Intellectual Property Office

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05 October 2023

PATENTS ACT 1977

APPLICANT	DANSTAR FERMENT AG
ISSUE	Whether application GB2206573.4 complies with s.1(1)(b) of the Patents Act 1977
HEARING OFFICER	Dr L Cullen

DECISION

Introduction

1 Patent application GB2206573.4 ("the application") in the name of DANSTAR FERMENT AG (the applicant) and entitled "*Expression of Heterologous Enzymes in Yeast for Flavoured Alcoholic Beverage Production*" was initiated on 5 May 2022 as a divisional application made under s.15(9), deriving its effective filing date of 1 March 2019) and its priority date of 5 March 2018 from the earlier "parent" patent application GB2015485.2. A combined search and examination report for the application issued on 25 May 2022 and the application was published on 10 August 2022.

2 During the examination of this application, the issue of inventive step (based on a combination of citations) has been raised at every round. With a failure to reach agreement, the examiner, Dr Jeremy Kaye, offered a hearing in his examination report dated 17 March 2023. In response, amended claims were submitted alongside argument which resulted in the examiner undertaking additional searching. A further examination report was issued on 19 April 2023 within which inventive step was again raised, however a new document was cited in support of this objection. The examiner again made the offer of a hearing. The applicant replied on 3 May 2023 requesting that a decision be made based on the papers on the file. The matter was referred to me and my decision is set out below.

3 On my invitation, the attorney, Dr David Gallagher for J.A. Kemp LLP submitted arguments in writing on 17 July 2023 to response to the newly formulated inventive step objection. It is on the basis of these submissions that I am asked to decide on the papers whether the latest claims now on file have an inventive step. I am assisted in this matter by Dr Graham Feeney.

4 The extended period for putting this application in order under Section 20 of the Patents Act 1977 ("the Act") expired on 14 April 2023. No further extensions are

available and should I find that this application in its present form does not comply with the Act (and Rules), there is no opportunity for further amendment.

The Invention

5 The invention as now defined by the amended claims concerns the brewing of sour beers, also referred to as 'sours'. Traditionally, sours are made by intentionally allowing lactic acid-producing wild yeast strains or lactic acid bacteria into the brew, for example, through the barrels or during the cooling of the wort in a vessel open to the outside atmosphere. In the present application, the sour flavour is achieved by the production of lactic acid within the brewing wort mixture via the actions of a recombinant (i.e., genetically modified) *Saccharomyces cerevisiae* yeast (hereafter *S. cerevisiae*) which expresses the enzyme lactate dehydrogenase (LDH). In this manner, a single yeast species contributes both ethanol and lactic acid to the brew. This is exemplified by the recombinant LDH expressing M16141 strain of *S. cerevisiae* which produces both lactic acid and ethanol (see figures 3 and 9 of the application) and which is mixed, in varying proportions, with its LDH-null M14629 parent strain which produces only ethanol.

The Claims

6 The sole independent claim, claim 1 defines a process for making an alcoholic sour beer as follows:

> *A process for making a flavoured and fermented alcoholic beverage, the process comprising (i) contacting a recombinant yeast host cell with a substrate comprising carbohydrates to provide a mixture and (ii) fermenting the mixture to accumulate a flavor compound and at least 5 g/L of ethanol in the fermented mixture, wherein the flavour compound comprises lactic acid, wherein the flavoured and fermented alcoholic beverage is a sour beer, wherein the substrate is a wort, and wherein the recombinant yeast host cell:*
>
> • *is from the genus* Saccharomyces*;*
>
> • *has a heterologous nucleic acid molecule encoding one or more heterologous polypeptide for the production of the flavour compound, wherein the heterologous nucleic acid molecule allows the production of the flavour compound in the fermentation medium, wherein the heterologous nucleic acid is operatively associated with an anaerobic-regulated promoter, wherein the recombinant yeast host cell accumulates at most 3.0 % (w/v) lactic acid in the fermentation medium after the fermentation, wherein the one or more heterologous polypeptide comprises a lactate dehydrogenase (LDH) enzyme having LDH activity, and wherein the LDH enzyme has the sequence of SEQ ID NO: 2, is a variant of SEQ ID NO: 2, or is a fragment of the amino acid sequence of SEQ ID NO: 2; and*

• *has a native ethanol production pathway.*

7 SEQ ID NO:2 is the polypeptide sequence encoding a lactate dehydrogenase enzyme derived from the filamentous heterothallic microfungus *Rhizopus oryzae*.

