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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte RAHUL SAREEN, SHAHIN FESHARAKI, and PARAG SHAH

Appeal 2019-003436
Application 15/640,823
Technology Center 1600

Before ERIC B. GRIMES, RAE LYNN P. GUEST, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellant[1] seeks our review, under 35 U.S.C. § 134(a), of the Examiner's decision to reject claims 24–39. (Appeal Brief filed November 8, 2018 ("Appeal Br.") 1.) We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM.

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[1] We use the word "Appellant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party-in-interest as Allergan Sales, LLC. (Appeal Brief filed November 8, 2018, 3.)

Appellant's specification is drawn to tablets that allow for immediate release of a drug at risk of being abused. (Specification ("Spec.") 1:4–5.) Appellant's Specification explains that the claimed compositions deter abuse by including a gelling agent to make extraction of the drug difficult and by including an effervescent agent to deter inhalation as a nasal irritant. (*See* Spec. 2:18–20.)

Appellant's claimed tablets consist essentially of a compressed core, which consists essentially of a drug, a gelling agent, an effervescent agent, and optionally other ingredients, wherein the tablet is formulated for immediate release of the drug. Appellant's claim 24 recites:

> A solid pharmaceutical tablet consisting essentially of:
> i) a compressed core; and
> ii) optionally an aesthetic or seal coating surrounding the compressed core,
> wherein the compressed core is a mixture consisting essentially of:
> a) a therapeutically effective amount of a drug that is subject to abuse, wherein the drug is selected from the group consisting of alfentanil, alimemazine, alprazolam, amphetamine, buprenorphine, butorphanol, clonazepam, codeine, cyclobenzaprine, diazepam, dihydrocodeine, dihydromorphine, dronabinol, estazolam, ezopiclone, fentanyl, flurazepam, hydrocodone, hydromorphone, lorazepam, methobarbital, methylphenidate, methadone, morphine, oxycodone, oxymorphone, phenobarbital, secobarbital, tempazepam, tramadol, triazolam, zaleplon, zopiclone, zolpidem and pharmaceutically acceptable salts thereof;
> b) about 1 to about 20 weight percent of a gelling agent selected from the group consisting of polyhydroalkylcellulose having a molecular weight greater than 50,000, a poly(hydroxyalkylmethacrylate) having a molecular weight of from 5,000 to 5,000,000; a poly(vinylpyrrolidone) having a molecular weight of from 100,000 to 3,000,000; a polysaccharide, a carboxyvinyl polymer, a polymer of acrylic acid crosslinked with a

> polyallyl ether of sucrose; polyacrylamides; polyethylene oxide polymers having a molecular weight of 100,000 to 7,000,000 and combinations thereof;
>
> c) about 1 to about 20 weight percent of an effervescent agent;
>
> d) optionally at least one conventional pharmaceutical processing excipient; and
>
> e) optionally a second aversive agent selected from the group consisting of a second nasal irritant, an antagonist agent, a bittering agent, a visual modifying agent, an emetic agent and combinations of the forgoing,
>
> wherein the tablet releases 40 - 90% of the drug in 30 minutes and 70 - 100% of the drug in 45 minutes when measured using a USP Apparatus Type 2 dissolution test at 50 rpms and 500 ml of purified water at 37°C.

(Appeal Br. 17–18.)

Claim 36 is similar but recites fewer drugs and is limited to specific effervescent agents and polyethylene oxide polymer having a molecular weight of 100,000 to 7,000,000 as the only gelling agent. Claim 36 recites:

> A solid pharmaceutical tablet consisting essentially of:
>
> i) a compressed core; and
>
> ii) optionally an aesthetic or seal coating surrounding the compressed core,
>
> wherein the compressed core is a mixture consisting essentially of:
>
> a) a therapeutically effective amount of a drug selected from the group consisting of buprenorphine, codeine, dihydrocodeine, dihydromorphine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone and pharmaceutically acceptable salts thereof;
>
> b) about 1 to about 20 weight percent of a polyethylene oxide polymer having a molecular weight of 100,000 to 7,000,000;
>
> c) about 1 to about 20 weight percent of an effervescent agent wherein the effervescent agent consists essentially of an alkaline source selected from the group consisting of a carbonate, bicarbonate and a mixture thereof and an acid source selected from the group

