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Datasheet for the decision of 28 July 2011

Case Number: T 2233/08 - 3.3.01

Application Number: 99912189.0

Publication Number: 0993447

IPC: C07D 211/90

Language of the proceedings: EN

Title of invention:
A process for the preparation of amlodipine benzenesulphonate

Patentee:
Adamed SP. Z O.O.

Opponent:
PFIZER LIMITED

Headword:
-

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Inventive step (yes) - improvement credible over whole scope claimed, solution not obvious, no pointer in the prior art"

Decisions cited:
T 0013/84, T 0386/89, T 0184/82, T 0344/89, T 0021/81, T 0226/88

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 2233/08 **-** 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 28 July 2011

Appellant: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 23 October 2008 rejecting the opposition filed against European patent No. 0993447 pursuant to Article 101(2) EPC.

Composition of the Board:

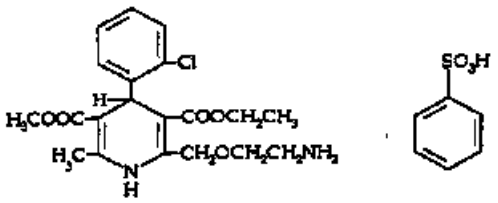
Chairman: P. Ranguis
Members: G. Seufert
D. S. Rogers

Summary of Facts and Submissions

I. The Appellant lodged an appeal against the decision of the Opposition Division dated 23 October 2008 rejecting the opposition against European patent No. 0 993 447.

II. The Patent was granted on the basis of 6 claims. Claim 1, the sole independent claim, reads as follows:

"A process for the preparation of amlodipine benzenesulphonate of the Formula I,



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characterized in that a salt of amlodipine with an inorganic or organic acid selected from acetate, formate, chloroacetate, hydrobromide, nitrate, hydrochloride or methanesulphonate is reacted with alkali metal benzenesulphonate in an aqueous medium or in a mixture water-alcohol C_1-C_2."

III. In this decision the following numbers will be used to refer to documents:

(1) EP-B-0 244 944
(2) EP-B-0 089 167
(3) S.S. Zumdahl, "Chemistry", Third Edition, 1993, pages 142-147
(4) R. Chang, "Chemistry", Second Edition, 1984, page 309, 310, 312
(5) F. H. Rhodes, A. W. Lewis, Industrial & Engineering Chem., 20(12), 1928, 1366-67

(6) EP-A-0 409 281

(7) WO-A-93/25547

(8) ES-A-548349 and translation into English (8a)

(9) Affidavit of Mr. Pettman filed with the statement of grounds of appeal

(13) Comparative Test Data submitted with letter of 13 June 2003 during the examination procedure of the patent in suit, in this decision referred to as "Annex IV"

(14) Repetition of Example 3 of the patent in suit along with an HPLC analysis sheet, submitted by the Respondent with letter dated 13 October 2009

(15) Experimental Report submitted by the Respondent with letter dated 28 June 2011

IV. Opposition was filed requesting revocation of the patent in suit in its entirety on the ground of lack of inventive step (Article 100(a) EPC).

The Opposition Division considered that starting from example 5 of document (1) as the closest state of the art and in view of the experimental evidence submitted in the course of the examination procedure, (document (13), i.e. Annex IV), the technical problem to be solved may be seen in the provision of an improved process, in terms of yield and purity, for the preparation of amlodipine benzenesulphonate. Regarding the obviousness of the solution the Opposition Division concluded that neither document (1) nor any of the documents (2) to (4) provided the skilled person with any incentive to select specific salts of amlodipine and to modify the benzenesulphonate counter-ion in order to solve the underlying technical problem.

V. With the statement of grounds of appeal, the Appellant submitted documents (5) to (9).

VI. In reply to the statement of grounds of appeal, the Respondent filed an auxiliary request restricting claim 1 as granted to the use of amlodipine hydrochloride as starting material.

VII. With letter dated 13 October 2009 the Respondent filed a reproduction of example 3 of the patent in suit in order to support its assertion that the yield in example 3 of the patent in suit was the result of an error (document (14)).

