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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte STIG HEMSTAD[1]

Appeal 2015-002798
Application 12/305,977
Technology Center 1600

Before ERIC B. GRIMES, ULRIKE W. JENKS,
and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to an imaging agent product comprising a radiopharmaceutical composition, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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[1] Appellant identifies the Real Party in Interest as GE Healthcare Limited. (Br. 1.)

STATEMENT OF THE CASE

Appellant's "invention relates to improved radiopharmaceutical compositions in sealed containers, where the container closure has an ETFE (ethylene-tetrafluoroethylene copolymer) coating." (Spec. 1:5–7.)

Claims 1–3, 5, and 7–22 are on appeal. Claim 1 is illustrative:

> 1. An imaging agent product which comprises a radiopharmaceutical composition supplied within a sealed container, wherein:
>
> (i) said radiopharmaceutical composition comprises a radioisotope suitable for medical imaging provided in a biocompatible carrier which comprises an injectable carrier liquid, in a form suitable for mammalian administration; and
>
> (ii) said sealed container is made of pharmaceutical grade glass, and is provided with a closure suitable for puncturing with a hypodermic needle whilst maintaining seal integrity, and said *closure is coated on those of its surface(s) which are in contact with the container contents with a coating comprising ethylene-tetrafluoroethylene copolymer (ETFE).*

(Br. 13 (Claims App'x) (emphasis added).)

The claims stand rejected as follows:

A. Claims 1–3, 5, 7–12, 15, and 16 under 35 U.S.C. § 103(a) over Martinussen,[2] Tomoyasu,[3] and Handreck.[4]

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[2] Martinussen et al., WO 2006/064175 A1, published June 22, 2006.
[3] Tomoyasu, EP 0 294 127 B1, published Nov. 9, 1994.
[4] Handreck et al., US 2002/0058647 A1, published May 16, 2002.

B. Claims 1–3, 5, 7–12, 15, and 16 under 35 U.S.C. § 103(a) over Forster,[5] Tomoyasu, Handreck, and/or Martinussen.

C. Claims 17–20 under 35 U.S.C. § 103(a) over Forster, Tomoyasu, Handreck, Hiscock,[6] and/or Martinussen.

D. Claims 1–3, 5, and 7–22 under 35 U.S.C. § 103(a) over Hiscock, Liu,[7] Tomoyasu, Handreck, Forster, and/or Martinussen.

DISCUSSION

Issue

Appellant relies on the arguments concerning Rejection A as applicable to all the rejections, and does not provide separate argument concerning Rejections B, C, or D. (Br. 2–11.) Accordingly, and because the same issues are dispositive for Rejections A–D, we address the rejections together on appeal.

The Examiner finds that Martinussen and Forster each disclose injectable ^{99m}Tc [technetium] radiopharmaceuticals (e.g., Myoview™ kits) suitable for human administration. (Ans. 3–4 (regarding Martinussen) and 9–10 (regarding Forster).) The Examiner further finds that Martinussen and Forster teach containers for housing radiopharmaceuticals fitted with a seal suitable for multiple punctures with a hypodermic needle. (*Id.* at 4 and 9.) The Examiner finds, however, that Martinussen and Forster do not teach "a closure [e.g., stopper] which is coated on those of its surfaces which are in

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[5] Forster et al., US 2004/0057899 A1, published Mar. 25, 2004.
[6] Hiscock et al., WO 2005/053752 A2, published June 16, 2005.
[7] Liu, US 6,713,042 B2, issued Mar. 30, 2004.

contact with the container contents with a coating comprising ethylene-tetrafluoroethylene copolymer [ETFE]." (*Id.* at 5 and 10.)

The Examiner turns to Tomoyasu and Handreck as teaching medical vials having a stopper coated with ETFE. (Ans. 5–8.) For example, the Examiner finds "Tomoyasu [] teach[es] an improved laminated rubber stopper for a medical bottle or vial having good sliding properties and mechanical properties as well as reducing the occur[re]nce of fine-particles from [the] rubber stopper and piercing fragments." (Ans. 5.) The Examiner further finds Tomoyasu teaches the stopper "is laminated with fluorine resin film . . . selected from ETFE." (*Id.* at 5–6; *see also id.* at 7 ("Handreck [] teach[es] . . . the stopper provides a source of potential contamination . . . [and so] the stopper is coated with fluorinated resin selected from the group consisting of tetrafluoroethylene polymer . . . [and] tetrafluoroethylene-ethylene copolymer.").)