> consisting of an organic acid, a salt of an organic acid and a mixture thereof;
>
> d) at least one conventional pharmaceutical processing excipient selected from the group consisting of fillers, binders, lubricants, glidants, disintegrants, coloring agents, and mixtures thereof;
>
> e) optionally a second aversive agent selected from the group consisting of a second irritating agent, an antagonist agent, a bittering agent, a visual modifying agent, an emetic agent and combinations of the forgoing;
>
> and wherein the tablet releases 40 - 90% of the drug in 30 minutes and 70 - 100% of the drug in 45 minutes when measured using a USP Apparatus Type 2 dissolution test at 50 rpms and 500 ml of purified water at 37°C.

(*Id*. at 20–21.)

The Examiner rejected all of Appellant's claims as being obvious under 35 U.S.C. § 103(a) over Tygesen[2] and McKenna.[3] (*See* Final Office Action mailed June 13, 2018 ("Final Act.") 3–11.)

Findings of Fact

1. Tygesen teaches pharmaceutical compositions for oral administration that are resistant to abuse, particularly when abused by being released faster, and therefore being absorbed faster, in the presence of alcohol. (*See* Tygesen ¶¶ 3 and 4.)

2. Tygesen teaches immediate release compositions that have a decreased release rate in the presence of ethanol. (*See* Tygesen ¶ 30.)

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[2] Tygesen et al., U.S. Patent Application Publication 2010/0204259 A1, published August 12, 2010.
[3] McKenna et al., U.S. Patent Application Publication 2009/0081290 A1, published March 26, 2009.

3. Tygesen teaches matrix compositions that comprise one or more low molecular weight polyglycols combined with one or more effervescent agents. (*See* Tygesen ¶¶ 3, 32, and 54.)

4. Tygesen teaches that polyethylene glycol ("PEG")/polyethylene oxide ("PEO")[4] having molecular weight of from about 900 to about 17,000 Daltons should be selected to formulate an immediate release composition of the drug substance, but with a decreased release rate when in the presence of alcohol. (*See* Tygesen ¶ 36 and 61–66.)

5. Tygesen teaches that "mixtures of PEO and/or mixtures of PEG materials with different average molecular weights can be used in order to obtain a desired average molecular weight for the polyglycol material utilized in immediate release compositions described herein." (*See* Tygesen ¶ 66.)

6. Tygesen teaches that in addition to polyglycol-type polymers, other polymers are suitable for the immediate release formulations including PVP, polyacrylamide, and Eudragit compounds. (*See* Tygesen ¶ 68.)

7. Tygesen teaches that the compositions can include many of the drugs recited in Appellant's claims, for example amphetamine, codeine, fentanyl, methadone, morphine, and oxycodone. (*See* Tygesen ¶¶ 45, 103, 121, 122, 126, 127, and 141.)

[4] Tygesen explains that PEG refers to polymers chains with molecular weights below 20,000, while PEO refers to higher molecular weights polymers. (*See* Tygesen ¶ 63.)

8. Tygesen teaches that the effervescent agent used in the immediate release composition can be an acid and a base that react together to release carbon dioxide gas. (*See* Tygesen ¶ 74.)

9. Tygesen teaches that the immediate release compositions can include plasticizers, such as polyethylene glycols or polyethylene oxides with a molecular weight of 1,000 – 500,000 Daltons. (*See* Tygesen ¶ 85.)

10. Tygesen teaches that the immediate release compositions may include pharmaceutically acceptable excipients, including fillers, binders, lubricants, glidants, disintegrants, and coloring agents. (*See* Tygesen ¶¶ 82–84.)

11. McKenna teaches pharmaceutical compositions that are tamper resistant because their release profiles do not change in alcohol and because they are resistant to crushing. (*See* McKenna ¶¶ 5, 7, and 8.)

12. McKenna teaches extended release (in contrast to immediate release) compositions comprising at least one PEO with a molecular weight of at least 1,000,000 Daltons and at least one polyethylene oxide having a molecular weight of less than 1,000,000. (*See* McKenna ¶¶ 15, 17–19, and 72–75.)

