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Datasheet for the decision of 24 October 2013

Case Number: T 0451/10 - 3.3.03

Application Number: 99909309.9

Publication Number: 985697

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Language of the proceedings: EN

Title of invention:
OXIRANE DERIVATIVES AND PROCESS FOR PRODUCING THE SAME

Patent Proprietor:
NOF CORPORATION

Opponents:
DR REDDYS LABORATORIES (UK) LIMITED
KAO CHEMICALS GmbH
BASF Aktiengesellschaft
Olswang Nominees Limited
Clariant Produkte (Deutschland) GmbH

Headword:

Relevant legal provisions:
EPC Art. 54(2), 56

Keyword:
Novelty (yes) -
Polymer defined by degree of purity and additional parameter
Inventive step (no) -
additional parameter does not contribute to an inventive step

Decisions cited:
T 0803/01, T 0990/96, T 0100/00, T 0728/98

Catchword:

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Case Number: T 0451/10 - 3.3.03

D E C I S I O N
of Technical Board of Appeal 3.3.03
of 24 October 2013

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 22 December 2009 revoking European patent No. 985697 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman: B. ter Laan
Members: F. Rousseau
C. Vallet

Summary of Facts and Submissions

I. The appeal by the Patent Proprietor (Appellant) lies from the decision of the Opposition Division posted on 22 December 2009 revoking European patent No. 0 985 697 (application no. 99 909 309.9).

II. Claim 1 as granted read as follows:

"1. An oxirane derivative represented by the following general formula [1]:

$$RO(C_2H_4O)_n \quad [1]$$

wherein R is a C_{1-7} hydrocarbon group; and n is the average number of moles of oxirane groups ranging from 20 to 900 obtainable by reacting ROH and oxirane in a reaction system whose water content is not more than 5 ppm; the derivative satisfying the following requirements:

(A) supposing that the straight line between the elution starting point and the elution end point on chromatogram obtained by gel permeation chromatography is PbaseL, the total peak area above PbaseL is Parea, the height of the top of the maximum peak of refractive index: Ptop, with respect to PbaseL is PtopH, and the peak area between the point at which the height of the elution curve from the elution starting point toward Ptop, with respect to PbaseL is 1/5 of PtopH and the point at which the height of the elution curve from Ptop toward the elution end point, with respect to PbaseL is 1/5 of PtopH is PareaM, Parea and PareaM satisfy the following relationship:

$$PareaM / Parea \geq 0.85 \text{ and}$$

(B) when thin layer chromatography is effected by development with a 85:15 (by volume) mixture of chloroform and methanol, followed by colour development with iodine and measurement of the purity of various spots by a densitometer, main spots having Rf value falling within the range of from 0.2 to 0.8 have a purity of not less than 98%."

III. Five notices of opposition had been filed requesting revocation of the opposed patent in its entirety *inter alia* for lack of novelty and inventive step under Article 100(a) EPC. The impugned decision was based on a set of claims submitted as the main request with letter of 13 July 2007, claim 1 of which corresponded to claim 1 as granted, a set of claims submitted as first auxiliary request with letter of 18 September 2009 and a set of claims submitted as second auxiliary request with letter of 13 July 2007. The contested decision refers in particular to documents:

D0 Experimental Report submitted by Opponent with letter of 27 September 2007
D9 US-A-5 298 410
D14 PL-B1-178039 and partial translation thereof in English
D25 M. Leonard et al, Makromol. Chem., vol 189, pages 1809-1817, 1988,
D69 Experimental Report submitted by Opponents 3 with letter of 24 September 2009.

