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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte TAMMY SAVAGE, STEPHEN WICKS, and JOHN MITCHELL

Appeal 2019-004798
Application 14/333,417
Technology Center 1600

Before JEFFREY N. FREDMAN, DEBORAH KATZ, and JOHN G. NEW, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134(a) involving claims to substituted sulphobutyl ether β-cyclodextrin. The Examiner rejected the claims as anticipated and obvious. We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM-IN-PART.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as Curadev Pharma Private Limited (*see* App. Br. 3).

[2] We have considered and herein refer to the Specification of Jan. 19, 2016 ("Spec."); Final Office Action of May 2, 2018 ("Final Act."); Appeal Brief of Dec. 19, 2018 ("App. Br."); Examiner's Answer of Apr. 2, 2019 ("Ans."); and Reply Brief of May 31, 2019 ("Reply Br.").

Statement of the Case

Background

"Sulphobutyl ether β-cyclodextrin (SBE-β-CD or SBECD) is one of a class of polyanionic, hydrophilic water soluble cyclodextrin derivatives" (Spec. 1:9–10). "SBE-β-CD is currently used as an effective pharmaceutical excipient, and has been given the trade name Captisol®" (*id.* 1:30–31). Known batch processes for preparing SBE-β-CD result in "a high proportion of lower substituted SBE-β-CD" (*id.* 1:25–26). "[T]he continuous flow process of the invention however results in a lower concentration of lower substituted [SBE-β-CD] (i.e.[,] a degree of substitution value of 1–4) and surprisingly much higher concentrations of the higher substituted . . . [SBE-β-CD] (i.e.[,] individual degrees of substitution values of 4–13)" (*id.* 4:6–10).

The Claims

Claims 21–25, 27, and 31–36 are on appeal.[3] Independent claims 21 and 36 are representative and read as follows:

> 21. A composition comprising sulphobutyl ether β-cyclodextrin (SBE-β-CD), wherein the average degree of substitution (ADS) is 7.3 or more and the composition comprises a range of individual degrees of substitution.
>
> 36. A composition comprising sulphobutyl ether β-cyclodextrin (SBE-β-CD), wherein the average degree of substitution (ADS) is 9 or more.

App. Br. 22–23.

[3] Claims 1–3, 5, 7, 9, 10, 12, 14, 15, 17–19, 29, and 30 were withdrawn (*see* App. Br. 20–23). Claims 4, 6, 8, 11, 13, 16, 20, 26, and 28 were cancelled (*see id.*).

The Issues

A. The Examiner rejected claims 21–25, 27, and 31–36 under 35 U.S.C. § 102(a)(1) as being anticipated by Mosher[4], as evidenced by Zia[5], Luna-1[6], and Luna-2[7] (Ans. 3–5).

B. The Examiner rejected claims 21–25, 27, and 31–36 under 35 U.S.C. § 103 as obvious over Shah[8], in view of Luna-2, Stella[9], and Zia (Ans. 10–12).

A. 35 U.S.C. 102(a)(1) over Mosher

The Examiner finds that Mosher teaches "a composition comprising [SBE-β-CD] having an average degree of substitution of 1–21" (Ans. 3). The Examiner finds that Mosher is an enabling reference as supported by the evidentiary references of Zia, Luna-1, and Luna-2 (*id.* at 5). The Examiner finds Zia teaches "SBE**12**-β-CD was produced and separated in order to conduct a binding study" thereby showing that "SBE-β-CD compounds having an average degree of substitution of 7.3 or more were known at least 10 years before the effective filing date of the instant invention" (*id.* at 4). The Examiner finds Luna-1 and Luna-2 teach SBE-β-CD with different

[4] Mosher et al., US 2010/0292268 A1, published Nov. 18, 2010.
[5] Zia et al., *Effect of Alkyl Chain Length and Degree of Substitution on the Complexation of Sulfoalkyl Ether β-Cyclodextrins with Steroids*, 86 J. Pharma. Sci. 220–224 (1997).
[6] Luna et al., *Fractionation and characterization of 4-sulfobutyl ether derivatives of cyclomaltoheptaose (β-cyclodextrin)*, 299 Carbohydrate Res. 103–110 (1997).
[7] Luna et al., *Evaluation of the utility of capillary electrophoresis for the analysis of sulfobutyl ether β-cyclodextrin mixtures*, 15 J. Pharma. Biomed. Analysis 63–71 (1996).
[8] Shah et al., EP 0889056 A2, published Jan. 7, 1999.
[9] Stella et al., US 5,134,127, issued July 28, 1992.

average degrees of substitution and a range of individual degrees of substitution" (*id.*).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that Mosher anticipates the claims?