13. McKenna teaches:

> In embodiments wherein the composition further comprises at least one low molecular weight polyethylene oxide is used[,] polyethylene oxides having, based on rheological measurements, an approximate molecular weight of less than 1,000,000, such as polyethylene oxides having, based on rheological measurements, an approximate molecular weight of from 100,000 to 900,000 may be used. The addition of such low molecular weight polyethylene oxides may be used to specifically tailor the release rate such as [to] enhance the release rate of a formulation that otherwise provides a release rate [too] slow for the specific purpose. In such embodiments at least one

> polyethylene oxide having, based on rheological measurements, an approximate molecular weight of 100,000 may be used.

(McKenna ¶ 238.)

Analysis

Claim 24

Appellant's claim 24 recites a tablet consisting essentially of a compressed core, which consists essentially of a drug selected from a list of possible drugs, a gelling agent selected from a list of possible gelling agents, and an effervescent agent, wherein the drug is released from the tablet at a rate within the recited limits. We agree with the Examiner that the tablet of claim 24 is obvious because Tygesen teaches a tablet with a compressed core of at least one of the drugs recited in claim 24 (*e.g.*, codeine, morphine, hydrocodone, oxycodone, or oxymorphone), a gelling agent recited in claim 24 (*e.g.*, polyvinylpyrrolidone (PVP) or polyacrylamide), and an effervescent agent. (*See* Final Act. 5, *see* Ans. 3–4; *see* FFs 3 and 6–8.)

Although Appellant argues that the Examiner erred in rejecting claim 24 because of the teachings in the prior art regarding polyethylene oxides, Appellant does not contest the Examiner's findings and does not argue that the teachings in Tygesen of other gelling agents fails to render a composition with the scope of claim 24 obvious.

Accordingly, Appellant fails to persuade us that the Examiner erred in rejecting claim 24 and we affirm the rejection. Appellant represents that claims 25–27, 30, 32–53, and 38 stand or fall with claim 24. (*See* Appeal Br. 9.) We affirm the rejection of each of these claims as being obvious over Tygesen and McKenna, as well.

Claim 36

Like claim 24, Appellant's claim 36 recites a tablet consisting essentially of a compressed core, which consists essentially of a drug selected from a list of possible drugs, an effervescent agent, an excipient, and a PEO having a molecular weight of 100,000 to 7,000,000. (*See* Appeal Br. 21.) In contrast to claim 24, claim 36 is limited to this PEO.

The Examiner bases the rejection of claim 36 on the teachings in McKenna that abuse-resistant tablets can include PEO of molecular weights with the range recited in claim 36. (*See* Final Act. 7–8; *see* FFs 11–12.) The Examiner also relies on the teaching in McKenna that one could specifically tailor the release rate by increasing it with the addition of lower molecular weight PEOs, when the release rate had been slowed for another, specific purpose. (*See* Final Act. 8, citing McKenna ¶ 238[5]; *see* FF 13.) Similarly, the Examiner relies on the teaching in Tygesen that mixtures of PEO and/or PEG materials with different average molecular weights can be used in order to obtain a desired average molecular weight for the polyglycol material utilized in immediate release compositions. (*See* Final Act. 6, citing Tygesen ¶ 66.)

[5] The Examiner cites to paragraphs 237 and 240 of McKenna for the statement that "[t]he low MW [molecular weight] PEO used to specifically tailor the release rate such as enhance the release rate of a formulation that otherwise provides a release rate to slow for the specific purpose." (Final Act. 8.) Because this language is almost identical to the language of McKenna paragraph 238, and the Examiner cites to paragraph 238 for similar language in the Answer (*see* Ans. 4), we assume that the citation to paragraph 237 was intended to be to paragraph 238. (*See also* Reply Brief filed March 25, 2019, 4.)

The Examiner reasons that it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a tablet as recited in claim 36 because Tygesen teaches including PEO polymers, opioids, and effervescent agents in compositions for tablets and because McKenna teaches a mixture of PEO of high and low molecular weight, including PEOs with the range claimed, can be used to specifically tailor the drug release rate from a tablet composition. (*See* Final Act. 8.) The Examiner finds from the cited references that it would have been reasonable to expect formulating an immediate release oral dosage in light of these teachings. (*See id*.)