IV. According to the decision, the compounds of formula [1] defined in claim 1 of the main request were known by themselves. In claim 1 they were only defined by their degree of purity expressed in terms of the criteria (A) and (B), whereby the process feature of that claim "in

a reaction system defined to contain not more than 5 ppm water" did not have any limitative function. However, the skilled person using conventional purification methods such as derivatization (described in D9), chromatography (described in D14) and fractionation (described in D25) would have been able to provide the degree of purity defined in claim 1 for those compounds. The feasibility of achieving the claimed degree of purity by using a derivatization method as described in D9, or chromatography as employed in D14, was demonstrated by experimental reports D0 and D69, respectively. It was also considered that the combined use of gel permeation chromatography (GPC) and thin layer chromatography (TLC) would on the balance of probabilities provide compounds of formula [1] exhibiting the purity required by claim 1. As the compounds of claim 1 were defined by their purity only, the opposition division, following the principles enounced in decisions T 0803/01 and T 0990/96, concluded that claim 1 of the main request lacked novelty. Furthermore, the subject-matter of auxiliary requests 1 and 2 did not meet the requirements of Articles 83 and 84 EPC.

V. With the statement setting out the grounds of the appeal dated 27 April 2010, the Appellant submitted "Experimental Report VI" (D71), as well as two sets of claims as the main and a first auxiliary request.

VI. Claim 1 of the main request corresponds to claim 3 as granted, i.e. the subject-matter of claim 1 as granted in which the average number of moles of oxiranes groups in the formula $RO(C_2H_4O)_nH$[1] has been amended from 20 to 900 to 100 to 900.

VII. Claim 1 of the auxiliary request differs from claim 1 of the main request in that between conditions (A) and (B) the word "and" has been deleted and at the end additional requirements (defined in claims 4 and 5 as granted) have been inserted:

"(C) Parea and PareaH satisfy the relationships PareaH/ Parea ≤ 0.05 wherein PareaH is the peak area between the elution starting point on the chromatogram and the point at which the height of the elution curve toward Ptop from PbaseL is 1/5 of PtopH; and

(D) the number of moles of oxirane added PtopEOmol determined by the following equation:

$$PtopEOmol = (PtopMw - ROHMw)/44$$

supposing that the molecular weight corresponding to the top of the peak on chromatogram is PtopMw and the molecular weight of the compound ROH (in which R represents a C_{1-7} hydrocarbon group) to be used as a starting material is ROHMw, satisfies the following relationship with the ratio PMmw/mn of weight-average molecular weight to number-average molecular weight of the region represented by PareaM determined by gel permeation chromatography:

$PMmw/mn - [1 + PtopE0mol/(l + PtopEOmol)^2] \leq 0.02$"

VIII. With their rejoinders, Respondent/Opponent 1 and Respondent/Opponent 3 submitted *inter alia* the following documents:

D72: Vogel's Textbook Of Practical Organic Chemistry, Fifth Edition, 1991, pages 196—235,

D74: Experimental Report dated 1 September 2010 (submitted by respondent 1 with letter of 21 October 2010) and

D75: Experimental report dated 25 August 2010 (submitted by respondent 3 with letter of 15 November 2010).

IX. In preparation for the oral proceedings, the Board issued a communication in which it was indicated that the mere fact that a prior art described a compound of formula [I] was not sufficient to conclude that said compound was disclosed with any degree of purity. Rather, evidence was required that the context of that disclosure implied such a degree of purity. The communication also indicated that the Board concurred with the Opposition Division's view that the process feature "in a reaction system defined to contain not more than 5 ppm water" in claim 1 had not been shown to add any limiting feature to the product claimed.

X. With telefax of 23 October 2013 Respondents/Opponents 3 submitted a partial translation in English of D14, supplementing the partial translation thereof provided before the first instance.

XI. In the course of the oral proceedings before the Board which took place on 24 October 2013, the representative of the Appellant explained that he was not in the possession of the supplementary part of the translation of D14, but that he had his own translation thereof. No objections were raised against the use of the supplementary translation provided by Respondent III.