Findings of Fact ("FF")

1. Mosher discloses "the sodium salt of sulfobutyl ether derivative of beta-cyclodextrin, with an average of about 7 substituents per cyclodextrin molecule (SBE7-β-CD), is being commercialized by CyDex Pharmaceuticals, Inc. (Kansas) as CAPTISOL® cyclodextrin" (Mosher ¶ 15).

2. Mosher discloses "[t]he SAE-CD used is available from CyDex Pharmaceuticals, Inc. . . . [], and is described in U.S. Pat. No. 5,376,645 and No. 5,134,127 to Stella." (Mosher ¶ 107).

3. Mosher discloses "a composition comprising clopidogrel and a sulfoalkyl ether cyclodextrin (SAE-CD)" "of the formula SAE_x-R-CD . . . [], wherein SAE is selected from the group consisting of . . . sulfobutyl ether . . . and x is 1–18, 1–21, or 1–24, when R is α, β, or γ, respectively" (Mosher 31, claim 108).

4. Zia teaches "SAE-β-CDs are a mixture of positional and regional isomers containing from one to as many as 12 SAE groups per CD" (Zia 220).

5. Zia teaches:

> To determine the effect of degree of substitution (DS) on . . . [] binding, mixtures of SAE-β-CDs with multiple substitution levels and varying average degrees of substitution were studied as well as mixtures of SAE-β-CDs that contained the same degree of substitution. Mixtures that contained SAE-β-CDs of the same degree or substitution were isolated from the multiple

> substitution level mixtures by ion-exchange chromatography and purified for investigation.

(Zia 220).

6. Zia teaches an electropherogram of SBE4-β-CD with an average degree of four substitutions per CD and up to 10 degrees of substitution (Zia 221, Fig. 2).

7. Zia teaches testing binding constants of SBE-β-CDs, including SBE12-β-CD, to testosterone and progesterone (Zia 223, Table 1).

8. Luna-1 teaches "SBE-β-CD mixtures can be reproducibly prepared with different average ds (i.e., 1, 4, 7) by varying . . . [] reaction conditions" (Luna-1 104).

9. Luna-1 teaches isolating SBE-β-CD, including SBE_{8b}-β-CD using capillary electrophoresis ("CE") analysis. However, "[t]he bands with ds 9 and 10 were not detected by CE or did not elute from the Sephadex under the experimental conditions" (Luna-1 105, Fig. 4).

10. Luna-2 teaches that changes in reaction conditions effect the pattern of distribution of substituted SBE-β-CD products (*see* Luna-2 69–70).

11. Luna-2 teaches "[n]either temperature nor reaction time appeared to affect the distribution of the product mixture (Fig. 10a and Fig. 10b)" (Luna-2 70).

12. Luna-2 teaches:

> However, changes in the amount of base caused a change in the composition pattern (Fig. l0c). The use of 7–12 equivalents of base produced a fairly narrow distribution pattern, but a drop to 6 equivalents of base caused a shift in the distribution from the lower level of substitution to a higher population of

> intermediate substituted materials. A change in the distribution pattern was also observed with the use of 14 and 21 equivalents of base. A high base concentration produced a broader distribution of materials with a shift of the maximum to a slightly lower level of substitution.

(Luna-2 70).

Principles of Law

"In patent prosecution, the examiner is entitled to reject application claims as anticipated by a prior art patent without conducting an inquiry into whether or not that patent is enabled . . . The applicant, however, can then overcome that rejection by proving that the relevant disclosures of the prior art patent are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003).

Analysis

Appellant contends that Mosher "is not enabled for the entire ADS range of 1 to 21" (App. Br. 9). Appellant submits two declarations by Stephen Wicks, Ph.D. and a publication by Ma[10] as evidence that Mosher is not enabled. Appellant contends that the Wicks Decl. I[11] explains that despite SBE-β-CD having "twenty-one hydroxyl groups which theoretically could be alkylated, i.e., substituted," "[p]revious researchers were unable to empirically . . . make SBE-β-CD having an ADS greater than 7.1" (App. Br. 11, citing Wicks Decl. I ¶ 12.). The Declaration explains that, consistent with the state of the art at the time, Mosher refers to Stella for a process of

[10] Ma et al., *The synthesis and process optimization of sulfobutyl ether b-cyclodextrin derivatives*, 72 Tetrahedron 3105–3112 (2016).
[11] Declaration of Dr. Stephen Wicks, dated July 21, 2016.

making SBE-CDs that results in SBE-CD compositions having an ADS of 7.0–7.1 (Wicks Decl. I ¶¶ 23–29). The Declaration states that "[a]t the time of the effective filing date of the instant application, the methods in Mosher could only produce SBECD having a maximum ADS of about 7.0" (*id.* ¶ 32).

