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Cooley LLP / Eurand
ATTN: Patent Group
1299 Pennsylvania Avenue, Suite 700
Washington, DC 20004

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WHEELER, THURMAN MICHAEL	

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte GOPI VENKATESH, LUIGI BOLTRI,
ITALO COLOMBO, JIN-WANG LAI, FLAVIO FABIANI,
and LUIGI MAPELLI,[1]

Appeal 2019-002951
Application 13/911,961
Technology Center 1600

Before DONALD E. ADAMS, JOHN G. NEW, and
RACHEL H. TOWNSEND, *Administrative Patent Judges.*

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1]We use the word "Appellant" to refer to the "applicant" as defined in 37 C.F.R. § 1.142". Appellant identifies Adare Pharmaceuticals, Inc. as the real party-in-interest. App. Br. 2.

SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Non-Final Rejection of claims 1, 3–15, and 17–21 as unpatentable under 35 U.S.C. § 103 as being obvious over Percel et al. (US 6,627,223 B2, September 30, 2003) ("Percel"), Holm et al. (WO 2005/053689, June 16, 2005) ("Holm"), Abramowitz et al. (US 2006/0165789 A1, July 27, 2006) ("Abramowitz"), and Venkatesh et al. (US 2005/0232988 A1, October 20, 2005) ("Venkatesh").

We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

NATURE OF THE CLAIMED INVENTION

Appellant's invention is directed to pharmaceutical compositions and dosage forms comprising timed pulsatile release ("TPR") beads, in which the TPR beads comprise a solid dispersion of at least one active pharmaceutical ingredient. Abstr.

REPRESENTATIVE CLAIM

Claim 1 is representative of the claims on appeal and recites:

> 1. A pharmaceutical composition comprising timed pulsatile release (TPR) beads and rapidly dispersing microgranules wherein said TPR beads comprise:
>
> a solid dispersion of at least one active pharmaceutical ingredient in at least one solubility-enhancing polymer wherein the active pharmaceutical ingredient comprises a weakly basic active pharmaceutical ingredient having a solubility of not more than 100 μg/mL at pH 6.8;

> a TPR coating comprising a water insoluble polymer and an enteric polymer;
>
> said rapidly dispersing microgranules comprising particles of at least one disintegrant, and a sugar alcohol and/or saccharide, wherein said particles of the disintegrant and sugar alcohol and/or saccharide have an average particle size of not more than 30 μm;
>
> wherein the average particle size of the TPR beads and rapidly dispersing microgranules is not more than 400 μm; and
>
> wherein the composition provides a therapeutically effective plasma concentration of the active pharmaceutical ingredient over a period of at least about 18 hours.

App. Br. 25.

ISSUES AND ANALYSES

We decline to adopt the Examiner's findings, reasoning, and conclusion that the claims on appeal are *prima facie* obvious over the cited prior art. We address the arguments raised by Appellant below.

Issue

Appellant argues the Examiner erred in failing to properly articulate a proper reason why a person of ordinary skill in the art would have been motivated to combine the cited prior art to arrive at the claimed invention. App. Br. 14.

Analysis

The Examiner finds that Percel teaches a pharmaceutical dosage form comprising delivering therapeutic agents into the body in a time-controlled

or position-controlled pulsatile release fashion. Non-Final Act. 3. The Examiner finds the dosage form of Percel comprises a multitude of multicoated particulates (e.g., beads, pellets, granules, etc.) made of one or more populations of beads. *Id.* The Examiner finds that Percel also teaches that each of these beads, with the exception of immediate release beads, has at least two coated membrane barriers: one of which is composed of an enteric polymer, and the other composed of a mixture of water insoluble polymer and enteric polymer. *Id.* at 3–4. The Examiner finds that Percel teaches that the active core of the novel dosage form may comprise an inert particle, such as a commercially available non-pareil sugar sphere. *Id.* at 4 (citing Percel col. 2, ll. 15–25).