XII. The Appellant's arguments that are relevant for the present decision can be summarised as follows:

a) The subject-matter of claim 1 of the main request corresponded to the subject-matter of claim 3 as granted, claim 1 of auxiliary request 1 included

in addition the features of claims 4 and 5 as granted.

b) The object of the present invention was to provide a high purity, high molecular weight polyethylene glycol derivative (R-PEG-OH) having a narrow molecular weight distribution that was useful as an intermediate in the production of activated PEG derivatives for PEGylating pharmacological substances.

c) Prior to the present invention, no high molecular weight R-PEG-OH had been synthesised free from high molecular weight impurities (diol, the molecular weight of which was approximately double that of the target R-PEG-OH), low molecular weight impurities (vinyl ether formed by termination of the polymerisation which had a molecular weight lower than that of the target R-PEG-OH formed by termination of the polymerisation) and other impurities revealed by TLC, which also had a molecular weight distribution showing good approximation to a Poisson distribution.

d) It had not been shown that a "conventional" purification technique was capable of purifying an R-PEG-OH sample to an extent that it satisfied both conditions (A) and (B) according to present claim 1. In that regard, the term “conventional” meant “conventional in view of the concrete technical context concerned” (in accordance with decisions T 0100/00 of 7 March 2003 and T 0803/01 of 9 September 2003), i.e. in the present case in the context of purifying R-PEG-OH samples. With the purification techniques disclosed in D9 and D14 it was not possible to prepare R-PEG-OH having

a purity that satisfied both conditions (A) and (B).

e) The purification technique adopted in D69 was not a faithful reproduction of that according to D14, because the height of the column and the amount of filler were not described in D14. Moreover, in D69 a mixed solvent of a fixed, predetermined ratio was used as the eluent, whereas in D14 the eluent, starting from 100% dry chloroform, was gradually modified by the addition of methanol. Also in experimental report D74 which was based on "Flash Column Chromatography", a different technique was used from the one of D14 so that D74, too, was not a reproduction of the process of D14.

f) Experimental report D71 which did represent a faithful reproduction of the purification technique described in D14, showed that with that technique it was not possible to prepare R-PEG-OH having a purity satisfying both conditions (A) and (B) according to present claim 1.

g) Furthermore, the technique used in D14 did not separate components by their molecular weight. Since the molecular weight distribution of the commercial methyl-PEG-OH (MPEG) to be purified in Example II of D14 was unknown, no information could be obtained about the molecular weight distribution of the product purified in Example II of D14.

h) Hence, no evidence had been provided that condition (A) according to present claim 1 was met by the compound disclosed in Example II of D14. The burden of proof that the claimed derivative

was already known in the art rested with the Opponents. Consequently, novelty of the claimed subject-matter had to be acknowledged.

i) Having regard to inventive step, D14 constituted the closest prior art. The technical problem solved by the patent in suit was to provide a derivative in a purer form in order, for example, to obtain regulatory approval for the drugs manufactured with that derivative. As D14 already claimed to have obtained a highly pure derivative, D14 could not provide any incentive for further purification steps.

j) The Patent Proprietor had provided a product that was purer and hence more useful than any product of the prior art. The product now being claimed had a greater homogeneity and utility than that of D14. The claimed product had received regulatory approval which, to the Patent Proprietor's knowledge, no other product of the same formula had achieved. Hence, arriving at the subject-matter of claim 1 of the main request starting from D14 could only be achieved with hindsight. An inventive step should therefore be acknowledged.

k) The same arguments were valid for the inventive step of claim 1 of the auxiliary request.

XIII. The arguments of the Respondents that are relevant for the present decision can be summarised as follows:

a) Conditions (A) and (B) according to claim 1 of the main request as well as conditions (C) and (D) for the auxiliary request were artificial parameters that merely defined a degree of purity for the

claimed derivatives. The amount of water used in the process, which could not contribute to the definition of the derivative, was not to be considered for assessing patentability of the claimed derivative.