The Examiner concludes "[i]t would have been obvious . . . to modi[f]y the radiopharmaceutical products taught by Martinussen [or Forster] . . . by simply using a siliconised pharmaceutically acceptable glass vial having low aluminum content and chlorobutyl rubber stopper laminated with ETFE as taught by Tomoyasu [] and Handreck []." (Ans. 8; *see also id.* at 10.) The Examiner reasons this modification "would advantageously reduce presence of contaminant metal cations in solution comprising chelating agents, prevent fragmentation due to needle penetration, and enable medical vial preparation with a high quality." (Ans. 8.)

Appellant contends Tomoyasu's teachings are broad, and that the Examiner erred for failing to consider Tomoyasu's disclosure "as a whole." (Br. 4–5.) As a whole, Appellant contends, Tomoyasu "teaches away" from the Examiner's proposed modification. (Br. 5–7.) Appellant argues the combination of Martinussen and Handreck results in a product with "essential features" absent from claim 1. (Br. 7). Further, Appellant contends, there is "no real motivation to combine Handreck with Martinussen and Tomoyasu" because the pharmaceuticals of Handreck and Martinussen include different compounds that would react differently with impurities (e.g., metal ions) that leach from the glass vial. (*Id.* at 7–8.)

The issue is whether the preponderance of the evidence supports the Examiner's conclusion that claims 1–3, 5, and 7–22 would have been obvious over Martinussen, Forster, Tomoyasu, and Handreck.

Findings of Fact

1. The Examiner's findings of fact and statement of Rejections A–D can be found at pages 3–14 of the Examiner's Answer. We adopt those findings and provide the following for emphasis.

2. Martinussen teaches "[t]he Myoview™ kit is a 10 ml vial containing the lyophilised formulation . . . which upon reconstitution with Sterile Sodium (^{99m}Tc) Pertechnetate Injection . . . yields a solution containing the heart imaging radiopharmaceutical ^{99m}Tc-tetrofosmin." (Martinussen 2:22–32.) Martinussen teaches a ready-to-inject form of Myoview™ (e.g., "aqueous solution in a syringe-vial, ie. a vial with separate plunger and needle") (*id.* at 3:3–6) as well as a "multi-dose [Myoview™] kit" comprising the formulation "in a sealed, sterile container fitted with a

closure which permits addition and withdrawal of solutions whilst maintaining sterile integrity. . . . The container is fitted with a gas-tight seal which is suitable for multiple puncturing with a hypodermic needle" (*id.* at 11: 10–21).

3. Forster teaches "stabilised ^{99m}Tc radiopharmaceutical compositions in a sterile form suitable for human administration in either a container or a pre-filled syringe. . . . [The] container [] has a seal which is suitable for multiple puncturing with a hypodermic needle (e.g. a crimped-on septum seal closure)." (Forster ¶¶ 58–59; *see also id.* at ¶¶ 85–92 (describing Myoview™ kits).)

4. Tomoyasu teaches "[i]n known rubber stoppers the part of the surface which comes into contact with pharmaceutical chemicals and the like is laminated with a fluorine resin film." (Tomoyasu 2:20–21.) Tomoyasu teaches "[w]hen a rubber stopper is pierced by the needle of a syringe . . . fragments of rubber called piercing-fragments break off from the stopper . . . caus[ing] contamination problems." (*Id.* at 2:34–36.) Tomoyasu teaches "an improved laminated rubber stopper for a medical bottle or vial . . . having better sliding properties and mechanical transporting properties as well as reducing the occur[r]ence of fine particles . . . and needle piercing fragments." (*Id.* at 2:40–43.) Tomoyasu teaches

> a resin laminated rubber stopper . . . in which the entire surface of the body [the portion protruding from the lower surface of the head and in contact with the pharmaceutical] is laminated with a fluorine resin film, characterized in that the upper surface and the side surface of the head are laminated with a fluorine resin film and the lower surface of the head is not laminated with fluorine resin film, said fluorine resin film being of a member selected from the group consisting of *tetrafluoroethylene-ethylene*

> *copolymers* [ETFE], tetrafluoroethylene-hexafluoropropylene copolymers [FEP] . . . .

(*Id.* at 2:44–48 (emphasis added); *see also id.* at 3:31–37 and Fig. 1 (G_2 representing the fluorine resin coating on the body portion, and G_1 the coating on the head portion).)