The Examiner finds that Percel teaches that the composition and the thickness of the polymeric membrane barriers determine the lag time and duration of drug release from each of the bead populations. Non-Final Act. 4. The Examiner finds that Percel further teaches that the pulsatile delivery comprises one or more pulses to provide a plasma concentration-time profile for a therapeutic agent, predicted based on both pharmacokinetic and pharmacodynamic properties and *in vitro*/*in vivo* correlations. *Id.* (citing e.g., Percel Abstr.).

The Examiner also finds that Percel teaches a pharmaceutical dosage form which comprises a plurality of core particles, each core particle containing a drug. Non-Final Act. 4. The Examiner finds that Percel teaches that the core particles are coated with a first membrane of an enteric polymer and a second membrane of a combination of a water-insoluble polymer and an enteric polymer, and that the first and second membranes can be coated on the core particle in either order. *Id.* (citing Percel claim 1).

The Examiner further finds that Percel teaches that the active core of the novel dosage form of the present invention may comprise an inert particle, such as a commercially-available non-pareil sugar sphere. *Id.* (citing Percel col. 2, ll. 15–25).

Finally, the Examiner finds that Percel teaches that the outer layer of the polymeric membrane, as well as the individual weights of the inner, intermediate, and outer membrane layers are optimized to achieve pulsatile release profiles for a given therapeutic agent or agents, based on *in vitro*/*in vivo* correlations. Non-Final Act. 4–5 (citing Percel col. 3, ll. 8–13).

The Examiner finds that Holm teaches a pulsatile release pharmaceutical composition comprising a solid dispersion of lercanidipine[2] and solubility enhancing polymers, e.g., polyvinyl pyrrolidones, hydroxypropyl methylcellulose ("HPMC"), and hydroxypropyl cellulose ("HPC"), and water-insoluble polymers, e.g., ethyl cellulose, polymethacrylic polymers, e.g., Eudragit RS and Eudragit NE, and polyvinylpolyvinyl acetate copolymers ("PVP-PVA"), where the plasma concentration leads to a therapeutic effect for at least 18 hours. Non-Final Act. 8 (citing Holm 9, ll. 6–32).

The Examiner finds that Abramowitz teaches that lercanidipine has an aqueous solubility of about 5 μg/ml, therefore lercanidipine has a solubility of not more than 100 μg/ml at pH 6.8, as recited in the claims. Non-Final Act. 5. The Examiner finds that Venkatesh teaches rapidly-dispersing microgranules prepared by granulating a sugar alcohol or a saccharide, or a

[2] Lercanidipine is the species of active pharmaceutical agent elected by Appellant. *See* Non-Final Act. 2 (citing Appellant's Reply, filed February 3, 2014).

mixture thereof, with an average particle size less than about 30 μm and a disintegrant that rapidly disintegrates in the buccal cavity, and which are structurally indistinguishable from the claimed microgranules. *Id.* at 6.

Summarizing, the Examiner finds that a composition having TPR beads, and rapidly-dispersing microgranules, as taught by the references and recited in the claims, would provide a composition identical to the claimed pharmaceutical composition. Non-Final Act. 6. The Examiner reasons that the claimed functional property of providing a therapeutically effective plasma concentration of the active pharmaceutical ingredient over a period of at least about 18 hours would consequently be the natural result of the combination of the prior art elements. *Id.* The Examiner notes that the recognition of latent properties in an invention that is otherwise known to the prior art does not render that invention nonobvious. *Id.* (citing *In re Wiseman*, 596 F.2d 1019, 1023 (C.C.P.A. 1979); MPEP § 2145(II).