The Relevant Law

8 Section 1(1) states that:

> *A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say –*
>
> *(a) the invention is new;*
>
> ***(b) it involves an inventive step;***
>
> *(c) it is capable of industrial application;*
>
> *(d) the grant of a patent for it is not excluded by subsections (2) and (3) or section 4A below;*
>
> *and references in this Act to a patentable invention shall be construed accordingly.*

9 Section 3 of the Act defines what is meant by 'inventive step' as follows:

> *An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of section 2(2) above (and disregarding section 2(3) above).*

10 Section 2(2) of the Act, which refers to the state of the art, reads:

> *The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use or in any other way.*

11 The examiner and applicant both agree that the correct and long-established approach for assessing inventive step is the structured approach set out in *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*[1], and reformulated as the "Windsurfing/Pozzoli" test in *Pozzoli SPA v BDMA SA*[2]. This test is as follows:

> *(1)(a) Identify the notional "person skilled in the art";*

[1] *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd, [1985] RPC 59*

[2] *Pozzoli SPA v BDMA SA [2007] EWCA Civ 588*

(1)(b) Identify the relevant common general knowledge of that person;

(2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;

(3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;

(4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

Analysis

Step (1)(a): Identify the notional "person skilled in the art".

12 It would appear that there is no disagreement with the examiner's assertion that the person skilled in the art is "*considered to be a team comprising brewers and microbiologists*". I concur.

Step (1)(b): Identify the relevant common general knowledge of that person.

13 The examiner states, in their examination report dated 17 March 2023, that:

> "*The common general knowledge…would include the fact that "sour beers" obtain their distinctive tastes via lactic acid, that lactic acid may be produced by organisms that express the lactate dehydrogenase enzyme and that a combination of yeast and lactic acid bacteria (LAB) may be used to produce the desired sour beer. It would also be known that Saccharomyces cerevisiae is one of the standard yeasts that is used in brewing and that its use will provide predictable results. Furthermore, it would also be known by the relevant skilled person that S. cerevisiae may be genetically modified*."

From reviewing the papers on file, I do not believe that this assessment of the common general knowledge (CGK) is a point of disagreement and I, too, concur.

Step (2): Identify the inventive concept of the claim in question or if that cannot readily be done, construe it.

14 I do not believe that the identity of the inventive concept has been at issue between the examiner and the applicant. Claim 1, as written and as currently amended, is straightforward to understand. The inventive concept concerns a method of fermenting wort to produce a sour beer using a recombinant yeast of the *Saccharomyces* genus that has been engineered to express the LDH enzyme from *Rhizopus oryzae* and simultaneously produces ethanol.

Step (3): Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed.

15 Two documents have been cited for consideration in combination with the common general knowledge:

(1) Bio/Technology. Vol.12, 1994, Dequin, S and Barre, P., "*Mixed lactic acid-alcoholic fermentation by Saccharomyces cerevisiae expressing the Lactobacillus casei L(+)-LDH*", pp.173-177, hereafter referred to as *Dequin & Barre*.

(2) J. Ind. Microbiol. & Biotechnol., Vol.30, 2003, Skory, C.D., "*Lactic acid production by Saccharomyces cerevisiae…*", pp.22-27, hereafter referred to as *Skory*.

