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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte STUART CORR and
TIMOTHY JAMES NOAKES[1]

Appeal 2020-001616
Application 14/784,798
Technology Center 1600

Before FRANCISCO C. PRATS, JOHN G. NEW, and
DAVID COTTA, *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] We use the term "Appellant" to refer to the "applicant" as defined in 37 C.F.R. § 1.142. Appellant identifies Mexichem Amanco Holding, S.A. de C.V. as the real party-in-interest. App. Br. 3.

SUMMARY

Appellant files this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 1–8 and 14–24. Specifically, claims 1–8 and 14–18 stand rejected as unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Lulla et al. (WO 2010/052466 A2, May 14, 2010) ("Lulla"), Weers et al., (US 2010/0329984 A1, December 30, 2010) ("Weers"), and Daikin, *HFC-152a*, Product Information (May 2009) ("Daikin").

Claims 19–23 stand rejected as unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Lulla, Weers, and HFC-152a, and Hoelz et al. (US 2009/0092559 A1, April 9, 2009) ("Hoelz").

Claim 24 stands rejected as unpatentable under 35 U.S.C. § 103 as being obvious over the combination of Lulla, Weers, and Berkel et al. (US 2007/0183982 A1, August 9, 2007) ("Berkel").[2]

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

We REVERSE.

NATURE OF THE CLAIMED INVENTION

Appellant's claimed invention is directed to pharmaceutical compositions suitable for delivery from a pressurized container, preferably free of polar excipients and comprising: (a) a propellant component that consists essentially of 1,1- difluoroethane (R-152a); (b) a surfactant

[2] Claim 22 was also rejected by the Examiner as unpatentable under 35 U.S.C. § 112(b) as being indefinite. Final Act. 3. The Examiner has withdrawn this rejection. Ans. 3.

component; and (c) a drug component that consists of salbutamol sulfate, which can be delivered using a metered dose inhaler ("MDI"). Abstr.

REPRESENTATIVE CLAIM

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

> 1. A pharmaceutical composition that is free of polar excipients, said composition comprising:
>
> (a) a propellant component consisting essentially of 1,1-difluoroethane (R-152a) propellant,
>
> (b) a surfactant component consisting essentially of polyvinylpyrrolidone surfactant; and
>
> (c) a drug component consisting of solid drug particles of salbutamol sulphate,
>
> wherein the 1,1-difluoroethane propellant and polyvinylpyrrolidone surfactant provide a propellant/surfactant mixture in which the solid drug particles of salbutamol sulphate are suspended, and
>
> wherein the salbutamol sulphate and the polyvinylpyrrolidone are included in the mixture with the propellant as separate components.

App. Br. 13.

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 combined cited prior art. We address the arguments raised by Appellant below.

Issue

Appellant argues that the Examiner erred because the combined references neither teach nor suggest the limitation reciting "wherein the salbutamol sulphate and the polyvinylpyrrolidone are included in the mixture with the propellant as separate components." App. Br. 6.

Analysis

The Examiner first construes the claim term "mixture" as including, in its broadest reasonable interpretation consistent with Appellant's Specification, "any mixture, homogenous [or] non-homogenous." Final Act. 5.

The Examiner finds that Lulla teaches aerosol compositions consisting of: (1) at least one hydrofluoroalkane ("HFA") propellant such as 1,1,1,2-tetrafluoroethane (HFA-134a), 1,1,1,2,3,3,3-heptafluoropropane (HFA-227), etc.; and (2) at least one active agent, such as salbutamol sulphate complexed with an adjuvant such as PVP; (3) in a suitable MDI-pressurized canister with a suitable valve. Final Act. 6. The Examiner points to exemplified composition 5 of Lulla, which consists of 3.6 mg of active-PVP 100% complex and a propellant (with a 1:1 ratio between the active and PVP). *Id.* (citing Lulla Abstr. and generally).