Appellant contends that the Wicks Decl. II[12] explains that the degree of substitution was limited by "the prior art *batch* methods of making SBE-β-CD" (App. Br. 12, citing Wicks II ¶¶ 17–18). The Declaration states:

> Although β-cyclodextrin has 21 hydroxyl groups available for alkylation, researchers were unable to make a β-cyclodextrin having an ADS greater than about 7.0–7.1 in a largely reproducible manner and suitable for commercialization simply by reacting β-cyclodextrin with an excess of 1,4-butane. This is likely due to steric hindrance caused by the substituted group on each of the glucopyranose units after each unit is alkylated once which disfavors, thermodynamically or kinetically, further substitution.

Wicks Decl. II ¶ 18.

Appellant contends that Ma teaches β-cyclodextrin has three hydroxyl groups C_2, C_3, and C_6 (multiplied by seven dextrose units for a total of 21 theoretical substitution sites) (App. Br. 12). Appellant contends that Ma "teaches that the C_3 hydroxyls are unreactive using prior art batch methods because the amount of base (i.e., strong base conditions) required to activate the C_3 hydroxyl competitively destroys the alkyl sulfone before it can react with the activated β-CD" (*id.*, citing Ma 3106, 3108–3110).

[12] Declaration of Dr. Stephen Wicks, dated Mar. 15, 2017.

The Examiner responds that "[o]ut of the 21 available hydroxyls there are only 7 hydroxyls at the C3 position. The other 14 hydroxyls are reactive according to Ma" (Ans. 7). The Examiner finds Luna-1 "shows complete resolution of CE peaks for DS 1–10. This shows that SBE β-cyclodextrins having DS above 7 have been detected, which means that they were produced" (*id. see* FFs 8, 9). The Examiner finds that Zia teaches the use of SBE**12**-β-CD, whereby the "artisan would clearly understand that SBE**12**-β-CD was produced, separated and characterized" (*id.* at 8, FF 7). "This means that before SBE**12**-β-CD was isolated and purified, it must have been present as a component in a mixture [of] SBE-β-CDs having a range of individual degrees of substitution" (*id.*). The Examiner finds that "Figure 10c of Luna-2 shows that there is a shift toward higher degree of substitution if base concentration is increased" and "comparing Fig. 10b with Fig. 10a shows that there is a slight shift toward higher substitution" when temperature is increased (*id.*, citing Luna-2 70, Figs. 10a–c).

We find Appellant's arguments and evidence persuasive as to the Examiner's rejection of anticipation by Mosher. Appellant's claim 21 requires SBE-β-CD with an average degree of substitution (ADS) of 7.3 or more and a range of individual degrees of substitution (IDS). Appellant's claim 36 requires SBE-β-Cd with an ADS of 9 or more. We find Dr. Wick's explanation of ADS and IDS instructive:

> Two compositions of SBE-β-CD can potentially have the same ADS but differ with respect to the distribution of, or presence of, different IDS(s) in the composition. For example, a composition comprising . . . [SBE-β-CD] can include a single type of SBE-β-CD such that the IDS is equal to the ADS. However, a composition can also include a range of SBE-β-CD which differ with respect to the number of substituents on the

> SBE-β-CD such that certain SBE-β-CD in the composition have an IDS not equal to the ADS.

(Wicks Decl. II ¶ 27). The Specification further provides methods for measuring and calculating the IDS and ADS, as well as incorporating the IDS into a calculation of ADS (*see* Spec. 25–30). As applied to claim 21, we interpret the claim to require SBE-β-CD with an ADS of 7.3 or more including multiple IDS that form a range. We interpret claim 36 to require an ADS of 9 or more, without limitation on IDS.

We agree with the Examiner that the prior art, e.g., Luna-1, Luna-2, and Zia, shows that individual SBE-β-CD having degrees of substitution greater than 7 had been produced (FFs 4, 6, 7, 9, 10). This is consistent with Mosher's teachings of SBE-β-CD having an ADS of about 7, which would necessarily encompass a range of IDS greater and less than 7 to obtain the average value (FF 1). However, these isolated compounds do not establish an ADS of more than 7.3, with a range of IDS.

Likewise, the prior art does not establish a method for practicing Mosher's entire ADS range of 1–21. As acknowledged by the Examiner, Ma teaches that an IDS, and consequently ADS, of greater than 14 would not have been expected at the time of filing. Mosher does not provide a method of preparing SBE-β-CD, but rather cites to Stella, which produces SBE-β-CD with an ADS of up to 7.1 (FF 2).