16 *Dequin & Barre* discloses a *S. cerevisiae* strain expressing the gene encoding L(+)-LDH from the bacterium *Lactobacillus casei*. The disclosure shows how the *S. cerevisiae* strain can simultaneously produce ethanol and lactic acid, which is contemplated to be useful for the "biological" acidification of fermentation products, specific examples being during cider or wine making and during baking. It is my view that that the skilled person would understand from the disclosure that the acidification is desirable for organoleptic purposes, specifically taste. As the attorney has pointed out in his argument, the lactic acid levels achieved were appropriately low, being up to 10g/L (i.e. 1% w/v) although this was achieved when the yeast was cultured on a synthetic medium under inevitably closely controlled experimental conditions. In the introduction, *Dequin & Barre* further teaches the skilled person that a single yeast strain expressing both ADH and LDH might be utilised to enhance the production of cider or wine by adding acidity where it was otherwise absent by dint of the choice of inferior or low-quality raw ingredients and also teaches the skilled person that sour breads which would otherwise be produced using a combination of conventional yeasts and lactic acid bacteria might be produced using a single yeast strain. The difference between *Dequin & Barre* and the claimed invention is that the LDH enzyme engineered into *S. cerevisiae* was bacterial in origin, that wort was not the fermented substrate and that that beer production was not explicitly contemplated. I do not believe that the examiner or applicant differ significantly in their views of the substance of this disclosure. I do note, however, that there is a divergence between examiner and applicant on the significance of this disclosure, (see my analysis under step 4 below).

17 *Skory* discloses what is reported to be the first example of the expression of a fungal (*Rhizopus oryzae*) LDH enzyme in yeast (*S. cerevisiae*). Both lactic acid and ethanol are produced during the fermentation of defined culture media, however when read as a whole, this disclosure is very clear that the aim is to use yeasts to produce industrial quantities of lactic acid, preferably whilst minimising the amounts of ethanol produced by deliberately disrupting the endogenous alcohol dehydrogenase genes. The disclosure does not concern the brewing of alcoholic beverages. The clear distinction between *Skory* and the claimed invention is the motivation in producing the recombinant *S. cerevisiae* strain, the generation of a strain that produces both lactic acid and ethanol representing an only intermediate step in the establishment of yeasts for the production of lactic acid.

Step (4): Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

18 The examiner has asserted that when reading *Dequin & Barre*, the skilled person would realise that the disclosed *S. cerevisiae* strain might also be used to produce sour beer. Countering this argument, the applicant asserts that *Dequin & Barre* does not disclose anything about baking beyond the inferred hypothetical use of the yeast strain in place of a combination of conventional baker's yeast and a lactic acid bacterium. The applicant goes on to assert that there is no reasonable expectation of success of transferring that principle to the brewing of sour beer.

19 In seeking to answer step (4) of the Windsurfing /Pozzoli test, I am reminded of the importance of the avoidance of hindsight or *ex post* facto analysis when assessing inventive step. In *Windsurfing*[1], the Court of Appeal held that the question of obviousness:

> "*has to be answered, not by looking with the benefit of hindsight at what is known now and what was known at the priority date and asking whether the former flows naturally and obviously from the latter, but by hypothesizing what would have been obvious at the priority date to a person skilled in the art to which the patent in suit relates".*

20 I would further observe that whilst much of the argument between the examiner and the agent during the prosecution of this application has concerned the balance between what is "obvious to try" and its counter argument "only when there is a fair expectation of success", that is just one consideration to be made when assessing the key question of "is it obvious?". This point was made by the UK Supreme Court in *Actavis v Icos*[3] where Lord Hodge (quoting from Novartis v Generics[4]) at paragraph 66 stated:

