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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Ex parte PHILIPPE PEROVITCH and MARC MAURY

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Appeal 2018-008666
Application 12/441,762
Technology Center 1600

_____

Before FRANCISCO C. PRATS, JEFFREY N. FREDMAN, and DEBORAH KATZ, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1] under 35 U.S.C. § 134 involving claims to a galenical form for the administration by transmucous means of one active ingredient. The Examiner rejected the claims as failing to further limit and as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm in part.

Statement of the Case

Background

The Specification teaches that when active pharmaceutical agents are administered by the digestive tract, the "active ingredients undergo the so-

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the joint inventors, Philippe Perovitch and Marc Maury, as the real party in interest (*see* Appeal Br. 2).

called first digestive pass effect, alterations and losses related to the stomach environment or to variations of intestinal physiologies" (Spec. 1). Next, the active ingredients "are then subjected to a so-called 'first hepatic pass' effect, which brings about their metabolization and/or their more or less intense degradation" (*id.*). In addition to issues of loss of active agent, the Specification teaches that "the beginning of the therapeutic effectiveness for the patient takes place at the earliest 45 minutes after intake" (*id.* 2).

"A need therefore persists for a galenical formulation that makes it possible to administer an immediately bioavailable quantity of active ingredient so as to be able to treat painful symptoms or incapacitating problems very promptly and effectively" (Spec. 3).

The Claims

Claims 1, 2, 11, 12, 15, and 31 are on appeal. Claim 1 is representative and reads as follows:

> 1. A galenical form for the administration by transmucous means of one active ingredient, said galenic form consisting of one active ingredient and a hydroalcoholic solution based on water and ethanol, said active ingredient being in a stable and complete dissolved state in said hydroalcoholic solution such that said active ingredient is in a molecular state in the hydroalcoholic solution, wherein said galenic form is in a liquid form, and said hydroalcoh[o]lic solution consists of at least 20% by mass of ethanol and 50% – 73% by volume of water and 27% – 50% by volume of ethanol so as to allow rapid absorption in less than 20 seconds of all of said active ingredient through the gingival and/or jugal mucous membranes of the buccal cavity, wherein the dose of said active ingredient is less than 300 mg and the volume of said hydroalcoholic solution is less than 5 ml.

The Issues

A. The Examiner rejected claim 12 under 35 U.S.C. § 112, fourth paragraph as failing to limit the subject matter of the claim upon which it depends (Final Act. 3).

B. The Examiner rejected claims 1, 2, 11, 12, 15, and 31 under 35 U.S.C. § 103(a) as obvious over Dobrozsi,[2] TWC,[3] and Latini[4] (Final Act. 4–6).

A. 35 U.S.C. § 112, fourth paragraph

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that claim 12 fails to further limit claim 1?

Findings of Fact

1. Claim 12 reads as follows:

> 12. The galenical form according to claim 1, wherein the volume for administration is less than 5 ml.

Principles of Law

A "violation of § 112, ¶ 4 renders a patent invalid . . . for failing to add a limitation [in a dependent claim] to those recited in the independent claim, as required by 35 U.S.C. § 112, ¶ 4." *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1292 (Fed. Cir. 2006).

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[2] Dobrozsi et al., US 2002/0086878 A1, published July 4, 2002.
[3] TWC, Terry White Chemists Amiodarone Tablets 1–14 (2008).
[4] Latini et al., *Myocardial Disposition of Amiodarone in the Dog*, 224 J. Pharm. Exp. Therapeutics 603–8 (1983).

Analysis

> Appellant contends
>
> the volume for *administration* is not equivalent to the volume of the *hydroalcoholic solution*.
>
> According to claim 1, the volume of the *hydroalcoholic solution* is less than 5 ml, and the hydroalcoholic solution consists of at least 20% by mass of ethanol and 50% - 73% by volume of water and 27% - 50% by volume. Thus, the volume of the hydroalcoholic solution of claim 1 *excludes* the active ingredient.
>
> Claim 12 refers to the volume *for administration*, which is the combined volume of ethanol, water, and the active ingredient, which is not defined in claim 1.

(Appeal Br. 4).