Moreover, we find that the art does not support the Examiner's conclusion as to the predictability of the method of achieving an ADS of 7.3 or more. Despite the Examiner's interpretation of the Figures 10a–c of Luna-2, the reference unambiguously states that "neither temperature nor reaction time appeared to affect the distribution of the product" (FF 11).

Moreover, Luna-2 teaches that decreasing, rather than increasing the amount of base, "causes a shift in the distribution from the lower level of substitution to a higher population of intermediate substituted materials" and that the largest amounts of base equivalents "shift the maximum to a slightly lower level of substitution" (FF 12).

Conclusion of Law

A preponderance of the evidence supports Appellant's argument that Mosher does not enable SBE-β-CD with an ADS range of 7.3 or more. Consequently, we do not sustain the Examiner's rejection of the claims as anticipated by Mosher, and we reverse the rejection of claims 21 and 36. The rejection of dependent claims 22–25, 27, and 31–35 falls with independent claim 21.

B. 35 U.S.C. § 103 over Shah, Luna-2, Stella, and Zia

The Examiner finds Shah teaches that the degree of sulfoalkylation of SBE-β-CD "can be controlled by using lower or higher amounts of alkylsulfone depending on whether a lower or higher degree of substitution is desired. Generally, a range of substitution of 4.5–7.5 can be achieved" (Ans. 10). The Examiner acknowledges that Shah "does not expressly teach SBE-β-CDs having the average degree of substitutions recited in the instant claims" (*id.*). The Examiner finds "the teachings of [Shah] and [Luna-2] can be used by one of ordinary skill in the art to optimize the reaction conditions and order of steps to be used . . . in order to produce SBE-β-CDs having the higher average degree of substitution as instantly claimed" (*id.* at 11).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the claims would have been obvious?

Findings of Fact

13. Shah teaches "a process of making a sulfoalkyl ether cyclodextrin having a predetermined degree of substitution" (Shah 3:8–9).

14. Shah teaches the process includes the steps of: A) combining cyclodextrin with alkyl sulfone in the presence of an alkali metal hydroxide; B) conducting sulfoalkylation within a pH range of about 8 to about 11; C) adding additional hydroxide to achieve the desired degree of substitution and proceed to completion; and D) adding additional hydroxide to destroy residual sulfone (Shah 3:26–36).

15. Shah teaches:

> Once the level of residual unreacted cyclodextrin has reached a desired level below 0.5% by weight during the pH control stage, the pH can be raised to above 11, for example a level above 12, by adding additional base to drive the reaction to completion. The pH is preferably at least 12 so that the reaction proceeds at a reasonable rate, but not so high that unreacted alkyl sulfone is hydrolyzed rapidly rather than reacting with cyclodextrin.

(Shah 4:24–27).

16. Shah teaches "[g]enerally the range of substitution that can be achieved is an average of from 4.5 to 7.5, preferably 5.5 to 7.5, most preferably 6.0 to 7.1" (Shah 5:15–16).

17. Shah teaches experimentally preparing SBE-β-CD with an "average degree of substitution . . . [of] 7.0 by NMR and 7.1 by elemental analysis" (Shah 7:24–32).

Analysis

Appellant contends "Shah does not disclose how a SBE-β-CD composition could be produced with an ADS of 7.3 or more" (Reply Br. 16). Rather, Appellant contends that Shah's method produces a highest ADS of 7.0 by NMR and 7.1 by elemental analysis (App. Br. 16, citing Shah '746 8:64–65)[13]. Appellant contends that "[b]ecause of the competing activation and alkylation reactions, the maximum ADS **empirically possible using prior art *batch* methods** such as Mosher, *et al.* and Shah, *et al.*, is 7.0 and 7.1, respectively" (*id.* at 15, citing Wicks Decl. II ¶ 18). Particularly, Dr. Wicks states:

> [I]mproved techniques resulted in methods for making SBECD with an ADS of up to 7.0–7.1 in a largely reproducible manner, and the process could therefore be commercialized. These methods are disclosed in [Shah] US Patent No. 6,153,746, which is of record in the instant case. Although β-cyclodextrin has 21 hydroxyl groups available for alkylation, researchers were unable to make a β-cyclodextrin having an ADS greater than about 7.0–7.1 in a largely reproducible manner and suitable for commercialization simply by reacting β-cyclodextrin with an excess of 1,4-butane. This is likely due to steric hindrance caused by the substituted group on each of the glucopyranose units after each unit is alkylated once which disfavors, thermodynamically or kinetically, further substitution.

