

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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*Ex parte* KAI-UWE BALDENIUS, CHRISTINE BECK, HANS-PETER  
HARZ, MARKUS LOHSCHIEDT, and DANIELA KLEIN

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Appeal 2007-2604  
Application 10/468,609  
Technology Center 1600

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Decided: January 15, 2008

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Before DONALD E. ADAMS, DEMETRA J. MILLS, and NANCY J.  
LINCK, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1 and 5-19, which are all the claims pending in the application.

The Examiner recognizes that this Appeal is related to Application 10/468,562, Appeal 2006-3250. According to the Examiner, the subject matter of Appeal 2006-3250 "is very similar to the instant claimed

invention, as each application claims a method of producing D-pantothenate salts by fermenting a bacterium of the family Bacillaceae. The difference is the purification method in each application - cation exchange in the instant application vs. anion exchange in the copending application” (Answer 2). On January 26, 2007, a Decision on Appeal 2006-3250 was entered into the record of Application 10/468,562 reversing the rejection of record.

Claim 1 is illustrative of the subject matter on appeal and is reproduced below:

1. A process for preparing D-pantothenic- acid and/or salts thereof which comprises
  - a) fermenting at least one bacterium from the Bacillaceae family which produces D-pantothenic acid and in which the biosynthesis of pantothenic acid (pan) and/or isoleucine/valine (ilv) is deregulated and which forms at least 2 g/l of salts of D-pantothenic acid by fermentation in a culture medium, wherein no free  $\beta$ -alanine and/or  $\beta$ -alanine salt is fed to the culture medium,
  - b) passing the D-pantothenate-containing fermentation solution through a cation exchanger, free D-pantothenic acid being formed from the salts of D-pantothenic acid,
  - c) adding a calcium base and/or magnesium base to set the free D-pantothenic acid-containing solution to a pH of 3-10, a solution or suspension being obtained which contains calcium and/or magnesium pantothenate and
  - d) subjecting the calcium pantothenate- and/or magnesium pantothenate-containing solution to drying and/or formulation.



drawbacks associated with the art recognized methods for chemically synthesizing D-pantothenic acid (Hikichi, col. 1, l. 62 - col. 2, l. 19).

In contrast to the chemical synthesis methods, the production of D-pantothenic acid biologically, through the fermentation of microorganisms, provides for the direct production of the D-pantothenic acid thereby avoiding the additional resolution steps required by chemical synthesis methods (*see e.g.*, Binder, col. 1, ll. 30-33; *see also* Hikichi, col. 3, ll. 8-14). Nevertheless, while Appellants recognize that a number of fermentation processes are known in the art for preparing D-pantothenic acid, Appellants point out that these processes suffer from a number of disadvantages, such as low D-pantothenate yield or the requirement for the addition of  $\beta$ -alanine (Specification 1-3)<sup>1</sup>. Therefore, Appellants disclose that “[i]t is an object of the present invention to provide an . . . improved process for preparing D-pantothenic acid and/or salts thereof which does not have the abovementioned disadvantages. For economical reasons, a process is desirable here in which supplying  $\beta$ -alanine is greatly decreased or is not required at all” (Specification 3).

Accordingly, Appellants’ claimed invention is directed to a process for preparing D-pantothenic acid and/or salts thereof. The process set forth in claim 1 comprises four required steps.<sup>2</sup> The first step requires that at least

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<sup>1</sup> While Appellants’ Specification does not discuss Hikichi or Binder, both of these patents disclose the fermentation of a microorganism to produce D-pantothenate. We note, however, that both of these patents require the addition of  $\beta$ -alanine (*see* Hikichi, col. 2, ll. 20-24; Binder, col. 8, ll. 32-34).

<sup>2</sup> All of the remaining claims before us on appeal ultimately depend from claim 1.

one bacterium is fermented to form at least 2 g/l of salts of D-pantothenic acid in a culture medium to which no free  $\beta$ -alanine and/or  $\beta$ -alanine salt is added. This step places three requirements on the bacterium: (1) the bacterium must be from the Bacillaceae family; (2) the bacterium must produce D-pantothenic acid; and (3) the bacterium is modified so that the biosynthesis of pantothenic acid (pan) and/or isoleucine/valine (ilv) is deregulated. According to Appellants' Specification, "[t]he word 'deregulation', for the purposes of the present invention, means changing or modifying at least one gene which codes for one enzyme in a biosynthetic metabolic pathway, so that the activity of the enzyme is changed or modified in the microorganism" (Specification 7). Included among the various modifications contemplated by Appellants' disclosure is deregulating the biosynthesis of pantothenic acid (pan) and/or isoleucine/valine (ilv) by "increasing the number of copies of the gene in the genome or by introducing a varying number of copies of plasmids" (Specification, page 8).

The second step of Appellants' process requires that the D-pantothenate-containing fermentation solution be passed through a cation exchanger, whereby free D-pantothenic acid is formed from the salts of D-pantothenic acid.