In addition, the Examiner finds that Tygesen teaches immediate release compositions may further include plasticizers, including PEO having a molecular weight between 1,000 and 500,000 Daltons. (*See* Final Act. 6, citing Tygesen ¶ 85; *see* FF 9; *see* Ans. 6.)

We are persuaded by the Examiner's reasoning because "the analysis [of obviousness] need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

In general, Appellant argues that the teachings of Tygesen and McKenna would not render the compositions recited in claim 36 obvious because Tygesen and McKenna demonstrate that PEOs with the high molecular weight would delay and extend the immediate release profile of the composition of Tygesen. (*See* Appeal Br. 8.) Appellant argues that Tygesen teaches that to obtain the desired immediate release properties for the tablet, PEGs/PEOs with a molecular weight from 900–17,000 should be

used. (*See* Appeal Br. 8.) Specifically, Appellant cites to a portion of Tygesen teaching that PEO of high MW (20,000 Daltons and above) allows for "controlled" release of drug, which is contrasted with immediate release. (*See* Appeal Br. 11, citing Tygesen ¶¶ 34–35, also citing Tygesen ¶¶ 64 and 66.)

Appellant argues further that Examples 22 and 24 of Tygesen show that increasing the molecular weight of the PEG/PEO slows the release profile of drug from a matrix. (*See* Appeal Br. 12–13; *see* Reply Brief filed March 25, 2018 ("Reply Br.") 5–6.) Appellants assert that in Example 22 a composition with PEG of molecular weight 17,000 Daltons released a drug more slowly than the same composition using PEG of 6000 Daltons. (*See id.*, citing Tygesen Figs. 21 and 23.) Appellant asserts that the Examiner erred because "merely replacing the lower molecular weight PEO of Tygesen with the higher molecular weight of McKenna would not result in a similar profile." (Appeal Br. 13.)

We are not persuaded by Appellant's argument because the Examiner's rejection[6] is not based on a simple substitution of the higher molecular weight PEG/PEOs of McKenna for the lower molecular weight PEG/PEOs of Tygesen. (*See* Ans. 9.) Instead, the Examiner's rejection is based on the knowledge in the art that the molecular weights of PEG/PEOs can be tailored to achieve a desired release rate. (*See* Final Act. 8.) In other words, the molecular weight of PEG/PEO is a result effective variable that

[6] The Examiner relied on this reasoning in regard to claim 24 as well as claim 36. (*See* Final Act. 4–10.) We affirm the rejection of claim 24 as discussed above, but also on the basis of this reasoning.

can be adjusted based on a desired immediate release rate. Indeed, Tygesen teaches that "mixtures of PEO and/or mixtures of PEG materials with different average molecular weights can be used in order to obtain a desired average molecular weight for the polyglycol material utilized in immediate release compositions described herein." (Tygesen ¶ 66; FF5; *see* Ans. 4.) In addition, Tygesen teaches that, even though PEG/PEO contribute to the release rate, they are not the only determinants. The Examiner cites Tygesen for teaching that the release rate of a composition is also determined by the polymer, disintegrant, and effervescent agent present. (*See* Ans. 9–10, citing Tygesen ¶ 72.)

Appellant focuses only on the difference between the PEG/PEOs used, without acknowledging that one of ordinary skill in the art would be able to tailor release rate by choosing a PEG/PEO that would give the desired characteristics, in light of the other ingredients present, such as effervescent agent, disintegrant, etc. (*See* Reply Br. 6.) Because Appellant's arguments do not address the basis for the Examiner's rejection, that it was known in the art that release rate can be tailored by choice of PEG/PEO, we are not persuaded that the Examiner erred.

Accordingly, Appellant's argument that the Examiner's reasoning of merely replacing the lower molecular weight PEO of Tygesen with the higher molecular weight of McKenna to achieve the claimed release profile does not address the Examiner's actual rejection. (*See* Appeal Br. 13.)

