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Datasheet for the decision of 8 August 2017

Case Number: T 1175/14 - 3.3.10

Application Number: 11179276.8

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Language of the proceedings: EN

Title of invention:
A reduced coenzyme Q10 crystal

Applicant:
KANEKA CORPORATION

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no) - obvious product not rendered inventive by process for its preparation

Decisions cited:
T 0595/90, T 0939/92, T 0990/96

Catchword:

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Case Number: T 1175/14 - 3.3.10

D E C I S I O N
of Technical Board of Appeal 3.3.10
of 8 August 2017

Appellant: (Applicant)	KANEKA CORPORATION 2-3-18, Nakanoshima, Kita-ku Osaka (JP)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 20 December 2013 refusing European patent application No. 11179276.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	P. Gryczka
Members:	J. Mercey
	F. Blumer

Summary of Facts and Submissions

I. The appeal lies from the decision of the Examining Division refusing European patent application No. 11 179 276.8.

II. Claim 1 of the main request underlying the decision under appeal reads as follows:

"A reduced coenzyme Q_{10} crystal with a reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} weight ratio of not lower than 96/4."

Claim 1 of auxiliary request 2 underlying the decision under appeal differs from claim 1 of the main request only in that the weight ratio of reduced coenzyme Q_{10}/ oxidized coenzyme Q_{10} in the crystal was not lower than 98/2.

III. *Inter alia* the following documents were cited in the examination proceedings:

(1) GB-A-947 643 and
(10) EP-A-956 854.

IV. In the decision under appeal, the Examining Division found *inter alia* that the subject-matter of claim 1 of the then pending main request and of auxiliary request 2 was not novel over document (1), said document disclosing in Example II a crystal of coenzyme Q_{10} and its manufacture, such that said low molecular weight chemical compound was available to the public in all levels of purity, the Examining Division citing decision T 990/96 (OJ EPO 1998, 489) in this respect.

V. With letter dated 29 April 2014, the Appellant submitted a main request and auxiliary requests 1 to 3, the main request and auxiliary request 1 corresponding to the main request and auxiliary request 2, respectively, on which the contested decision was based. During the oral proceedings before the Board held on 8 August 2017, the Appellant withdrew auxiliary requests 2 and 3.

VI. In a communication dated 12 April 2017, the Board indicated *inter alia* that the subject-matter of both the main and auxiliary request 1 would not appear to be inventive, document (10) already teaching that the reduced form of coenzyme Q_{10} had a higher bioavailability than the oxidised form, such that providing a crystal with a higher proportion of the reduced form appeared to be an obvious way of increasing the bioavailability of the end product. Furthermore, the inventiveness of the claimed subject-matter could not lie in the fact that the prior art had not been able to provide such a crystal, since said crystal could have been prepared by conventional crystallisation methods which were within the common general knowledge of those skilled in the art.

VII. The Appellant argued that the subject-matter of both requests was novel, and with letter dated 8 July 2017, submitted an experimental test report repeating Example II of document (1), which showed that a product falling within the present claims was not produced by the method disclosed therein.

With regard to inventive step, the Appellant submitted that the mixture of reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} having a weight ratio of 95/5 of Sample 1 of document (10) represented the closest prior art. The

problem to be solved was the provision of a coenzyme Q_{10} product with a higher level of oral bioavailability which could also be manufactured conveniently and efficiently. Document (10) itself taught away from using higher amounts of reduced coenzyme Q_{10} in the mixture. Furthermore, neither document (10), nor any other prior art, taught how to obtain crystals of coenzyme Q_{10} with a reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} weight ratio of higher than 95/5. Indeed the crystallisation of reduced coenzyme Q_{10} described in Example II of document (1) resulted in crystals of reduced coenzyme Q_{10} crystal having a reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} weight ratio of only 95.2 to 4.8. The claimed subject-matter was thus inventive.

VIII. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or auxiliary request 1, both requests filed with letter dated 29 April 2014.

IX. At the end of the oral proceedings, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. Novelty

In the decision under appeal, the Examining Division held that the subject-matter claimed was not novel over document (1) (see point IV above). In view of the negative conclusion in respect of lack of inventive step as set out below, a decision of the Board on the issue of novelty is unnecessary.

3. Inventive step

3.1 The application in suit is directed to a reduced coenzyme Q_{10} crystal with a high level of oral absorbability (see page 1, lines 7 to 10 of the description).

