Pacetti claims a medical article "wherein by increasing the ratio of the additive polymer to the bulk polymer, the rate of release of the drug is increased" (Pacetti 7, claim 24).

*Principles of Law*

A prima facie case for obviousness "requires a suggestion of all limitations in a claim," *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) and "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the

claimed new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

*Analysis*

We adopt the Examiner's findings of fact and reasoning regarding the scope and content of the prior art (Final Act. 3–7; FF 1–10) and agree that the claims are rendered obvious by Davila, Lunn, Whitbourne, and Pacetti.

We begin with claim interpretation, since before a claim is properly interpreted, its scope cannot be compared to the prior art. The phrase at issue in Claim 1 is the requirement for "an elution profile that includes an initial release rate and a subsequent release rate." The phrase appears to broadly encompass three possible situations: (i) where the initial release rate is lower than the subsequent release rate; (ii) where the initial release rate is the same as the subsequent release rate; and (iii) where the initial release rate is higher than the subsequent release rate.

We first turn to the Specification which is, "[i]n most cases, the best source for discerning the proper context of claim terms." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1360 (Fed. Cir. 2004). The Specification teaches that "the release rate of a water insoluble drug may be increased in the presence of a bioactive polyelectrolyte complex. In contrast, the release rate of a water-soluble drug may be reduced in the presence of a bioactive polyelectrolyte complex" (Spec. ¶ 22). The Specification further explains that the "bioactive polyelectrolyte complex may alter the diffusion rate of the polymer matrix. That is, the bioactive polyelectrolyte complex may increase or decrease the diffusion rate of a drug from the polymer matrix" (Spec. ¶ 23). Thus, the Specification appears to encompass both increased and decreased release rates.

The Specification teaches one factor is the "desired release rate (e.g., initial burst and subsequent release rate)" (Spec. ¶ 28), but provides no discussion on whether the initial burst is lower, the same, or higher than the subsequent release rate.

As the Specification does not define the relationship between the initial release rate and the subsequent release rate, we interpret claim 1 as broadly encompassing all three situations discussed above, where the initial release rate may be lower, the same, or higher than the subsequent release rate. *See Sjolund v. Musland*, 847 F.2d 1573, 1581 (Fed. Cir. 1988) ("while it is true that claims are to be interpreted *in light of* the specification and with a view to ascertaining the invention, it does not follow that limitations from the specification may be read into the claims").

Having interpreted claim 1, we now turn to a comparison of the prior art and the limitations of claim 1. Davila teaches regulating the release of drugs from a drug delivery system ("control release of different agents placed in different layers" FF 5). Davila teaches a method comprising providing a coating composition that comprises: the water insoluble drug rapamycin (FF 1); a water insoluble polymeric matrix such as poly(ethylene-co-vinyl acetate) (FF 2; *cf.* Spec. ¶ 25 "poly(ethylene- vinyl acetate)") and a bioactive polyelectrolyte complex that comprises heparin and a quaternary ammonium salt that is soluble in organic solvents (FF 3). Davila teaches selecting the composition to control release rates (FF 5) of the drug as placed on a stent implanted into a body that allows elution of the drug over time (FF 4).

While Davila does not specifically suggest optimization of the heparin amounts on stents, Lunn teaches that amounts of heparin may be optimized

finding "the more heparin coated, the less thrombogenic the stent when emplaced at a lesion and expanded beyond its elastic limit" (FF 7). Whitbourne evidences that different coatings provide different release rates at the initial time point and later time points (FF 8–9).

We therefore agree with the Examiner that Davila, Lunn, and Whitbourne render claim 1 obvious[7] because we agree that it would have been obvious to administer optimized amounts of bioactive polyelectrolyte complex that comprises heparin and a quaternary ammonium salt in stents to patients along with rapamycin as suggested by Davila and Lunn. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955).