(Wicks Decl. II ¶ 18). Dr. Wicks states that "[u]ntil the disclosure of this improved batch-continuous flow synthetic method, the aforementioned

[13] Appellant refers to Shah as the U.S. publication, US 6,153,746, issued Nov. 28, 2000 ("Shah 746").

thermodynamic or kinetic barriers for producing SBECD having an ADS greater than about 7.0 were not overcome" (Wicks Decl. I ¶ 31).

The Examiner responds that although "Shah does not teach SBE-β-CD with an ADS above 7.1 . . . one of ordinary skill in the art will recognize that the base concentration, and therefore the pH, can be adjusted to increase the degree of substitution while minimizing the hydrolysis of the sulfone" (Ans. 14). The Examiner finds that "[f]rom the teachings of Shah one can also adjust the contact time and also adjust the ratio of the CD to sulfone for increasing the DS" (*id.*). The Examiner finds Luna-2 teaches "increasing temperature shifts the ADS slightly higher toward higher value" and "[i]f one looks at Fig. 10c, base equivalents from 6–10 show a shift toward higher substitution values" (*id.*). The Examiner concludes "Applicants have not convincingly shown that there is no reason to modify Shah, Luna-2 and Zia in order to arrive at the instant invention" (*id.* at 15).

We find Appellant's arguments and evidence persuasive as applied to the rejection of claim 21. As discussed above, we agree that the evidence establishes that the state of the art at the time of filing indicated the upper limit of ADS for SBE-β-CD was 7.1 (FFs 1, 6, 8, 16, 17). We also agree that a person of ordinary skill in the art would not have been motivated to further increase the amount of base in Shah, as Shah cautions against destruction of the sulfone, and Luna-2 indicates that more base decreases rather than increases the maximum substitutions (FFs 11, 12, 15). Because the evidence supports Appellant's argument that SBE-β-CD having an ADS of 7.3 or more and a range of IDS would not have been obvious at the time the invention was made in view of the applied prior art, we do not sustain the Examiner's rejection of claim 21.

We do not find Appellant's arguments and evidence persuasive as to the rejection of claim 36. Claim 36 recites SBE-β-CD having an ADS of 9 or more. Claim 36 lacks the limitation found in claim 21 that the "composition comprises a range of individual degrees of substitution." Therefore, claim 36 is open to a composition with a single degree of substitution.

Appellant acknowledges that Zia "is directed to purified samples in which the IDS is equal to the ADS" (Reply Br. 11 (emphasis omitted)). Dr. Wicks' Declaration also explains that "a composition comprising . . . [SBE-β-CD] can include a single type of SBE-β-CD such that the IDS is equal to the ADS" (Wicks Decl. II ¶ 27). Zia teaches an isolated SBE12-β-CD having an IDS of 12 (FF 7). Zia therefore teaches a purified sample in which the IDS of 12 is equal to an ADS of 12, i.e., 9 or more, as required by Claim 36. "It is well settled that 'anticipation is the epitome of obviousness.'" *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002). Because Zia confirms and exemplifies that it was known to obtain SBE-β-CD having an ADS of 9 or more, it would have been obvious for a person of ordinary skill in the art to do so in view of the combination of Shah, Luna-2, Stella, and Zia. We note the Board may rely on less than all of the references applied by the Examiner in an obviousness rationale without designating it as a new ground of rejection. *In re Bush*, 296 F.2d 491, 496 (CCPA 1961). Accordingly, we sustain the rejection of claim 36.

Conclusion of Law

A preponderance of the evidence of record does not support the Examiner's conclusion that claim 21 would have been obvious over the prior

art. Consequently, we reverse the rejection of claim 21, and its dependent claims 22–25, 27, and 31–35.

A preponderance of the evidence of record supports the Examiner's conclusion that claim 36 would have been obvious over the prior art. Consequently, we affirm the rejection of claim 36.

CONCLUSION

We reverse the rejection of claims 21–25, 27, and 31–36 under 35 U.S.C. § 102(a) as anticipated by Mosher.

We reverse the rejection of claims 21–25, 27, 31–35 under 35 U.S.C. § 103 as obvious over Shah, Luna-2, Stella, and Zia.

We affirm the rejection of claim 36 under 35 U.S.C. § 103 as obvious over Shah, Luna-2, Stella, and Zia.

Claims Rejected	**35 U.S.C. §**	**Basis**	**Affirmed**	**Reversed**
21–25, 27, 31–36	102(a)(1)	Mosher		21–25, 27, 31–36
21–25, 27, 31–36	103	Shah, Luna-2, Stella, Zia	36	21–25, 27, 31–35
Overall Outcome			36	21–25, 27, 31–35

AFFIRMED-IN-PART