The Examiner finds, however, that Lulla does not expressly teach the use of R-152a[3], also an HFA, as a propellant. Final Act. 6. The Examiner finds that Weers teaches pressurized aerosol compositions in metered dose

[3] "R-152a" and "HFC-152a" both refer to 1,1, difluoroethane. *See* Weers ¶ 20; Daikin, 1; Spec. 4.

inhalers ("MDIs") consisting of: (1) a medicament, including salts of salbutamol; (2) a hydrofluorocarbon propellant such as HFA-134a, HFA-227, R-152a, etc.; and (3) a surfactant. Final Act. 6 (citing Weems Abstr., ¶¶ 20, 28, 30, 33–36, 77, 94, 95, 144–147,167, claims 1–4 and 10). The Examiner finds that Weems teaches compositions containing salbutamol sulfate[4] in Example III. *Id.* The Examiner also points to Daikin, which the Examiner finds teaches that HFC-152a has a lower global warming potential compared to other fluorocarbons such as HFC-134a. *Id.*

The Examiner concludes that it would have been *prima facie* obvious to a person of ordinary skill in the art to combine the teachings of Lulla, Weers, and Daikin, by replacing HFA-134a or HFA-227 as a propellant, as taught by Lulla, with R-152a. Final Act. 7. The Examiner finds that HFA-134a, HFA-227, and R-152a are interchangeable as propellants for delivering pressurized aerosol compositions in MDIs and, because HFC-152a has a lower global warming potential compared to other fluorocarbons such as HFC-134a, a skilled artisan would have been motivated to substitute HFC-152a for the HFAs taught by Lulla. *Id.* The Examiner further concludes that, absent any demonstration of unexpected result, it would have been obvious to a skilled artisan to replace HFA-134a or HFA-227 with R-152a, because such routine substitution would also yield predictable results. *Id.*

Appellant argues that Lulla teaches that the pharmaceutical active agent, which may apparently be salbutamol sulfate, is complexed with the

[4] Except when directly quoting a reference or a brief, we employ herein the American spelling of "sulfate."

adjuvant, such as polyvinylpyrrolidone ("PVP"). App. Br. 6. According to Appellant, this complex is obtained by dissolving both the drug and the adjuvant in a solvent system for those compounds followed by removal of the solvent; the resulting solid complex is then dispersed in the HFA propellant. *Id.* (citing Lulla 11). Appellant also points to the Declaration of Dr. Stuart Corr[5], filed September 7, 2018 (the "Corr Declaration") in support of this teaching of Lulla as being known in the art at the time of invention. *Id.* (citing Corr Decl. ¶ 12). Appellant contends that it is evident from the teachings of Lulla that the pharmaceutical active is dissolved in a suitable solvent followed by the adjuvant and the resulting solution is then treated to remove the solvent, leaving the solid drug-adjuvant complex behind. *Id.* Appellant asserts that this dissolution is not possible with HFA propellants such as R-152a (which is specifically recited in the claims), because salbutamol sulfate has negligible solubility in HFA propellants. *Id.* (citing Corr Decl. ¶ 15).

Appellant emphasizes that Lulla teaches that the PVP is complexed with the drug and is not included in the composition as a distinct species, as recited in the claims. App. Br. 6. Appellant contends that the claims also require the solid drug particles of salbutamol sulfate to be dispersed or suspended in the HFA-152a/PVP) mixture. *Id.* Appellant asserts that a person of ordinary skill in the art would have understood that Appellant's claimed composition, in which the salbutamol sulfate and the PVP are included in the mixture with the propellant as separate components, is

[5] Dr. Corr is one of the named inventors of the claimed invention.

inconsistent with Lulla's teaching that the PVP is complexed with the salbutamol sulfate. *Id.*

Appellant also points to Lulla's teaching that:

> The inventors further observed that the dispersion of surfactant in the pharmaceutical aerosol composition with other pharmaceutically acceptable excipients rendered the composition unstable during the storage. In particular it was observed that the fine particle mass does not remain [the] same or decreases in timely manner during the storage. But, it was surprisingly found that when the drug was complexed with an adjuvant such as PVP K 25, PVP K 17 or PVP K[ ]30 etc., along with the addition of propellant(s) or optionally with one or more bulking agent and/or co-solvent(s), aggregation of fine drug particles was reduced significantly and hence keeping the composition stable during the storage period. It was also found that the composition continued to exhibit uniform delivered dose characteristics throughout the life of the MDI.