As to the elution profile, we agree with the Examiner that "[t]he existence of an initial and subsequent drug release rate is an inherent feature of any drug delivery system that contains a drug" (Final Act. 6). That is, the stent rendered obvious by Davila and Lunn must necessarily have an initial release rate that is lower, the same, or higher than the subsequent release rate, consistent with our claim interpretation discussed above. "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product."

[7] We note the Board may rely on less than all of the references applied by the Examiner in an obviousness rationale without designating it as a new ground of rejection. *In re Bush*, 296 F.2d 491, 496 (CCPA 1961). Here, we find no reason to rely on Pacetti.

*In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). Appellant provides no evidence that the release rate of the method <u>*as claimed*</u> differs from that rendered obvious by Davila and Lunn.

> Appellant contends
>
> > that the Examiner has not established a prima facie case of obviousness because the cited references fail to disclose "selecting a concentration of the bioactive polyelectrolyte complex for the coating composition, *wherein the concentration of the bioactive polyelectrolyte complex* modulates the drug release from the drug delivery system according to an elution profile that includes an initial release rate and a subsequent release rate."

(App. Br. 4). Appellant specifically contends "the presence of the polymeric matrix maintains the stability of the bioactive polyelectrolyte complex. Accordingly, there is no hydrophilic heparin component in the coating composition" (App. Br. 4).

We are not persuaded because Davila teaches an embodiment that uses a bioactive polyelectrolyte complex containing heparin and a hydrophobic quaternary ammonium salt soluble in organic solvent (FF 3) as required by claim 1. The presence or absence of "hydrophilic heparin" is irrelevant because claim 1 neither requires nor excludes the presence of hydrophilic heparin and to the extent that the Examiner or Appellant address "hydrophilic heparin", these arguments are not addressed to claim 1 as written.

Claim 1 simply requires the heparin/quaternary ammonium salt complex results in initial and subsequent release rates. As discussed above, claim 1 may encompass embodiments where the initial rate is lower, the same, or higher than subsequent release rates. We agree with the Examiner

that Davila necessarily and inherently anticipates at least one of these embodiments in claim 1 (*see* Final Act. 6). To the extent that Appellants disagree, we are not persuaded and conclude that "appellant's arguments fail from the outset because . . . they are not based on limitations appearing in the claims." *In re Self*, 671 F.2d 1344, 1348 (CCPA 1982).

Appellant then discusses the hydrophilicity or hydrophobicity of benzyalkonium heparin and submits "that heparin alone is hydrophilic, but ben[z]alkonium heparin is hydrophobic" (App. Br. 5; *cf.* Reply Br. 3). Appellant asserts "the Examiner has not provided any reasoning that a hydrophobic component (benzalkonium heparin) would behave the same way as a hydrophilic component (heparin). . . . there is no reasonable expectation of success for using a hydrophobic component in lieu of a hydrophilic component" (App. Br. 6; *cf.* Reply Br. 3).

We find this argument regarding hydrophilicity/hydrophobicity unpersuasive because it sidesteps the central obviousness issue, which is whether the prior art, as represented by Davila, Lunn, and Whitbourne, suggest a method of drug release on an implanted stent coated with a water insoluble rapamycin, a complex of heparin and quaternary ammonium salt, where the complex results in elution with an initial release rate that is either lower, the same, or higher than the subsequent release rate, where the drugs are eluted into the patient (FF 1–9). Appellant provides no persuasive evidence that Davila's composition would not inherently achieve an initial release rate followed by a subsequent release rate, whether or not it included an additional form of heparin other than the heparin and quaternary ammonium salt complex.

*Conclusion of Law*

A preponderance of the evidence of record support the Examiner's conclusion that Davila, Lunn, and Whitbourne render the claims obvious.

## DECISION SUMARY

In summary:

| Claim(s) Rejected | 35 U.S.C. § | Reference(s)/Basis | Affirmed | Reversed |
|---|---|---|---|---|
| 1, 3, 4, 9–11, 23–25 | 103(a) | Davila, Lunn, Whitbourne | 1, 3, 4, 9–11, 23–25 | |

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