5. Tomoyasu teaches working examples, including Examples 1–4 wherein "[t]he body portion was laminated with the following ETFE film . . . , while the head portion was laminated with the following four fluorine resin films 1) to 4) . . . Example 1) ETFE film . . . Example 2) PTFE film . . . Example 3 PFA film . . . [and] Example 4) FEP film." (*Id.* at 5:1–32.) Tomoyasu teaches

> Examples 1 to 4 showed fewer fragments . . . [,] the rubber stopper of the present invention shows very little eluate or elution materials . . . [,] surface lubricity is increased and occurrence of fragments during needle penetration can be prevented . . . [, and the stopper] is capable of exhibiting better properties at any stage of preparation of a drug using a medical vial, storage and application and thus largely serve to a medical vial preparation with high quality.

(*Id.* at 9:3 through 10:14.)

6. Handreck teaches "[w]here the [pharmaceutical] solution is stored in a stoppered vial, the stopper provides a potential source of contamination." (Handreck ¶ 8.) Handreck teaches "to reduce the possibility of contamination . . . [p]referably the stopper has low calcium, magnesium and ash content and is coated on the contact surface (being the surface of the stopper which when placed in a vial is exposed to the contents of the vial) with fluorinated resin such as tetrafluoroethylene polymer . . .

ethylene-tetrafluoroethylene copolymer, [etc.]." (*Id.*) Handreck teaches "[f]or example, the stopper can be a FLUROTEC™ stopper." (*Id.*)

Principles of Law

"[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007), citing *United States v. Adams*, 383 U.S. 39, 50-51 (1966).

Analysis

As noted above, Appellant did not provide separate argument for Rejections A–D, relying instead on the arguments for Rejection A as applicable to all the pending rejections. Neither did Appellant provide separate argument for the individual claims rejected on appeal. We thus address the rejections together and select claim 1 as representative.

We agree with, and adopt, the Examiner's findings of fact, reasoning, and conclusion that claim 1 would have been obvious over the cited art. It would have been prima facie obvious to modify a sealed vial containing radiopharmaceuticals, such as disclosed in Martinussen or Forster (FF 2–3), with an ETFE-coated closure, such as the stopper disclosed in Tomoyasu or Handreck (FF 4–6) — thus arriving at a product encompassed by claim 1. As the Examiner determined, the skilled person would have predictably made this modification to obtain, *inter alia*, a high-quality medical container that is less susceptible to fragmentation of the closure when pierced by a

needle and contamination of the container's contents. (*See e.g.*, Ans. 8 and 18; FF 5.)

Appellant contends "Tomoyasu teaches the reduction of fine particles . . . but that teaching applies to all the closure coatings taught at page 2 lines 44-55." (Br. 3.) Appellant further contends "the teaching of Tomoyasu is broad and intended to encompass any such copolymer falling within the scope of each of the 4 chemical names used." (*Id.*) Thus, Appellant argues, "Tomoyasu does not in fact provide a clear teaching towards ETFE-coated closures." (*Id.*)

This argument is unpersuasive. Tomoyasu teaches a handful of suitable fluorine resins for coating its stopper and expressly identifies ETFE among them. (FF 4–5.) We are unpersuaded that the number of combinations is so large that the skilled artisan would not have predictably used an ETFE-coated stopper. *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) ("[D]isclos[ing] a multitude of effective combinations does not render any particular formulation less obvious.") Notably, and as Appellant acknowledges, *every working example* of Tomoyasu coated the body portion of the stopper — the portion that would be in contact with the container's contents — with ETFE. (FF 5; Br. 6 ("the 'body portion' of all the closures tested in the Examples is coated with ETFE").) Thus, this is not a case of unsupported picking-and-choosing to support the obviousness rejection. To the contrary, had the skilled person merely picked *any* one of the stoppers in Tomoyasu's working examples, and combined it with a container and radiopharmaceutical of Martinussen, they would have arrived at Appellant's claim 1. And, as noted above,

Tomoyasu provides express reasons to select its stoppers, such as to reduce or prevent fine particles/fragments from entering the container. (Ans. 8 and 18; FF 5.)