> "*First, it is relevant to consider whether at the priority date something was "obvious to try", in other words whether it was obvious to undertake a specific piece of research which had a reasonable or fair prospect of success: Conor v Angiotech (above) para 42 per Lord Hoffmann; MedImmune Ltd v Novartis Pharmaceuticals UK Ltd [2012] EWCA Civ 1234; [2013] RPC 27, paras 90 and 91 per Kitchin LJ. In many cases the consideration that there is a likelihood of success which is sufficient to warrant an actual trial is an important pointer to obviousness. But as Kitchin LJ said in Novartis AG v Generics (UK) Ltd [2012] EWCA Civ 1623, para 55, there is no requirement that it is manifest that a test ought to work; that would impose a straitjacket which would preclude a finding of obviousness in a case where the results of an entirely routine test are unpredictable. As Birss J observed in this case (para 276), some experiments which are undertaken without any particular expectation as to result are obvious. The relevance of the "obvious to try" consideration and its weight when balanced*

[3] *Actavis Group PTC EHF & Ors v ICOS Corporation & Anor [2019] UKSC 15.*

[4] *Novartis AG v Generics (UK) Ltd [2012] EWCA Civ 1623*

against other relevant considerations depend on the particular facts of the case."

21 Returning now to the question at hand, would the unimaginative skilled person having the agreed common general knowledge (CGK) and considering the disclosure of *Dequin & Barre* with that of *Skory* find that the production of sour beer using a recombinant *Saccharomyces* yeast that expresses the LDH enzyme from the fungus *Rhizopus oryzae* and simultaneously produces ethanol is obvious? Whilst I note that the production of wine and cider is discussed by *Dequin & Barre*, this document does not, in my view, teach the skilled person to brew sour beer. As such, I find that I do not agree with the examiner as to the significance of this disclosure when seen through the eyes of the unimaginative skilled worker. Without the benefit of hindsight, I do not agree that the skilled worker is taught to use a recombinant *Saccharomyces* yeast which expresses LDH in the brewing of sour beers. On this basis alone, the inventive step must be acknowledged.

22 Further, I also consider that even if the examiner's view of the significance to the skilled person of the teaching of *Dequin & Barre* had prevailed, *Skory* teaches away from the claimed invention. The skilled person would understand that the disclosure in *Skory* teaches a recombinant *S. cerevisiae* strain that synthesises lactic acid and preferentially synthesises little or no ethanol. The objective is to maximise the amount of lactic acid. Indeed, *Skory* notes that in *Dequin & Barre* the bacterial LDH (from Lactobacillus casei) was only able to convert 20% of the utilised glucose to lactic acid during fermentation while the majority of the fermentation product was ethanol (see column 2, p 22, final paragraph). In *Skory* the use of fungal LDH over bacterial LDH in the recombinant *S. cerevisiae* strain was explored to see if the lactic acid production could be made more efficient.

23 On balance, I do not think that *Skory* would suggest that such a strain could be used to deliver both ethanol and lactic acid at the same time because the motivation in Skory is to produce lactic acid on an industrial scale, not to brew beer. In my view, without prior knowledge of the invention, the skilled person would not realise that the yeast transformed with *Rhizopus oryzae* LDH, as disclosed in *Skory*, could be used to make sour beer

24 Overall, the combined teachings of *Skory* with *Dequin & Barre*, viewed by the unimaginative skilled person, having the agreed common general knowledge, do not render claim 1 obvious to the skilled person.

Other matters

25 I note that paragraph 13 of the examination report dated 19 April 2023 alludes to a potential conflict and/or support issue relating to the parent application. Although the exact nature of this observation is not altogether clear to me, I am satisfied that the invention has support (see figure 11) and that the claims, as amended and currently on file, which relate to a process, do not conflict with those of the granted parent patent directed to a recombinant yeast *per se*.

Conclusion

26 Taking all of the above into account, I consider that patent application GB2206573.4, in the name of Danstar Ferment AG, is inventive over the cited prior art and that, as a result, when the section 20 compliance period expired on 14 April 2023, this application complied with the requirements of the Act and Rules.

27 As a consequence, and as no further matters were outstanding, this application is remitted to the examiner for completion of the necessary steps to grant this patent.

Appeal

28 Any appeal must be lodged within 28 days after the date of this decision.

Dr L Cullen
Deputy Director, acting for the Comptroller