b) The purpose of the process described in D14 was to remove diols from the MPEG sample. This was successfully achieved by the method proposed in D14, as demonstrated in the same document by a TLC test and measurement of a degree of purity of 99%. In view of paragraph [0022] of the patent in suit stating that an oxirane derivative was homogeneous from the standpoint of polarity and molecular weight when high purity had been demonstrated by thin layer chromatography, it had to be concluded that condition (A) of claim 1 of the patent in suit was also fulfilled by the purified derivative of Example II of D14. In fact, the achievement of condition (B) in the particular case of D14 resulted in achieving condition (A), i.e. the TLC technique itself also provided a separation of the components by their molecular weight. In view of the statement in paragraph [0022] of the patent in suit, the burden of proof that the process of D14 allowed to meet condition (B) of present claim 1 without meeting at the same time condition (A) lay with the patent proprietors.

c) The desirability to prepare R-PEG-OH products as pure as possible was widely recognized as shown for example in D9 and D14. Various methods were known for the purification of impure R-PEG-OH products, for example, D9 (derivatisation), D14 (chromatography) and D25 (fractionation). Following T 0990/96 of 12 February 1998 , T 100/00

(loc. cit.) and T 0728/98 of 12 Mai 2000 the novelty of the known oxirane derivative according to formula [1] should be denied when the degree of purity defined by conditions (A) and (B) could be achieved by conventional techniques. Experimental reports D74 using thin layer chromatography (TLC) and D75 using column chromatography showed that with conventional chromatography techniques a known methyl-PEG-OH (MPEG) sample could be purified so as to meet those conditions. In particular, TLC of the compound obtained in Example II of D14 resulted in the claimed product, as demonstrated by D74. In fact, the product was separated as soon it was subjected to TLC. Therefore, even if one considered that the method disclosed in D14 did not result in a product meeting condition (A), it was possible to purify that product by gel permeation chromatography, so as to obtain a product the molecular distribution of which met condition (A). Thus, the claimed subject-matter lacked novelty over D14.

d) Contrary to the opinion of the Opposition Division, Example 4 of D9 employed a "methoxypolyethylene glycol" having an average molecular weight of 5000 daltons as starting material. A skilled person seeking to repeat that example would select a commercially available methoxypolyethylene glycol such as that sold by Sigma-Aldrich. Experimental report D0 demonstrated that such a material with a molecular weight of 5000 could be successfully purified by the method of D9 resulting in a material satisfying the claims of the patent. Therefore the procedure of Example 4 of D9, if repeated, produced the oxirane derivative now being claimed. On this basis,

Example 4 of D9 anticipated claim 1 of the main request.

e) Hence, novelty of the claimed derivatives should be denied.

f) Concerning inventive step, the problem addressed by the opposed patent was providing high molecular weight oxirane (R-PEG-OH) derivatives having a narrow molecular weight distribution and high purity, which were useful as starting materials for medical purposes. Reference D14 could be considered as the closest prior art, as it concerned the same oxirane compounds as starting materials for medical purposes and expressly recognised the difficulties caused by the presence of diol in the product.

g) Starting from D14 and in the absence of tests related to a pharmaceutical use of the claimed derivative or any indication that meeting condition (A) solved a specific technical problem, the problem solved by the claimed subject-matter could only be seen in providing a further R-PEG-OH derivative for pharmaceutical use.

h) GPC which was used in the opposed patent as an analytical technique for measuring condition (A), was also known as a preparative technique. Hence, should condition (A) not be fulfilled for the derivatives obtained in Example II of D14 - meaning that they contained derivatives having an inappropriate molecular weight - it was obvious for the skilled person to use conventional purification methods such as GPC. By collecting the middle fraction of the samples obtained by GPC

in order to provide a further derivative for pharmaceutical uses, the skilled person would have arrived at the presently claimed derivative.

i) Furthermore, the issue of regulatory approval was of no relevance to the issue of inventive step.

j) It followed that the claimed product lacked an inventive step.

XIV. The Appellant (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or alternatively on the basis of the first auxiliary request submitted with the statement setting out the grounds of appeal dated 27 April 2010 and in both cases with a description to be adapted.