Appellant argues that the Examiner erred by "focus[ing] on only the Examples of Tomoyasu and not the disclosure of the document as a whole." (Br. 4.) It is, however, clear the Examiner did not focus only on Tomoyasu's "Examples" — the Examiner cited teachings throughout Tomoyasu that ETFE is a preferred stopper coating. (Ans. 5–6.) The fact that the working examples all use ETFE to coat the body portion of the stopper further buttresses the Examiner's conclusion. Our review of Tomoyasu is consistent with the Examiner's and Appellant cites to no disclosure in Tomoyasu (or the other applied art) teaching against the use of ETFE-coated vial closures.

Appellant argues the fluorine resins in Tomoyasu could include many components and Tomoyasu "does not specify the percentage composition" of the components. (Br. 4.) Nor does claim 1. (9/8/14 Adv. Act. 2 ("Instant claims do not limit percent composition of the co[]polymer.) Rather, it includes open-ended "comprising" language — any amount of ETFE would suffice. *See also In re Self*, 671 F.2d 1344, 1348 (CCPA 1982) ("[A]ppellant's arguments fail from the outset because . . . they are not based on limitations appearing in the claims.").

Appellant argues Tomoyasu "teaches away from the presently claimed invention" because Tomoyasu's closures can have different fluorine-resin coatings on different surfaces. (Br. 5–7.) Appellant misapprehends what it means to teach away. "The prior art's mere disclosure of more than one

alternative does not constitute a teaching away from . . . alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed." *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Appellant cites nothing in Tomoyasu criticizing or discouraging ETFE-coated stoppers. There is no teaching away here: Example 1 of Tomoyasu coats the head and body portion with ETFE, and *all* the working examples coat the portion of the stopper that would come into contact with the pharmaceutical agent with ETFE. (FF 5.)

Turning to Handreck, Appellant contends "the combination of Martinussen/Handreck inevitably also possesses the essential features of: (i) glass vial coated with silicone or silica; (ii) glass vial with low aluminum content of the glass." (Br. 7.) Appellant argues, "claim 1 does not have those essential features. Consequently, Handreck cannot remedy the deficiencies of Tomoyasu." (*Id.*)

This argument is unpersuasive. First, Tomoyasu is not deficient for the reasons discussed. Second, claim 1 may not expressly recite the "essential features" called out by Appellant, but it does not exclude them either. (Ans. 19.) The claim uses open-ended "comprising" language and Appellant's Specification suggests embodiments where at least some of these features are included. (*See*, *e.g.*, Spec. 4:10–13 ("The glass of the container may optionally be coated to suppress leachables from the glass as is known in the art. A preferred such coating is silica (SiO_2).").)

Finally, Appellant argues the skilled person would have no "real motivation" to combine Handreck and Martinussen. (Br. 8.) In support, Appellant contends the "person skilled in the art could therefore have no

reason to expect that the phosphorous donor atoms of the tetrofosmin compositions described in Martinussen would also suffer from the problem of formation of aluminum, magnesium or calcium metal complexes as per the pamidronic acid of Handreck." (*Id.*)

This argument is not persuasive. As the Examiner noted, "Handreck teaches that Fluorotec (ETFE coated stopper) can advantageously reduce possible contamination" such as from calcium, magnesium, or zinc ions which leach from an uncoated stopper. (Ans. 19–20.) Appellant provides insufficient evidence that the chelating agent in Martinussen (or Forster) would not form metal complexes with such ions. *See In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997) (argument by counsel cannot take the place of evidence). Even assuming Appellant's characterization is correct — and that the chelating agent of Handreck would react differently and form, for example, calcium metal complexes — we remain unpersuaded that the skilled artisan would not have made the modification of the art proposed by the Examiner. To the contrary, the ETFE coated stopper would still be desirable for the reasons disclosed in Tomoyasu and to reduce contamination and impurities leaching into the pharmaceutical composition.

Conclusion of Law

For the reasons above, we conclude the Examiner established by a preponderance of the evidence that claim 1 would have been obvious over Martinussen, Forster, Tomoyasu, and Handreck.

Claims 2, 3, 5, and 7–22 have not been argued separately and fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

We affirm the rejection of: (i) claims 1–3, 5, 7–12, 15, and 16 over Martinussen, Tomoyasu, and Handreck; (ii) claims 1–3, 5, 7–12, 15, and 16 over Forster, Tomoyasu, Handreck, and/or Martinussen; (iii) claims 17–20 over Forster, Tomoyasu, Handreck, Hiscock, and/or Martinussen; and (iv) claims 1–3, 5, and 7–22 over Hiscock, Liu, Tomoyasu, Handreck, Forster, and/or Martinussen.

TIME PERIOD FOR RESPONSE

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