In regard to the teaching in Tygesen of including PEO within the claimed molecular weight range as a plasticizer in the immediate release composition, Appellant argues that PEO with a molecular weight of 1,000 to 500,000, within the claimed range, was provided in paragraph 85 only as

"boilerplate laundry lists of over 100 plasticizers" and that Tygesen fails to provide any "blaze marks" or suggestions leading one of ordinary skill to select such ingredients. (Appeal Br. 14.) We are not persuaded by this argument because the rejection is based on obviousness, not anticipation. *See in re Arkley*, 455 F.2d 586 (CCPA 1972) ("Such picking and choosing may be entirely proper in the making of a 103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art . . . ."); *see also In re Malagari*, 499 F.2d 1297, 1303 (CCPA 1974) (claimed invention is rendered prima facie obvious by the teachings of a prior art reference that discloses a range that touches the range recited in the claim). In other words, Tygesen teaches that one of ordinary skill in the art would have recognized immediate release properties even with compositions having PEO with a molecular weight of up to 500,000.

Appellant also argues that a skilled artisan would not be motivated to select such a PEO because it would extend the release profile of a drug. (*See* Appeal Br. 14.) This argument is also unpersuasive because paragraph 85 of Tygesen demonstrates that it was known that PEO within the claimed range would not necessarily inhibit immediate release because it is included in a composition for immediate release.

Appellant argues that the Examiner's reliance on paragraph 238 of McKenna is inappropriate because McKenna refers only to PEOs having a molecular weight of 100,000 to 1,000,000 and 1,000,000 – 8,000,000 to adjust a controlled release profile. (*See* Reply Br. 4–5.) Appellant's claim 36 recites a PEO of 100,000 to 7,000,000 daltons. Tygesen teaches an

immediate release composition including PEG with a molecular weight up to 500,000, which overlaps both the range recited in the claims and the range taught by McKenna. Thus, we are not persuaded that paragraph 238 of McKenna would not have suggested to one of ordinary skill in the art to tailor the release rate of a drug formulation with a PEO within the claimed range.

Appellant does not persuade us that the Examiner erred in rejecting claim 36. Accordingly, we affirm the rejection of claim 36 as being obvious over Tygesen and McKenna.

Other Dependent Claims

Appellant argues that claims 28, 37, and 39 stand or fall with the patentability of claim 36. (*See* Appeal Br. 9.) Because we are not persuaded that the Examiner erred in rejecting claim 36, we affirm the rejections of claims 28, 37, and 39 as well.

Appellant argues separately for the patentability of claim 29 and claim 31. (*See* Appeal Br. 15–16.) Claim 29 depends on claim 28 and recites a tablet as in claim 24, "wherein the gelling agent is a polyethylene oxide with an approximate molecular weight of about 900,000 to about 5,000,000." (*Id.* at 19.) Claim 31 depends directly from claim 24 and recites "wherein the gelling agent comprises at least two different types of polyethylene oxides wherein the first polyethylene oxide has an approximate molecular weight between 500,000 and 1,000,000 and the second polyethylene oxide has an approximate molecular weight between 2,000,000 and 5,000,000." (*Id.* at 19.)

Appellant argues only that "for the same reasons" as claim 24, a skilled artisan would not have been either motivated to combine PEO

polymers of the recited molecular weights or have reasonably expected them to result in an immediate release tablet. (*Id.* at 15–16.)

As explained above, we are persuaded by the Examiner's findings and reasoning that it would have been obvious to one of ordinary skill in the art to provide a tablet with PEO having a molecular weight within the claimed ranges because Tygesen and McKenna teach that PEO of high MWs and low MWs can be used to specifically tailor the drug release rate from a tablet composition. (*See* Final Act. 8.) Appellant has neither argued nor demonstrated any unexpected or surprising results commensurate in scope with the narrower ranges recited in these claims over the lower molecular weights encompassed in the broader ranges of the other claims, which would be expected to be equally useful for an immediate release drug composition according to the general teachings of Tygesen and McKenna discussed above. Accordingly, we are not persuaded that the Examiner erred in rejecting these claims.

Conclusion

Upon consideration of the record and for the reasons given, we affirm the Examiner's rejection.

In summary:

Claims Rejected	**Basis**	**Affirmed**	**Reversed**
24–39	§ 103 Tygesen, McKenna	24–39	

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

AFFIRMED