The Examiner therefore concludes that it would have been obvious to a person of ordinary skill in the art to constitute a pharmaceutical composition comprising TPR beads and rapidly-dispersing microgranules, as taught by the combination of Percel, Holm, Abramowitz, and Venkatesh. Non-Final Act. 9. The Examiner concludes that a skilled artisan would have been motivated to devise TPR beads comprising a solid dispersion of lercanidipine and rapidly-dissolving microgranules, because the TPR beads would provide a pulsatile delivery system in which lercanidipine is provided by one or more immediate release pulses at predetermined times after a controlled lag time or at specific sites. *Id.*

Appellant takes issue with the Examiner's conclusion that a skilled artisan would have been motivated to provide lercanidipine in "one or more

immediate release pulses at predetermined time points after a controlled lag time or at specific sites, which can be provided in higher concentration during the time of greatest need and in lesser concentrations when the need is less…." App. Br. 14 (quoting Non-Final Act. 9–10). However, argues Appellant, the Examiner has not cited to any teaching or suggestion in the cited prior art of record to support the assertion that a person of ordinary skill in the art would desire to administer lercanidipine (the elected species of drug) in a pulsatile manner, as taught by Percel. *Id.*

Appellant asserts, rather, that the Examiner's conclusion is contradicted by the evidence of record. App. Br. 14. Appellant contends that Abramowitz teaches that lercanidipine should be dosed in a sustained release manner without a lag time or pulses. *Id.* (citing Abramowitz ¶ 12). Furthermore, argues Appellant, Holm teaches that lercanidipine should be dosed in either an immediate release or a controlled release manner. *Id.* Appellant contends that Percel, the only reference directed to pulsatile release compositions, is entirely silent with respect to lercanidipine. *Id.* Appellant therefore alleges that the motivation articulated by the Examiner is improperly based on hindsight analysis, and is contradicted by the evidence of record. *Id.*

Appellant argues further that Percel expressly teaches that TPR coatings are designed to treat indications "where maintaining a constant blood level of a drug is not desirable." App. Br. 14–15 (quoting Percel col. 1, ll. 13–15). Appellant contends that Percel's TPR coating is therefore formulated to release the drug over a short period of time, with "almost complete drug release occurring within 90 min" or within 6 to 7 hours and after a lag time. *Id.* at 15 (citing Percel col. 5, ll. 19–22, col. 7, ll. 39–40,

Tables 2, 4, 5, 7). Appellant asserts that these teachings are inconsistent with the claims' requirement of providing therapeutically effective blood plasma levels for at least about 18 hours. *Id.* Appellant argues that, to achieve the claimed duration of therapeutic effect, it would be necessary to modify Percel's TPR coating to achieve a fundamentally different pharmacokinetic profile than that for which it was designed. *Id.* It is Appellant's contention that such a modification would render Percel's TPR coating no longer suitable for its stated purpose of providing pulsatile release at predetermined time points after a controlled lag time or at specific sites to treat indications "where maintaining a constant blood level of a drug is not desirable." *Id.* (quoting Percel col. 1, ll. 13–15). Appellant points out that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *Id.* (citing *In re Gordon*, 733 F.2d 900, 901 (Fed. Cir. 1984)).

Likewise, Appellant contends, a TPR coating would be contrary to the teachings of Holm, which is directed to enhancing drug release and bioavailability, and not delaying drug release, whereas Percel teaches that a TPR coating delays drug release. App. Br. 15 (citing Holm 3–5, Percel Tables 2, 4, 5, 7). Appellant therefore asserts that a skilled artisan would not have been motivated to apply a TPR coating to the solid dispersion taught by Holm, because doing so would prevent drug release, thus making the drug not bioavailable during the lag time taught by Percel, a result that is contrary to Holm's stated purpose. *Id.*

The Examiner responds that a person of ordinary skill in the art would have been motivated to combine Percel's TPR bead coating with Holm's

solid dispersion of lercanidipine, because the TPR beads would beneficially provide a pulsatile delivery release profile comprising multiple pulses. Ans. 7. The Examiner finds that this combination would produce a plasma concentration time profile for lercanidipine, based on both its pharmacokinetic and pharmacodynamic properties, that would provide a therapeutically effective level of lercanidipine for at least 18 hours. *Id.* The Examiner finds that this would provide higher concentrations during the time of greatest need and lesser concentrations when the need is less, as taught by the cited references as a whole. *Id.*

We are persuaded by Appellant's arguments. Percel teaches that:

> [T]here are instances where *maintaining a constant blood level of a drug is not desirable*. In such cases…, a 'time-controlled' pulsatile drug delivery system may be more advantageous.
> ….
> A pulsatile delivery system is capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites.