XV. The Respondents (Opponents 1, 3 and 5) requested that the appeal be dismissed. Respondents-Opponents 4 had not submitted any request.

XVI. 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

Meaning of claim 1

2. Claim 1 is directed to an oxirane (ethylene oxide) derivative obtainable by reacting ROH (R being a C_{1-7} hydrocarbon group) and ethylene oxide in a reaction system with no more than 5 ppm water. The claimed derivative is furthermore defined by the general formula $RO(C_2H_4O)_nH$[1], wherein n represents the average number of moles of polymerized ethylene oxide units, and additional conditions (A) and (B) which express, as was not disputed by the parties, the degree of homogeneity of the claimed derivative in terms of molecular weight and polarity, respectively.

2.1 According to paragraph [0003] to [0006] of the patent in suit, the product of the reaction of ethyleneoxide with a mono-alcohol, is a product comprising polyethyleneoxide monoether molecules of various lengths, as well as side-products such as polyethylene glycols (hereafter diols), the existence of which is due the presence of water competing with the mono-alcohol starter during polymerisation. Therefore, the composition obtainable by reacting ROH (R being a C_{1-7} hydrocarbon group) and ethylene oxide may contain various products of that reaction.

2.2 Hence, claim 1 is not to be read as defining the mere compound of formula [1], i.e. of absolute purity and absolute homogeneity in terms of chain length (polydispersity of 1,0), but rather as the composition comprising the compound of formula [1] obtainable by reacting ROH (R being a C_{1-7} hydrocarbon group) and ethylene oxide, which composition may contain the

various products of that reaction in accordance with conditions (A) and (B).

2.3 As confirmed by paragraph [0010] and Figure 1 of the patent in suit, condition (A), the inequality PareaM / Parea ≥ 0.85, provides an indication of the degree of narrowness of the molecular weight distribution of the the composition comprising the derivative of formula [1] as determined by gel permeation chromatography, the main peak being assumed to correspond to the pure derivative of formula [1]. Increasing values of the ratio PareaM / Parea indicate a decrease of the amount of high molecular and/or low molecular compounds in the obtained mixture.

2.4 The second condition (B) refers to thin layer chromatography which is a technique with which compounds are separated by their polarity. Condition B therefore defines a degree of homogeneity of the composition comprising the derivative of formula [1] in terms of polarity, not in terms of size or molecular weight as does condition (A). The main spot defined to appear at Rf values of 0,2 to 0,8 corresponds to the pure derivative.

It was undisputed that the purity value within the meaning of condition (B), which is measured by TLC / densitometry means, is the ratio of the (area x density) value for the main spot appearing at Rf values of 0,2 to 0,8 to the sum of the various (area x density) values obtained for all spots, as described in paragraphs [0022] to [0025] of the patent in suit.

2.5 Since the absence of water is desirable in order to avoid the formation of the above mentioned side-products, it follows that the process feature “in a

reaction system whose water content is not more than 5 ppm;" does not introduce any limiting feature to the claimed product, as the level of homogeneity of the claimed product in terms of molecular weight and polarity is already expressed in claim 1 by the definition of criteria (A) and (B). This was not contested by the Appellant.

Novelty

3. The question to be answered in relation to the novelty of the subject-matter of claim 1 is whether or not a prior art document has been invoked that provides a direct and unambiguous disclosure, either explicit or implicit, of the composition of present claim 1. Hence, the relevant question is not merely whether known derivatives of formula $RO(C_2H_4O)_nH$[1] according to claim 1 could be purified, using conventional techniques, so as to meet conditions (A) and (B) of present claim 1. The question that has to be answered is whether a concrete prior art describing said known derivatives, actually also discloses, either explicitly or implicitly, that purification steps are applied to those derivatives in such a way as to meet conditions (A) and (B). The only documents cited by the Respondents that describe derivatives of formula $RO(C_2H_4O)_nH$[1] according to claim 1 are D14 and D9.