App. Br. 7 (quoting Lulla 6). Appellant thus asserts that Lulla expressly teaches that unless a PVP/salbutamol sulfate complex is formed, the resulting suspension will not be suitable, regardless of the propellant. Therefore, Appellant argues, Lulla teaches away from the presently claimed pharmaceutical composition in which the solid drug particles are suspended in an HFA-152a propellant/PVP surfactant mixture. *Id.*

The Examiner replies that the limitation of claim 1 requiring that the surfactant and drug "are included" in the mixture with the propellant "as separate components" is a product-by-process limitation and reads on the components being added at various timeframes. Ans. 4. More specifically, the Examiner finds that the language of the claim does not exclude salbutamol sulfate and PVP from being first combined to form a premix (i.e., the complex) and then being added to the propellant. *Id.*

The Examiner invites us to compare the disclosures of Appellant's Specification and the teachings of Lulla. Specifically, the Examiner points to pages 9–10 of the Specification, which discloses:

> The pharmaceutical compositions of the invention can also be prepared within the confines of a pressurised container, such as an aerosol canister or vial, from which the compositions are ultimately released as an aerosol spray using a medication delivery device, such as a MDI. In this method, a weighed amount of the salbutamol sulphate is introduced into the open container. A valve is then crimped onto the container and the 152a-containing propellant component, in liquid form, introduced through the valve into the container under pressure, optionally after first evacuating the container through the valve. **The surfactant component can be mixed with the salbutamol sulphate or, alternatively, introduced into the container after the valve has been fitted, either alone or as a premix with the propellant component. The whole mixture can then be treated to disperse the drug in the propellant or propellant/surfactant mixture, e.g.[,] by vigorous shaking or using an ultrasonic bath**. Suitable canisters may be made of plastics, metal or glass.

(Emphasis added by Examiner). The Examiner notes that Lulla teaches:

> The present invention further provides a process of manufacturing a pharmaceutical aerosol dispenser for delivering the aerosol pharmaceutical formulation to a patient in need thereof, comprising:
>
> (a) **weighing the complexed drug particles in a suitable metal canister**,
>
> (b) optionally mixing the complexed drug particles with one or more suitable excipients selected from cosolvents, bulking agents, antioxidants, lubricants and optionally with one or more surfactants or with other similarly complexed or non-complexed drugs,

> (c) **crimping the canister with a suitable valve and charging with HFA Propellant**.

Lulla 11 (emphasis added by Examiner).

The Examiner therefore finds that Lulla teaches that the individual components may be added in various sequences, individually or as premixes, but, in both Lulla and the claims, one obtains a product which is a salbutamol sulfate-PVP-propellant suspension. Ans. 5.

We find Appellant's argument persuasive. As an initial matter, we do not agree with the Examiner that the limitation reciting "wherein the 1,1-difluoroethane propellant and polyvinylpyrrolidone surfactant provide a propellant/surfactant mixture in which the solid drug particles of salbutamol sulphate are suspended" is a product-by-process limitation, or, put more accurately, a process limitation in a product claim. *See SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1322 (Fed. Cir. 2006). The limitation does not expressly or implicitly recite steps of a method or process by which the composition is formed, or by which the limitation is a "structural" part of the product (e.g., a molded plastic). *Id.* To the contrary, a plain reading of the language of the limitation recites the component constituents of the claimed composition, *viz.*, an HFC-125a mixture in which the solid drug particles of salbutamol sulfate are suspended, and in which the salbutamol sulfate and the PVP are included in the mixture with the propellant as separate components.

Furthermore, we do not interpret the claim language reciting "wherein the salbutamol sulphate and the polyvinylpyrrolidone are included in the mixture with the propellant as separate components" to recite that there is any specific method or process for incorporating the salbutamol sulfate and

the PVP into the composition. Rather, we interpret the claim language as meaning that, in the composition, the salbutamol sulfate and the PVP exist as separate components. We find that this is consistent with the preceding limitation, which requires that the solid salbutamol sulfate particles be suspended in the HFC-125a/PVP mixture.

We therefore construe the language of claim 1 as requiring that the HFC-152a (i.e., the 1,1-difluoroethane) and the PVP surfactant are in a mixture in which the solid drug particles of salbutamol sulfate are suspended. The claim further requires that the salbutamol sulfate and the PVP are included in the mixture as separate, i.e., discrete, components — solid particles suspended in the HFC-125a/PVP mixture. Lulla is directed to pharmaceutical aerosol compositions "comprising at least one hydrofluoroalkane propellant; at least one active agent *complexed* with an adjuvant; and, optionally, at least one pharmaceutically acceptable excipient." Lulla Abstr. (emphasis added). Lulla does not provide an express definition of the term "complexed." Lulla does, however, provide examples of how the drug component (which can include salbutamol sulfate) and the adjuvant (which can be PVP) are "complexed." Specifically, Lulla teaches:

> In another aspect, the present invention provides a process of manufacturing a complex of an active agent and an adjuvant comprising:
>
> (a) mixing the active agent in an organic solvent (e.g. acetone),
>
> (b) heating the mixture from step (a) to a suitable temperature and adding water to form a clear solution;