3.2 The Board considers, in agreement with the Appellant, that the disclosure of document (10) is the closest prior art, since it also addresses the problem of providing a reduced form of coenzyme Q_{10} with enhanced absorption after oral administration (see page 3, lines 5 to 6). More particularly, document (10) discloses in Sample 1 (see page 5, line 15) a mixture of reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} having a weight ratio of 95/5.

3.3 In view of this state of the art, the Appellant submitted that the problem underlying the present application was the provision of a coenzyme Q_{10} product

with a higher level of oral bioavailability which could also be manufactured conveniently and efficiently.

3.4 As the solution to this problem, claim 1 of the main request proposes a reduced coenzyme Q_{10} crystal with a reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} weight ratio of not lower than 96/4.

3.5 The Board holds that it is plausible that the technical problem as defined above in point 3.3 has been solved, since document (10) itself teaches that reduced coenzyme Q_{10} has a considerably higher bioavailability than the oxidized form (see page 3, lines 8 to 11).

3.6 It remains to be decided whether or not the proposed solution to the problem underlying the present application is obvious in view of the cited prior art.

3.6.1 The skilled person looking to improve the bioavailability of a coenzyme Q_{10} product knows from document (10) that the higher the ratio of reduced coenzyme Q_{10} to oxidized coenzyme Q_{10}, the higher the bioavailability of the composition (see page 3, lines 7 to 11 and 55 to 57, page 6, lines 25 to 41 and Fig. 2). In particular, Fig. 2 shows that on orally administering mixtures of oxidized coenzyme Q_{10} to reduced coenzyme Q_{10} having weight ratios varying from 100:0 to 5:95, the total plasma coenzyme Q_{10} concentration continuously increases with increased proportion of reduced coenzyme Q_{10}. The Board thus holds that it was obvious for the skilled person, seeking to provide a composition having even better bioavailability, to increase the amount of reduced coenzyme Q_{10} in the mixture even further, such that no inventiveness can be seen in increasing the weight

ratio of reduced reduced coenzyme Q_{10} to oxidized coenzyme Q_{10} from 95:5 to at least 96:4.

3.7 The Appellant submitted that starting from document (10), the skilled person had no motivation to increase the weight ratio of reduced coenzyme Q_{10} to oxidized coenzyme Q_{10}, since document (10) (see page 4, lines 20 to 22) taught that this would result in the production process being complicated and the cost of production increased. These negative effects of complication and cost would offset any gains in the bioavailability, such that the skilled person would not have attempted such a step. On the contrary, although document (10) did indeed show a trend of higher bioavailability with increased ratio of reduced coenzyme Q_{10} to oxidized coenzyme Q_{10} in the mixture, the authors thereof did not go beyond a ratio of 95:5 and in fact actively added reduced coenzyme Q_{10} to oxidized coenzyme Q_{10}, in order to reduce said ratio (see page 4, lines 9 to 13) and chose a ratio of 85:15 for the formulation of the "main medicine" therein (see page 6, lines 42 to 44).

However, although additional costs resulting from the manufacture of mixtures with a higher ratio of reduced coenzyme Q_{10} to oxidized coenzyme Q_{10} may play a role in relation to economic considerations, this cannot amount to a technical prejudice against the application of the teaching of document (10) to increase this ratio and thereby the bioavailability of the product. That the authors of document (10) chose a ratio of 85:15 for the formulation of the "main medicine" does not teach away from providing a higher ratio, since commercial reasons may have played a role in their choice.

3.7.1 The Appellant submitted that increasing the ratio of reduced coenzyme Q_{10} to oxidized coenzyme Q_{10} was only

one of many possible alternatives that the skilled person had at his disposition when seeking to improve the bioavailability of the composition of Sample 1 of document (10), other cited documents on file teaching, for example, derivatisation of coenzyme Q_{10} to achieve this aim.

However, a mere arbitrary choice from a host of possible solutions does not in itself involve inventive ingenuity (see e.g. T 939/92, OJ EPO 1996, 309, points 2.5.2 and 2.5.3 of the reasons). For this reason, this argument is rejected.

3.8 The Appellant argued further that the claimed product was inventive because at the priority date of the present application there was no known method in the art to make it.

3.8.1 The Board acknowledges that there are indeed situations in which a product which can be envisaged as such together with its properties in use, may become nevertheless non-obvious and claimable as such if there was no known way or applicable (analogy) method in the art for making it and the method for its preparation was therefore the first to achieve this and do so in an inventive manner (see T 595/90, OJ EPO 1994, 695, last paragraph of point 5 of the reasons).