The third step of Appellants' process requires that a calcium and/or magnesium base be added to the D-pantothenic acid-containing solution to set the solution to a pH of 3-10, thereby obtaining a solution or suspension which contains calcium and/or magnesium pantothenate.

The final step in Appellants' process requires that the calcium and/or magnesium pantothenate-containing solutions is dried and/or formulated.

According to the Examiner, the process outlined above, would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made in view of the combination of Hikichi, Baigori, and Binder (Answer 3-7).

It is clear from Appellants' Specification that a number of microorganisms are capable of producing D-pantothenic acid (Specification 5-6; *see also* Hikichi col. 3, ll. 39-50; Baigori 4240; and Binder, col. 1, ll. 34-43). Figure 1 of Baigori outlines the metabolic pathway for the production of D-pantothenate in *E. coli* and *S. typhimurium* (Baigori 4241: FIG. 1)<sup>3</sup>. In addition, Baigori teach a number of genes involved in the synthesis of D-pantothenate, which include *pan B*, *pan C*, *pan D*, and *pan E* (*id.*; *see also* Hikichi, col. 7, ll. 27-31).

According to the Examiner, Hikichi discloses a fermentation method for producing D-pantothenic acid or calcium D-pantothenate (Answer 3). In this regard, the Examiner finds that Hikichi discloses a method wherein *E. coli* are cultured in the presence of  $\beta$ -alanine, then passing the culture medium over a cation exchange column and neutralizing the resulting solution with  $\text{Ca}(\text{OH})_2$  (Answer 3-4). The Examiner finds that Hikichi teaches that “[t]o improve purity and yield, calcium chloride may [be] added to this solution to produce high purity calcium D-pantothenate . . . which may be dried” (Answer 4).

The Examiner recognizes, however, that Hikichi differs from Appellants' claimed invention by not disclosing, *inter alia*,

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<sup>3</sup> Baigori also teaches that *S. typhimurium* is capable of reducing ketopantoate to pantoate by both ketopantoate reductase (the product of the *pan E* gene) and acetohydroxy acid isomerase (the product of the *ilvC* gene) (Baigori 4241: col. 1 - col. 2, bridging paragraph).

1. the use of an organism of the Bacillaceae family (e.g., *Bacillus subtilis*); or
2. the use of a culture medium that does not contain  $\beta$ -alanine (*id.*).

To make up for these deficiencies in Hikichi, the Examiner relies on Baigori to teach that *Bacillus subtilis* “produces its own  $\beta$ -alanine from aspartic acid” and that D-pantothenic acid can be produced by culturing *Bacillus subtilis* in the absence of  $\beta$ -alanine (*id.*). The Examiner, however, fails to appreciate that Baigori also teaches that *E. coli*, the bacteria used by Hikichi, also produces its own  $\beta$ -alanine from aspartic acid (Baigori 4241: FIG. 1). Further, while *E. coli* produces its own  $\beta$ -alanine, Hikichi requires that the culture medium be supplemented with  $\beta$ -alanine in order to produce large quantities of D-pantothenic acid (Hikichi, col. 2, ll. 20-24 and col. 3, ll. 58-61).

Nevertheless, the Examiner reasons that since both *E. coli* and *Bacillus subtilis* produce D-pantothenic acid, a person of ordinary skill in the art at the time the invention was made would have found it prima facie obvious to substitute *Bacillus subtilis*, for *E. coli* in the method taught by Hikichi (Answer, page 4). According to the Examiner a person of ordinary skill in the art would have been motivated to make this substitution to avoid adding  $\beta$ -alanine to the culture medium (Answer 5). We disagree.

Even if a person of ordinary skill in the art would have been modified Hikichi’s method by substituting *Bacillus subtilis* for *E. coli*, there is no suggestion in either reference that one would obtain at least 2 g/l of salts of D-pantothenic acid without supplementing the fermentation media with additional  $\beta$ -alanine. The Examiner admits as much by recognizing that “one of ordinary skill in the art would not have known in advance exactly

how much pantothenic acid would have been produced in a recombinant fermentation with *B. subtilis* as a host cell in which no  $\beta$ -alanine is added” (Answer 5-6). While it is true that both organisms produce their own  $\beta$ -alanine, as discussed above, Hikichi requires that the culture medium be supplemented with  $\beta$ -alanine in order to produce large quantities of D-pantothenic acid. Accordingly, we disagree with the Examiner’s assertion that due to the similarities between *E. coli* and *B. subtilis* with respect to D-pantothenic acid synthesis, the skilled artisan would have expected to have produced at least 2 g/L (Answer 6). The Examiner provides no evidentiary basis to support this assertion.<sup>4</sup>