> (c) adding the adjuvant to the above solution from step (b);
>
> (d) concentrating the clear solution under reduced pressure, preferably under vacuum, to form a residue;
>
> (e) washing the residue with the same solvent used in step (a); and
>
> (f) drying (for example at suitable temperature, or preferably 50°C) the washed residue from step (e) to form a drug-adjuvant complex.
>
> The solvent used in the above process may be selected from acetonitrile, methanol, water, dimethyl formamide, acetone, tetrahydrofuran, dimethyl sulfoxide. Most preferable solvent is acetone.
>
> Alternatively, the complex of an active agent and an adjuvant can be isolated by lyophilization or by flash-evaporating the solvent using suitable techniques known in the art such as spray-drying. Flash-evaporating technique with respect to the present invention means removal of the solvent by applying heat and vacuum.

Lulla 11–12. Lulla thus teaches dissolving the salbutamol sulfate and the PVP in a heated organic solvent to form a clear solution, after which the solvent is removed, either *via* concentration and drying or *via* lyophilization.

Appellant's Specification teaches no comparable methods of forming a salbutamol sulfate/PVP complex. Appellant's Specification discloses that:

> The pharmaceutical compositions of the invention can be prepared by a simple blending operation in which the R-152a-containing propellant component, the surfactant component, and the salbutamol sulphate *are mixed together in the required proportions in a suitable mixing vessel. Mixing can be promoted by stirring as is common in the art.* Conveniently, the R-152a-

> containing propellant component is liquefied to aid mixing. If the pharmaceutical composition is made in a separate mixing vessel, it can then be transferred to pressurised containers for storage, such as pressurised containers that are used as part of medication delivery devices and especially MDIs.

Spec. 9 (emphasis added). The Specification also discloses:

> The pharmaceutical compositions of the invention can also be prepared within the confines of a pressurised container[…]. In this method, a weighed amount of the salbutamol sulphate is introduced into the open container. A valve is then crimped onto the container and the 152a-containing propellant component, in liquid form, introduced through the valve into the container under pressure, optionally after first evacuating the container through the valve. The surfactant component can be mixed with the salbutamol sulphate or, alternatively, introduced into the container after the valve has been fitted, either alone or as a premix with the propellant component. *The whole mixture can then be treated to disperse the drug in the propellant or propellant/surfactant mixture, e.g. by vigorous shaking or using an ultrasonic bath*.

Id. at 9–10 (emphasis added). Both of these methods thus employ simple mixing (e.g., stirring, shaking) of the constituents. However, we can discern no disclosure in the Specification that teaches "complexing" as provided for in the teachings of Lulla.

The Examiner points to the teachings of Lulla at page 11, and quoted *supra*, as supporting the finding that Lulla teaches that the individual components may be "added in various sequences, individually or as premixes." *See* Ans. 5. We are not persuaded by this finding, because the quoted portion of Lulla expressly states: "weighing the *complexed drug particles*" and "optionally mixing the *complexed drug particles* with one or more suitable excipients." Lulla 11 (emphasis added). Lulla thus teaches

that, in this process, the salbutamol sulfate particles have been previously complexed with the PVP in a manner that is not consistent with the simple "mixing" disclosed by Appellant's Specification.

More importantly, the Examiner does not articulate any reason as to why a person of ordinary skill in the art would have been motivated to abandon the method of complexing the salbutamol sulfate with the PVP, taught by Lulla as a central part of its invention, in favor of mere mixing, stirring, or shaking as disclosed by the Specification. Furthermore, the Examiner adduces no persuasive evidence that the complexing method of Lulla would produce the same end result, *viz.*, a "propellant/surfactant mixture in which the solid drug particles of salbutamol sulphate are suspended" as would the simple mixing of the constituents disclosed by Appellant's Specification. Absent any such reasoning or evidence, we are unable to sustain the Examiner's conclusion that the claims are *prima facie* obvious over the combined cited prior art. Furthermore, because we find that our conclusion in this respect is dispositive of this appeal, we do not reach Appellant's additional arguments.

CONCLUSION

The Examiner's rejection of claims 1–8 and 14–24 under 35 U.S.C. § 103 is reversed.

REVERSED

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–8, 14–18	103	Lulla, Weers, HFC-125a		1–8, 14–18
19–23	103	Lulla, Weers, HFC-125a, Hoelz		19–23
24	103	Lulla, Weers, and Berkel		24
Overall Outcome				1–8, 14–24