> The Examiner responds
>
> contrary to Appellant's assertion, claim 1 explicitly requires that the volume of hydroalcoholic solution consist of the active ingredient, water, and ethanol because claim 1 requires the active ingredient be dissolved in "said hydroalcoholic solution" of water and ethanol. Therefore, the volume of the hydroalcoholic solution and the galenic form are identical. Since claim 12 merely recites the same volume parameters of the same composition, claim 12 fails to further limit the subject matter of claim 1 upon which it depends.

(Ans. 9–10).

We agree with the Examiner because the hydroalcoholic solution recited in Claim 1 is the entire volume that is administered in Claim 1, and is therefore identical to the volume for administration in Claim 12. That is, Claim 1 states that the "galenical form for the administration" consists of an active ingredient that is in a "complete dissolved state in said hydroalcoholic solution." Thus, the entire volume of the galenical form in claim 1 is limited to the hydroalcoholic solution with the dissolved active ingredient. Claim 1

then further recites that "said hydroalcoholic solution is less than 5 ml," and since "said hydroalcoholic solution" includes the dissolved active ingredient, the volume of the hydroalcoholic solution in Claim 1 does not exclude the active ingredient and does not differentiate from the "volume for administration is less than 5 ml" limitation in Claim 12.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that claim 12 fails to further limit claim 1.

B. 35 U.S.C. § 103(a) over Dobrozsi, TWC, and Latini

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that Dobrozsi, TWC, and Latini render the claims obvious?

Findings of Fact

2. Dobrozsi teaches a "preferred composition is in the form of an anhydrous, hydrophilic liquids in a very stable enviro[n]ment for rapid delivery of actives . . . [including] rapid transmucosal delivery" (Dobrozsi ¶ 11).

3. Dobrozsi teaches the composition "comprising dextromethorphan [may] preferably comprise from about 0.1% to about 9.3% . . . and most preferably from about 1.16% to about 4.6% dextromethorphan" (Dobrozsi ¶ 34).

4. Dobrozsi teaches the "solvent portion of compositions of the present invention comprises from about 60% to about 99.975% . . . . Solvents of the present invention are preferably selected from the group consisting of . . . ethanol" (Dobrozsi ¶¶ 37–38).

5. Dobrozsi teaches "the maximum level of water is about 10%, preferably from about 1% to about 10% more preferably from 5% to about 10%" (Dobrozsi ¶ 40).

6. Dobrozsi teaches "[t]ypical dosage forms of the composition of the present invention contain no more than about 3 ml" (Dobrozsi ¶ 59).

7. Dobrozsi teaches "a large increase in bioavailability with very rapid absorption can be achieved when the subject compositions are placed against any of the mucosal membranes of the mouth" (Dobrozsi ¶ 59).

8. Example IX of Dobrozsi is reproduced below:

Liquid Elixir

Items #	Material	% Comp. (w/w)
1	Ethanol (100%)	88.534
2	Water	10.000
3	Dextromethorphan Base	1.466
	Total	100.00

Example IX shows a composition comprising 88.534% ethanol, 10% water and 1.466 % Dextromethorphan base (*see* Dobrozsi ¶ 85). The Examiner calculates that 1.466% Dextromethorphan base is equivalent to 27.05 mg.

9. Dobrozsi teaches "[s]urprisingly, adding water to a composition, [particularly] one comprising low water-soluble actives improves the active's stability in such compositions" (Dobrozsi ¶ 8).

10. The Examiner does not identify a teaching in Dobrozsi suggesting water volumes of 50–73% or ethanol volumes of 27–50% (*see* Final Act. 4–6).

11. TWC teaches "[a]miodarone hydrochloride is a white or almost white, fine crystalline powder, very slightly soluble in water, freely soluble in methylene chloride, soluble in methanol, sparingly soluble in alcohol" (TWC 1).

12. Latini teaches "amiodarone was administered i.v. over 20 sec as a dose of 5 mg/kg dissolved in 50% ethanol in water" (Latini 604, col. 1).