Novelty over D14

3.1 D14 discloses a method of purification of MPEG contaminated with polyethylene glycol. The sole indication in that document of the molecular weight of the MPEG compound to be purified is given in Examples I and II describing the purification of MPEG having a molecular weight of 2000 and 5000, respectively.

According to present claim 1, the average number of moles of oxirane groups present in the derivative of formula $RO(C_2H_4O)_nH$ [1], is 100 to 900, which approximately corresponds to an average molecular weight range between 4400 and 39600.

Therefore, only Example II of D14, describing the purification of a commercially available MPEG with a molecular weight of about 5000, which corresponds approximately to an n value of 113 in formula $RO(C_2H_4O)_nH$ [1], might anticipate the subject-matter of claim 1.

3.1.1 In example II of D14 the MPEG 5000, which is stated to have a purity of more than 90%, is subjected to silica gel (column) liquid chromatography (LC), using a mixture of chloroform/methanol as the eluent, with a gradually increasing amount of methanol, in line with the method described in the claim of that document. In Example II the content of methanol in the eluent is gradually increased to 2% over the first 1 - 20 fractions, then kept constant over fractions 21-51 and then gradually increased from 2 to 10% over fractions 52-89. The fractions obtained by LC were subjected to thin layer chromatography (TLC). Fractions 23-61 showed one spot, which is stated to be indicative of pure MPEG 5000. Moreover, a purity of 99% of the collected MPEG 5000 was confirmed by 1H-NMR after treatment of the purified compound with anhydrous trifluoroacetic acid. In view of the degree of purity determined in D14 for the purified derivative and the description of the existence of one spot on the silica gel plate when analysing the purified derivative by TLC, it has to be concluded that D14 in its Example II discloses the separated product as having a degree of homogeneity in

terms of polarity corresponding to that expressed in present claim 1 by condition (B).

3.1.2 The parties submitted various experimental reports meant to describe a reproduction of the purification technique described in D14. Experimental Report D71 submitted by the Appellant uses, as in Experimental Reports D69 and D75 of Respondent/Opponent 3, a mixed solvent eluent system chloroform/water/methanol (93/0,4/6,6 in volume). As correctly noted by the Appellants, the eluent used in the separation technique of D14 differs from that used in the Experimental Report of D69, and consequently also from that of Experimental Reports D71 and D75, in that the composition of the eluent in D14 starting from chloroform, is gradually modified by the addition of methanol up to an amount of 10%. It is, however, well recognized in the art, as illustrated by D72, page 215, second paragraph, that elution of the components adsorbed on the stationary phase depends on the polarity of the eluent. Consequently, no experiment using eluents of a fixed composition can be considered to be a faithful reproduction of the procedure according to D14. Therefore, neither D69, nor D71 or D75 which all use an eluent having a constant composition, can serve to assess the efficiency of the purification method described by D14. The same holds true for experimental report D74 using an eluent having a fixed composition of chloroform:methanol in a 85:15 ratio.

3.1.3 In the absence of any evidence to the contrary, D14, in view of in particular example II, is therefore considered to provide an enabling disclosure of a purification method of a sample of MPEG contaminated with PEG that results in a derivative of the general

formula [1] fulfilling condition (B) as set out in present claim 1, as shown above in point 3.1.1.

3.2 The question remains whether the MEPG 5000 purified in Example II by silica gel liquid chromatography also satisfies condition (A) of claim 1 of the patent in suit, as the molecular weight distribution of the purified MPEG is not described in D14.

3.2.1 Considering that the purification technique used in D14 will separate the various compounds in the sample as a function of their polarity, it can be accepted that impurities having a vinyl ether group - which are known to have a low molecular weight - and PEG diols - which are known to have a high molecular weight - will be separated from the MPEG molecules.