VIII. In a communication accompanying the summons to oral proceedings, the Board expressed its preliminary opinion. In particular, the Board expressed doubts with regard to the significance of comparative test data. It was also pointed out that document (1) did not mention amlodipine salts or other benzenesulphonate salts as starting materials which raised the question whether or not these modifications were obvious for the skilled person without the benefit of hindsight.

IX. In reply to the summons, the Appellant, with letter of 9 May 2011, informed the Board that it would not attend the oral proceedings. An English translation of document (8) was filed with the same letter (document (8a)). No further observations or comments concerning substantive issues were submitted.

X. With letter dated 28 June 2011, the Respondent filed an additional experimental report (document (15)) as well

as auxiliary requests 1-4 replacing the auxiliary request previously filed.

XI. Oral proceedings before the Board took place on 28 July 2011 in the absence of the duly summoned Appellant. During the oral proceedings the Respondent withdrew auxiliary requests 1-4 as well as its request not to admit documents (5) to (9).

XII. The arguments of the Appellant provided with the statement of grounds of appeal, to the extent that they are relevant for this decision, can be summarized as follows:

The Opposition Division applied the problem-solution approach incorrectly. It reformulated the technical problem to be solved as the provision of an improved process for the preparation of amlodipine benzenesulphonate, this improved process being related not just to the elimination of hazardous starting material but also to improved purity and yield of the amlodipine benzenesulphonate product. This reformulation of the technical problem was impermissible given that the technical problem to be solved as stated in the application vis-à-vis document (1) neither referred to improved purity or yield of the amlodipine benzenesulphonate product, nor were these effects deducible from the application as filed or implied or related to the initially suggested technical problem of eliminating hazards and difficulties relating to the starting materials and reagents.

Furthermore, the so reformulated problem was not the correct objective technical problem, since it was not solved over the whole scope of the claims. Three of the seven examples of the patent in suit achieved yields which were lower than in example 1 of document (1), and there was no example for the use of a C_1-C_2 alcohol water mixture. Furthermore, the processes in document (1) were not optimised, the yields reported in the patent and the comparative data of Annex IV were questionable in view of the possibility of hydrate formation and the comparative data were not properly comparative. Accordingly, the problem to be solved was the provision of a further process for the preparation of amlodipine benzenesulphonate, which eliminated the use of hazardous solvents and starting materials.

The proposed solution lacked inventive step, because it was obvious to the skilled person that it was identical in terms of basic chemistry to the process disclosed in document (1). Document (1) taught the bringing together of the protonated amlodipine cation and the benzenesulphonate anion in order to obtain amlodipine benzenesulphonate. The use of salts would be seen by the skilled person as an immediately obvious way of providing these ions. Such a process was well known in the art as illustrated by documents (6)-(8) and confirmed by Mr Pettman's affidavit (document (9)). Furthermore, to the skilled person it was immediately obvious that the process of document (1) could be performed in water if the amlodipine base was converted into a water soluble form. Document (1) already taught that amlodipine hydrochloride had good solubility in water. Document (1) also taught that the hazardous benzenesulphonic acid could be replaced by a salt, and

it would be immediately obvious to the skilled person that the ammonium salt of document (1) could be replaced by an alkali metal salt thereby avoiding the elimination of the dangerous and toxic ammonia. These considerations were also confirmed by Mr. Pettman's affidavit.

Even if an improvement in yield was acknowledged, the invention was nevertheless obvious because this technical effect was merely a bonus effect, which could not be taken into account for the assessment of inventive step.

XIII. The arguments of the Respondent provided in the written proceedings as well as during oral proceedings, to the extent that they are relevant for the present decision, can be summarized as follows:

Document (1), more precisely example 5 of document (1) disclosing the reaction of amlodipine base with ammonium benzenesulphonate to yield amlodipine benzenesulphonate, was the closest state of the art. The claimed process differed from example 5 of document (1) in that specific salts of amlodipine instead of the amlodipine free base and an alkali metal benzenesulphonate instead of ammonium benzenesulphonate was used. The experimental data (document (15)) confirmed in a fair comparison that the process according to the invention provided a better yield than example 5 of document (1). Therefore, the objective technical problem was to provide an improved process, in terms of yield, for the preparation of amlodipine benzenesulphonate. Higher purity was no longer relied

on as a technical result for defining the problem to be solved.