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 begin with claim interpretation, because before a claim is properly interpreted, its scope cannot be compared to the prior art. Claim 1 recites a "said galenic form consisting of one active ingredient and a hydroalcoholic solution based on water and ethanol" where "said hydroalcohlic solution consists of at least 20% by mass of ethanol and 50% - 73% by volume of water and 27% - 50% by volume of ethanol." We therefore interpret the claims as limited to a three component solution of active ingredient, water, and ethanol.

Appellant contends Dobrozsi does not teach "a hydroalcoholic solution consisting of <u>50% - 73% by volume water</u> and 27% - 50% by volume ethanol as defined in instant claim 1" and "explicitly limits water to <u>a maximum of about 10% by weight, i.e. or about 10% by volume</u>" (Appeal

Br. 6). Appellant contends that Latini "does not disclose the 50% ethanol mixture for trans-mucosal delivery of amiodarone" and "discloses (1) an intravenous delivery system having the 50% ethanol mixture and (2) oral delivery system in solid tablet form" (*id.* at 9). Appellant contends "the skilled person would have had no reason to consider LATINI or TWC in relation with a trans-mucosal administration, as there was no indication of an expectation of success for a 50% ethanol mixture for trans-mucosal delivery of amiodarone" (*id.*).

The Examiner cites *In re Aller*, 220 F.2d 454 (CCPA 1955), for the proposition that optimization of result effective variables is obvious and that Dobrozsi teaches "that the addition of water is a result-effective variable for determining optimum or workable ranges by routine experimentation based on the explicit teaching that 'adding water to a composition, particularly one comprising low water-soluble actives improves the active's stability in such compositions' (para [0008])" (Ans. 12). The Examiner finds that

> Latini et al and TWC were cited for teaching that amiodarone is a low-soluble active that may be solubilized in a hydroalcoholic solution consisting of 50% ethanol and water as set forth, *supra*. Dobrozsi et al teach stable compositions using hydroalcoholic solvents that solubilize low-water soluble actives. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute one low-soluble active for another, both dissolvable in a hydroalcoholic solution within the recited concentrations with a reasonable expectation of success.

(Ans. 14).

We agree with Appellant because even if Dobrozsi teaches that the amount of water is a "results-effective variable," there is nothing in Dobrozsi suggesting that five-fold increase from the maximum amount

suggested in Dobrozsi's disclosed range (FF 5, 9). This is different from the situation in *Brandt*, for example, where the non-overlapping ranges were "so mathematically close that the examiner properly rejected the claims as *prima facie* obvious." *In re Brandt*, 886 F.3d 1171, 1177 (Fed. Cir. 2018).

Instead, we find the instant situation with a five-fold increase in water concentration to be more like *Stepan*, which found that "[a]bsent some additional reasoning, the Board's finding that a skilled artisan would have arrived at the claimed invention through routine optimization is insufficient to support a conclusion of obviousness." *In re Stepan Co.*, 868 F.3d 1342, 1346 (Fed. Cir. 2017). That is, while Dobrozsi may have reasonably been understood to permit routine optimization of amounts of water greater than the 10% maximum value in the disclosed ranges, the Examiner does not persuasively explain why the artisan would optimize to generate a five-fold increase from 10% to the claimed 50% of water because there is no evidence that drugs with poor water solubility would have been expected to have greater stability when the amount of water is increased five-fold.

We also agree with Appellant that Latini's example of an intravenous composition with 50% water/50% ethanol would not have been suggestive of a transmucosal composition as recited in claim 1 because these modes of administration differ significantly. We interpret the recitations in claim 1 of "administration by transmucous means" and "to allow rapid absorption in less than 20 seconds of all of said active ingredient through the gingival and/or jugal mucous membranes of the buccal cavity" as functional recitations that limit claim 1. These functional limitations require that the final composition has rapid absorption through mucous membranes. Latini's

teaching of an intravenous composition provides no guidance suggesting the benefit of rapid absorption through a mucous membrane (FF 12).

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that Dobrozsi, TWC, and Latini render the claims obvious.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
12	112, fourth paragraph	Improper Dependency	12	
1, 2, 11, 12, 15, 31	103(a)	Dobrozsi, TWC, Latini		1, 2, 11, 12, 15, 31
Overall Outcome			12	1, 2, 11, 15, 31

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 IN PART