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<sup>4</sup> As the Examiner recognizes Hikichi “did not measure the amount of pantothenic acid produced by their bacteria in a medium containing no  $\beta$ -alanine” (Answer 12). Therefore it is unclear from this record why a person of ordinary skill in the art would have expected to produce at least 2 g/l of D-pantothenic acid by culturing *B. subtilis* in a medium lacking  $\beta$ -alanine as the Examiner suggests. While the Examiner’s asserts that Hikichi did measure the amount of pantoic acid produced by bacteria in a medium containing no  $\beta$ -alanine (*id.*), the Examiner provides no evidence to suggest that there is a relevant (e.g., 1:1) relationship between the amount of pantoic acid and the amount of D-pantothenic acid produced by the bacteria in the absence of a culture medium supplemented with  $\beta$ -alanine. Contrary to the Examiner’s intimation, the evidence on this record teaches that in order to produce D-pantothenic acid the bacteria must be fermented in a culture medium containing  $\beta$ -alanine (*see* Hikichi, col. 3, ll. 58-61 and col. 13-14, examples 3 and 4; and Binder, col. 8, ll. 32-34).

We recognize the Examiner's assertion that since Baigori teaches the genes involved in the biosynthetic pathway of D-pantothenic acid<sup>5</sup>, "one of ordinary skill in the art would have known how to manipulate the expression of these genes to substantially increase the production of pantothenic acid, because such genetic manipulation was used in many other cases to increase the expression of genes" (Answer, page 5). We agree that a person of ordinary skill in the art would have appreciated that the genes involved in biosynthesis of D-pantothenic acid could have been manipulated.

In this regard, we recognize that Hikichi discloses a method for the production of D-pantothenic acid "wherein said microbe is a microbe transformed with a plasmid DNA carrying the region of a gene involved in biosynthesis of pantothenic acid . . . or a part of the region" (Hikichi, col. 2, l. 66 - col. 3, l. 3). Stated differently, Hikichi teaches the use of a bacteria wherein the biosynthetic pathway of pantothenic acid is deregulated by introducing a varying number of copies of plasmids (*Cf.* Specification 7-8: bridging paragraph).

In particular Hikichi discloses that "[t]he gene involved in the pantothenic acid biosynthesis mentioned herein is the panB, panC or panD gene, corresponding to the enzymes ketopantoate hydroxymethyltransferase, pantothenate synthetase and aspartate- $\alpha$ -decarboxylase, respectively" (Hikichi, col. 7, ll. 27-31). We note, however, that while Hikichi discloses the "deregulation" of one or more of the genes involved in the biosynthetic

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<sup>5</sup> We recognize the Examiner's reliance on Sorokin to teach the sequences of the *B. subtilis* genes involved in the synthesis of pantothenic acid (Answer 10-11). According to the Examiner, Sorokin confirms "the teaching of Baigori et al. that *B. subtilis* and *E. coli* share a common pantothenic acid synthesis pathway" (Answer 11).

pathway of D-pantothenic acid, Hikichi still requires that the organism be grown in a medium that contains  $\beta$ -alanine in order to obtain large amounts of D-pantothenic acid (*see e.g.*, Hikichi, col. 3, ll. 58-61 and col. 13-14, examples 3 and 4).

Therefore, we agree with the Examiner that a person of ordinary skill in the art could not have predicted, from the combination of Hikichi and Baigori, “exactly how much pantothenic acid would have been produced” by culturing a microorganism modified to contain a gene or genes involved in the involved in the biosynthesis of pantothenic acid in the absence of  $\beta$ -alanine (Answer 5-6). Accordingly, we disagree with the Examiner that due to the similarities between *E. coli* and *B. subtilis* with respect to D-pantothenic acid synthesis, the skilled artisan would have expected to have produced at least 2 g/L by fermenting *B. subtilis* in the absence of  $\beta$ -alanine (Answer 6). We find no evidence on this record to support this assertion. To the contrary, the evidence on this record teaches the addition of  $\beta$ -alanine to the culture medium is required. In this regard, we note that the United States Supreme Court recently stated that the analysis under 35 U.S.C. § 103 “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). However, in emphasizing this flexible approach to the obviousness analysis, the Court also reaffirmed the principle that claims would likely be unobvious when “when the prior art teaches away” from their practice. *Id.* at 1740.

As for Binder, the Examiner finds that Binder discloses that in a method of producing D-pantothenic acid from bacteria or yeast, the calcium

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or magnesium salts of D-pantothenate are produced at the end of the culture phase by adjusting the pH “by adding a solution or suspension of an alkaline earth-containing compound, such as  $\text{Ca}(\text{OH})_2$  or  $\text{Mg}(\text{OH})_2$ , . . . at a concentration of 5-50 wt. %” (Answer 6). Binder, however, fails to make up for the deficiencies in the combination of Hikichi and Baigori. On the contrary, Binder complements Hikichi by disclosing a method of producing D-pantothenic acid by fermenting the bacteria in the presence of  $\beta$ -alanine (Binder, col. 8, ll. 32-34).

For the foregoing reasons we reverse the rejection of claims 1 and 5-19 under 35 U.S.C. § 103 as being unpatentable over the combination of Hikichi, Baigori, and Binder.

#### CONCLUSION

In summary, we reverse the rejection of record.

REVERSED

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