3.2.2 This, however, does not necessarily imply that pure MPEG molecules in terms of polarity were also separated by their size so as to obtain a molecular weight distribution meeting condition (A). In the absence of any evidence in this respect and in view of the separation technique in D14 based on the difference in polarity between the various compounds to be separated, it cannot be concluded that the method employed in Example II of D14 will also separate the MPEG molecules contained in the commercially available sample of MPEG 5000 by their size or molecular weight as far as molecules homogeneous in terms of polarity are concerned. Under these circumstances, the molecular weight distribution of the purified MPEG 5000 is considered to be dependent on the initial molecular weight distribution of the MPEG 5000 molecules contained in the commercially available sample, which molecular weight distribution is not disclosed in D14. In the absence of any indication in this respect in

D14, no conclusion can be drawn on the molecular weight distribution of the MPEG molecules separated in Example II. Consequently, D14 does not disclose the molecular weight distribution of the derivative of formula [1], as expressed by present condition (A).

3.2.3 The argument of the Appellants on which the Opposition Division reasoning was based, namely that conventional purification methods would allow to purify the MPEG 5000 disclosed in D14 as to provide the compound of claim 1 fails to convince. As stated above (point 3), the question that has to be answered is whether a specific prior art describing said known derivatives, also discloses - even implicitly - that purification steps are actually applied to those derivatives in such a way as to meet conditions (A) and (B). This question has to be answered taking into account the relevant context of that prior art, as understood by the skilled person. In the Case Law invoked by the parties and the Opposition Division, in particular T 803/01 and T 990/96, it had been considered that, since the claimed compounds were disclosed to be used in pharmaceutical compositions, there were generally prevailing needs and requirements for highly pure compounds in that technical field. The implicit level of purity required by the pharmaceutical use was therefore that which could be achieved through conventional techniques in the field concerned.

3.2.4 The Board, however, is unable to find anywhere in D14 – no passage in this respect was cited by the parties - the desirability, even implicit, of adjusting the molecular weight distribution so as to meet the requirement set out by condition (A). Therefore, D14 does not provide a disclosure, even implicit, of a step in addition to the silica gel (column) liquid

chromatography disclosed in that document. Consequently, in the absence of any indication of the molecular weight distribution of the commercial MPEG sample employed in Example II of D14 and of an additional treatment of that sample before or after the silica gel (column) liquid chromatography which would result in a molecular weight distribution meeting condition (A) defined in present claim 1, novelty of claim 1 over D14 has to be acknowledged.

Novelty over other cited documents

4. On the same basis, novelty has to be acknowledged over the additional prior art documents cited which disclose a derivative of formula $RO(C_2H_4O)_nH$[1] with n lying between 100 and 900, as those prior art documents have not been shown to disclose, even implicitly, a molecular weight distribution of the disclosed derivatives that would fulfil condition (A).

In Example 5 of D9 an MPEG 5000 obtained after derivatization was held by the Respondents to anticipate the subject-matter of present claim 1. However, the molecular weight distribution of the MPEG compound before or after derivatization is not disclosed. Nor is any purification step disclosed, before or after derivatization, so that there is no reason to consider the disclosure of Example 5 of D9 as novelty destroying. In view of the following conclusions regarding inventive step, it is however not necessary to go into further detail in that respect.

Inventive step

Closest prior art

5. The patent in suit concerns oxirane derivatives of formula $RO(C_2H_4O)_nH$[1] with n ranging from 100 to 900 which are suitable as intermediate in the manufacture of PEG-modified physiologically active substances (see paragraph [0001] and claim 10 of the patent in suit). Similar oxirane derivatives are described in D14, which aims at providing pure MPEG compounds for biomedical purposes. As shown in above points 3.1.1 to 3.1.3, in example II D14 describes the purification of a MPEG compound with about 113 oxirane repeating units using silica gel (column) liquid chromatography resulting in a compound meeting purity condition (B) of present claim 1. Thus, the Board considers, in agreement with the Appellant and the Respondents that the oxirane derivative of document D14 represents the closest state of the art.