3.8.2 However, in the present case, document (10) teaches (see page 3, line 58) that there is no particular limitation on the technology for providing the reduced form of coenzyme Q_{10}, the Appellant conceding at the oral proceedings before the Board that by the methods disclosed therein, a solution of reduced coenzyme Q_{10} containing no oxidised coenzyme Q_{10} could be prepared. Thus, document (10) teaches that reduced coenzyme Q_{10}

may be prepared by harvesting a coenzyme Q_{10} from a synthetic reaction mixture, a fermentation broth, or a natural source by procedures known in the art and subjecting it to chromatography to separate and concentrate the reduced form of coenzyme Q_{10} fraction, and where necessary, followed by the procedure of adding a conventional reducing agent such as sodium borohydride or sodium dithionite to the above coenzyme Q_{10} to reduce the oxidized form of coenzyme Q_{10} fraction of said coenzyme Q_{10} and, then, concentrating the reduced Q_{10} by chromatography. As a further alternative, the reduced form of coenzyme Q_{10} can be obtained by permitting said reducing agent to act on the available high-purity coenzyme Q_{10} (see page 4, lines 1 to 7). The skilled person thus knew from document (10) how to prepare a solution of reduced coenzyme Q_{10} comprising virtually no oxidised coenzyme Q_{10}.

3.8.3 The skilled person would also know how to prepare a crystal of reduced reduced coenzyme Q_{10} from such a solution of reduced coenzyme Q_{10}, crystallisation methods belonging to their common general knowledge. Indeed, the application in suit itself (see page 23, lines 26 to 31) states that the method of crystallisation is not particularly restricted, it being possible to utilise "a conventional crystallization method". More particularly, the crystallisation methods used in the application in suit to achieve ratios of reduced coenzyme Q_{10} to oxidized coenzyme Q_{10} of greater than 99:1 (see Exs. 1 and 6 to 14) consist of cooling a solution comprising reduced coenzyme Q_{10} and oxidized coenzyme Q_{10}, filtering the slurry obtained under reduced pressure, washing the crystals obtained, and then drying under reduced pressure, said steps being standard for the skilled

person. Furthermore, the crystallisation solvents used in the aforementioned Examples are usual crystallisation solvents, namely heptane, hexane, ethyl acetate, acetonitrile, sometimes with methanol as an auxiliary solvent, the Appellant submitting at the oral proceedings before the Board that the presence or absence of air did not greatly affect the ratio of reduced coenzyme Q_{10} to oxidized coenzyme Q_{10} obtained, citing Example 12 of the application in suit in this respect.

3.8.4 Alternatively, the skilled person could start from the mixture of reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} having a weight ratio of 95/5 disclosed in sample 1 of document (1) and recrystallise it in order to increase the proportion of reduced form therein.

3.8.5 Thus, the Board holds that there were known ways in the art for making a crystal of reduced coenzyme Q_{10}/ oxidized coenzyme Q_{10} having a weight ratio not lower than 96/4, such that the inventiveness of this product cannot be attained *via* its method of preparation.

3.9 The Appellant argued that the fact that the various samples for which the plasma concentration levels were given in Fig. 2 of document (10) differed from each other by the same incremental step, apart from the final sample, which had a ratio of 95:5 and not 100:0, suggested that a higher ratio was not previously achievable. The special crystallisation methods disclosed in the application in suit required very particular solvents not disclosed in the art for the crystallisation of reduced reduced coenzyme Q_{10}.

3.9.1 However, although document (10) teaches that if the proportion of the reduced form of coenzyme Q_{10} is too

large, the production process will be complicated and the cost of production increased, it does not teach that it is not **possible** to achieve a reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} ratio higher than 95:5. With regard to the choice of solvent for the crystallisation, as indicated in point 3.8.3 above, these are not unusual solvents, a reasonable amount of trial and error being part of the standard practice of the skilled person when searching for suitable solvents for crystallising a particular compound. And as indicated in point 3.8.3 above, each step of the crystallisation process, including work up, described in the application in suit, and the combination of these steps, was not "special" but rather entirely conventional.