Percel col. 1, ll. 13–28 (emphasis added). To that end, Percel teaches a:

> [M]ethod for manufacturing a pharmaceutically elegant multi-particulate dosage form having timed pulsatile release characteristics, i.e., a well time-controlled series of pulses occurring several hours after oral administration, with or without an immediate release pulse upon oral administration. The present invention also provides a novel multicoated particulate dosage form having an active core and a first membrane of an enteric polymer and a second membrane of a mixture of water insoluble and enteric polymers.

Id. at cols. 1–2, ll. 66–4. With respect to the function of the enteric polymer coating mentioned in the preceding passage, Percel teaches that:

> [T]he mechanism of release is believed to be as follows: The second coating, which is a matrix coating, is held in place by the ethylcellulose polymer. During the first two hours of dissolution testing in 0.1N hydrochloric acid, drug is not released because the enteric polymer in both the inner and outer membranes is impermeable to 0.1N HCl [i.e., when in the stomach]. When the dissolution medium is changed to pH 6.8 [modeling when the composition passes out of the stomach], the enteric polymer starts dissolving from the outer membrane, and pores and channels are formed. It takes a while for the dissolution medium to enter the core to dissolve the active and trigger its release, and hence results in additional lag time.

Id. at cols. 5–6, ll. 65–9.

Holm, in contrast, teaches that:

> [T]he present invention relates to a pharmaceutical composition comprising lercanidipine or an analog or a pharmaceutically acceptable salt thereof as an active substance and a pharmaceutically acceptable vehicle, which composition upon oral administration to a mammal in need thereof releases the active substance *in a controlled manner*. Lercanidipine may be fully dissolved in the vehicle to form a solid solution at ambient temperature or may [be] partly dissolved in the vehicle to form a mixture of solid dispersion and solid solution at ambient temperature or may be dispersed or suspended in the vehicle to form a liquid suspension or solid dispersion at ambient temperature.

Holm 4 (emphasis added). With respect to the controlled manner of release, Holm teaches:

> The controlled release formulation of the invention shows improved bioavailability which results in improved treatment because it will be possible to obtain the same therapeutic response with a single dosing of lercanidipine once daily, possibly with a lower daily dosing (compared to commercially available Zanidip® tablets). This in turn may lead to a reduction in dose-related side effects. Furthermore, it is contemplated that

> the controlled release formulation if the invention *reduces the peak values on the plasma curves and secure 24 hours trough level above the therapeutic plasma concentration*.

Id. at 5 (emphasis added). Holm also teaches an enteric coating of the active ingredient:

> In some embodiments of the invention, the compositions are designed to release lercanidipine in a pH-dependent manner so as to avoid release in the stomach and delay the release until the composition after oral administration passes the stomach and reaches the small intestine. Delayed release is mainly brought about by some kind of enteric coating.

Id. at 11.

> Furthermore, Holm teaches at least one embodiment in which:
>
> [A]t least about 70% w/w lercanidipine is released after at least about 3 hours, such as, e.g., at least about 4 hours, at least about 5 hours, at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, at least about 11 hours, at least about 12 hours, at least about 13 hours, at least about 14 hours, at least 15 about 15 hours, at least about 16 hours, at least about 17 hours, or at least about 18 hours.

Holm 13. We find that this is significant, in that Holm also teaches that:

> By virtue of its high lipophilicity and high membrane coefficient, lercanidipine is said to combine a short plasma half-life with a long duration of action. Thus, the distribution of the drug into membranes of smooth muscle cells results in membrane controlled pharmacokinetics characterized by a prolonged pharmacological effect. In comparison to other calcium antagonists, lercanidipine is characterized by gradual onset and

> longer-lasting duration of action despite decreasing plasma levels.