Problem solved and solution

5.1 Having regard to the oxirane derivative disclosed in Example II of D14, the Appellants submitted that the technical problem solved by the subject-matter of claim 1 of the main request was to provide a derivative in a purer form in order to obtain regulatory approval for the drugs manufactured with that derivative.

However, it has not been shown that the indication in present claim 1 of conditions (A) and (B) is sufficient to define oxirane derivatives that would obtain regulatory approval for the drugs manufactured with those derivatives. The file does not contain any test related to a pharmaceutical use of the claimed

compound. Moreover, in the absence of any indication of the molecular weight distribution of both the commercial MPEG 5000 sample used in Example II of D14 and the purified MPEG 5000 obtained in that example, it cannot be concluded that condition (A) of present claim 1 defines an oxirane derivative exhibiting a more homogeneous or a narrower molecular weight distribution than that of the closest prior art. Considering furthermore that the purified MPEG of Example II of D14 already fulfils condition (B) set out in present claim 1, it cannot be concluded that the presently claimed derivative successfully solves the problem to provide a derivative in a purer form in order to obtain regulatory approval for the drugs manufactured with that derivative, as proposed by the Appellant. The problem effectively solved over the oxirane derivative disclosed in Example II of D14 can therefore only be seen as to provide a further oxirane derivative for pharmaceutical use.

5.2 As a solution to this problem the patent in suit proposes the oxirane derivative defined in claim 1 of the main request, which, compared to that of the closest prior art, is characterized in that it meets condition (A) of present claim 1, which condition constitutes an indication of the molecular weight distribution of the claimed oxirane derivative (see point 2.3 above).

Obviousness

5.3 It remains to be decided whether or not the proposed solution involves an inventive step in view of the state of the art. Starting from the disclosure of D14, which is silent on the molecular weight distribution of the purified MPEG compound of Example II, the question to be answered is whether it would be obvious for the skilled person to define a narrow molecular weight distribution for that derivative. The degree of narrowness of the molecular weight distribution of the oxirane derivative (1) expressed by condition (A) is neither critical nor purposive for solving the objective problem underlying the patent in suit, since no technical effect has been shown to be associated with that particular choice.

Furthermore, it was not contested by the Appellant that it would be a routine activity for a skilled person starting from the purified MPEG compound of Example II of D14 to provide a fraction of that polymer having a narrow molecular weight distribution by preparative GPC, for example by collecting the middle fraction(s) of that additive, thereby arriving at an MPEG compound meeting condition (A).

On this basis, the choice of an MPEG compound meeting condition (A) can only be seen as an arbitrary choice lying within the routine activity of the skilled person faced with the problem of providing a further derivative for pharmaceutical use. In that context, it is clearly desirable to control the molecular weight of drug delivery polymers in order to optimize the reproducibility of the pharmaceuticals produced therewith. Therefore, it cannot provide the claimed derivative with any inventive character.

6. Therefore, the Appellant's main request which encompasses an obvious embodiment is not allowable for lack of an inventive step.

Auxiliary Request

7. Claim 1 of the auxiliary request differs from that of the main request exclusively in that the oxirane derivative should fulfil the additional conditions (C) and (D) (see above point VII), which conditions, as does condition (A), express a degree of homogeneity of the molecular weight distribution. The Appellant's arguments in support of the auxiliary request are the same as those in support of the main request. Since the definition of additional conditions (C) and (D) has not been shown, nor argued, to provide a molecular weight distribution other than that which would be obtained by preparative GPC in collecting the middle fraction(s) of the purified compound obtained in Example II of D14 (see point 5.3 above), the embodiment of the main request which had been found to be obvious is also encompassed by the auxiliary request.

Hence, the above considerations in respect of inventive step of the subject-matter of claim 1 of the main request are not affected by the definition of the added conditions (C) and (D).

Thus, claim 1 of the auxiliary request is obvious and does not involve an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

1. The appeal is dismissed.

The Registrar: The Chairwoman:

E. Goergmaier B. ter Laan

Decision electronically authenticated