3.9.2 In this respect, the Board agrees with the decision T 990/96 insofar as it states that most low molecular weight compounds may be manufactured in all grades of purity by conventional purification methods within the common general knowledge of those skilled in the art, such as recrystallisation (see point 7 of the reasons). It also agrees with this decision insofar as this general rule is no longer applicable in **exceptional situations** where it was proved on the balance of probability that all prior attempts to achieve a particular degree of purity by conventional purification processes had failed, and that the burden of proving the existence of such an extraordinary situation lies with the party alleging its existence (see point 8 of the reasons).

3.9.3 In the present case, the Board is not satisfied that the Appellant has discharged this burden.

3.9.4 In this connection, the Appellant argued that there was evidence that a crystal having a reduced coenzyme Q_{10} to oxidized coenzyme Q_{10} weight ratio of at least 96:4 could not previously be obtained, since a prior art crystallisation of reduced coenzyme Q_{10} which apparently resulted in "pure" reduced coenzyme Q_{10}, namely the hydroquinone of coenzyme Q_{10} (III) of Example II of document (1) having a m.p. of 47°C, in fact resulted in a crystal with a reduced coenzyme Q_{10}/ oxidized coenzyme Q_{10} weight ratio of only 95.2 to 4.8. The Appellant supported this argumentation with an experimental test report submitted with letter dated 8 July 2017 wherein Example II of document (1) was repeated with a necessary variation in order to produce reduced coenzyme Q_{10} at all, and the product was crystallised in air using the solvent mixture taught by document (1), namely petroleum ether and methanol, and the ratio of reduced reduced coenzyme Q_{10} to oxidized coenzyme Q_{10} was determined by HPLC.

3.9.5 However, firstly, a single "failure" is not sufficient to justify the exceptional situation referred to in decision T 990/96, but rather the Appellant would have had to show that the successful crystallisation methods represent a very small island amongst a large number of conventional methods that did not succeed.

3.9.6 Furthermore, Example II of document (1) is not concerned with providing reduced coenzyme Q_{10} comprising as little oxidised coenzyme Q_{10} as possible, but rather with providing reduced coenzyme Q_{10} (III) merely as an intermediate from which the desired end product chroman (II) is then prepared. Thus, said Example is not suitable for demonstrating that previous attempts to provide a crystal with a reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} weight ratio of not lower

than 96/4 had failed, this not even being the aim of the authors of document (1). In addition, should the skilled person, wishing to crystallise reduced coenzyme Q_{10}, have indeed looked to document (1) in order to seek guidance on how to perform the crystallisation, they would not have given up when the first solvent (mixture) they tested resulted in a crystal with a reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} weight ratio of only 95.2 to 4.8, said weight ratio already being extremely close to the desired weight ratio, but would have tried alternative solvents, solvents such as hexane and heptane disclosed in the application in suit as successfully resulting in ratios of greater than 99:1 being structurally very similar to petroleum ether, which is merely a mixture of short-chain aliphatic hydrocarbons.

Therefore, the Board concludes that the existence of an exceptional situation such as is mentioned in point 3.9.2 above has not been established. Consequently, it is thus considered that the principles set out in T 595/90 (see point 3.8.1 above), namely that "an otherwise obvious entity, may become nevertheless non-obvious and claimable as such, if there is no known way or applicable (analogy) method in the art to make it", do not apply to the present case, since it would appear that the claimed product could have been made by conventional methods, for example methods analogous to that described in document (1).

3.10 Therefore, in the Board's judgement, the subject-matter of claim 1 represents an obvious solution to the problem underlying the patent application. As a result, the Appellant's main request is not allowable as the subject-matter of claim 1 lacks an inventive step pursuant to Article 56 EPC.

Auxiliary request 1

4. Inventive step

4.1 The subject-matter of auxiliary request 1 differs from that of claim 1 of the main request only in that the weight ratio of reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} in the crystal was not lower than 98/2.

4.2 Said subject-matter is not inventive for the same reasons as the main request, since crystals comprising reduced coenzyme Q_{10} to oxidized coenzyme Q_{10} in a weight ratio of greater than 99:1 are obtained according to the application in suit by conventional crystallisation methods (see point 3.8.3 above), the Appellant not having provided any further arguments as to why a crystal having such a weight ratio could not have been obtained by the skilled person at the filing date of the present application.

4.3 The subject-matter of claim 1 of auxiliary request 1 is thus also not allowable for lack of inventive step pursuant to Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

C. Rodríguez Rodríguez P. Gryczka

Decision electronically authenticated