Id. at 2.

In summary, Holm teaches a delayed-release dosage form of lercanidipine, with an enteric coating, that is capable of sustained, controlled release of the active agent over a period exceeding 18 hours and that, due to its high lipophilicity, lercanidipine has a prolonged duration of action. Furthermore, Holm teaches that its controlled-release mechanism desirably avoids the peaks and troughs of plasma levels of the active agent associated with more periodic dosages.

Given these disparate teachings of Percel and Holm, i.e., delayed pulsatile-type release (Percel) *versus* delayed, controlled release resulting in a more steady-state duration of action (Holm), we are not persuaded that the Examiner has articulated sufficient "reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l. Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Specifically, we are not persuaded that the Examiner has sufficiently demonstrated "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." *Id.*

The Examiner reasons that a person of ordinary skill in the art:

> [W]ould have been motivated to provide TPR beads comprising a solid dispersion of lercanidipine and rapidly-dissolving microgranules, because the TPR beads would provide a pulsatile delivery system wherein lercanidipine is provided by one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites, which can be provided in higher concentrations during the time of greatest need and in

> lesser concentrations when the need is less in accordance with the teachings of the references, as a whole.

Non-Final Act. 9–10. However, the claims on appeal do not recite, or inherently require, delivery of the active agent "at specific sites" or "at predetermined time points after a controlled lag time,"[3] but functionally require only that the composition provides "a therapeutically effective plasma concentration of the active pharmaceutical ingredient over a period of at least about 18 hours." App. Br. 4. Nor does the Examiner point to any teaching of Percel that would teach the skilled artisan that the pulsatile release mechanism of Percel's TPR beads would be capable, expressly or inherently, of sustaining the required 18-hour duration of a therapeutically effective plasma concentration of the active agent.

As we have explained, Holm teaches this latter functional limitation, but this is contrary to the principle of action of Percel, which teaches a "pulsatile delivery system [ ] capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time." Percel col. 1, ll. 26–28. Even if we acknowledge that Percel teaches certain of the structural limitations of Appellant's claim 1, *viz.*, "a solid dispersion of at least one active pharmaceutical ingredient in at least one solubility-enhancing polymer," the Examiner nevertheless provides no persuasive reason why a person of ordinary skill would have looked to combine the

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[3] We note here that the enteric coating would inherently provide a lag time in that it delays release of the active agent until the dosage has passed from the acidic environment of the stomach into the more pH neutral region of the small intestines. However, because both references expressly teach an enteric coating specifically designed to achieve this delay, we need not rely on Percel as teaching this delay.

teachings of Holm with those of Percel, which teaches a different, and contrary mechanism and regime of active agent release.

In summary, it is evident to us that the Examiner has relied upon Percel as teaching the structural requirement of "a TPR coating comprising a water insoluble polymer and an enteric polymer" recited in claim 1, despite the teachings of Percel concerning the nature of the functional implications of this structure, which are contrary to those taught by Holm and do not support the functional limitation of the claim. It is the Examiner's initial burden to prove that it would nevertheless have been *prima facie* obvious to a person of ordinary skill in the art to combine the references, and to explain why a skilled artisan would have been motivated to combine the references to arrive at Appellant's claimed invention. For the reasons we have explained, we conclude that the Examiner has failed to meet this burden and, consequently, we reverse the Examiner's rejection of the claims.

Furthermore, because we find this issue to be dispositive of the appeal, we do not reach Appellant's additional arguments.

DECISION

The Examiner's rejection of claims 1, 3–15, 17–21 under 35 U.S.C. § 103 is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

REVERSED

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 3–15, 17–21	103	Percel, Holm, Abramowitz, Venkatesh		1, 3–15, 17–21