Contrary to the Appellant's opinion, the skilled person could deduce the effect of an increase in yield directly from the application as filed by comparing the examples of the application and example 5 of document (1). Moreover, obtaining higher yields was a common objective pursued in synthetic chemistry.

The technical problem was solved over the whole claimed area. Each of the seven examples of the patent in suit showed a higher yield than example 5 of document (1). There was no evidence for the formation of hydrates. The Appellant's allegation that no example with a mixture of C_1-C_2 alcohol and water was present was erroneous in view of example 4 of the patent in suit. Contrary to the Appellant's opinion, there was no need to compare the process of example 5 of document (1) with a process wherein amlodipine benzenesulphonate is made from amlodipine free base. This upstream step is not the object of the patent in suit.

The Appellant's opinion that the claimed invention was obvious because it was identical in terms of basic chemistry to the process disclosed in document (1) was based on hindsight. Documents (3) and (4) referred to theoretical principles in chemistry for teaching purposes and did not reflect the specific conditions as they existed in the present case, which were rather more complicated due to the presence of further ions. In particular, these documents could not help the skilled person in solving the technical problem of improving the yield of amlodipine benzenesulphonate.

Moreover, when aiming at an improvement in yield, document (1) taught the use of free acid and free base. Documents (6) to (8) refer to specific reactions not in the least related to the preparation of amlodipine benzenesulphonate. The affidavit of Mr. Pettmann (document (9)) regarding the obviousness of the claimed process described that the skilled person could have come to the present solution, but did not provide reasons why he would have done so when aiming at a product with high yield.

XIV. The Appellant requested in writing that the decision under appeal be set aside, and the patent be revoked

The Respondent requested that the appeal be dismissed.

XV. At the end of the oral proceedings the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Non-appearance at oral proceedings before the Board

2.1 The oral proceedings before the Board took place in the absence of the Appellant, who was duly summoned but chose not to attend.

2.2 According to Article 15(3) RPBA, the Board shall not be obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be

treated as relying only on its written case. In deciding not to attend oral proceedings the Appellant chose not to avail itself of the opportunity to present its arguments and observations orally, but instead to rely solely on its written case. The Appellant could reasonably expect that during oral proceedings the Board would consider any arguments or issues raised by the Respondent or the Board in its communication. Hence, in the present case the Board was in a position to announce its decision at the conclusion of the oral proceedings, despite the absence of the Appellant.

3. Inventive step

3.1 The patent in suit is directed to a process for the preparation of amlodipine benzenesulphonate reacting specific amlodipine salts with alkali metal benzenesulphonate in an aqueous medium or in a mixture of water and C_1-C_2-alcohol.

Similar processes are already disclosed in document (1). This document relates to amlodipine benzenesulphonate and pharmaceutical compositions thereof and discloses two processes for its preparation, namely the reaction of amlodipine base with a solution of benzenesulphonic acid or, alternatively, with its ammonium salt in an inert solvent, preferably industrial methylated spirit (see page 2, lines 33 to 36). Example 1 of document (1) discloses the reaction of a slurry of amlodipine base with a benzenesulphonic acid solution in industrial methylated spirit, whereas example 5 discloses the preparation of adding ammonium benzenesulphonate to a

slurry of amlodipine base in industrial methylated spirit.

Among the two single teachings for preparing the amlodipine benzenesulphonate, the process involving the ammonium benzenesulphonate, i.e. example 5 of document (1), has the most relevant features in common with the presently claimed process, because a salt of benzenesulphonic acid, i.e. the ammonium benzenesulphonate, has been used as starting material. In example 1 of document (1) none of the starting materials are in salt form. The Board thus concurs with the Opposition Division and the Respondent that the process illustrated by example 5 of document (1) can be regarded as the most appropriate starting point for assessing inventive step.

3.2 In the light of this prior art the Respondent formulated the technical problem to be solved as the provision of an improved process, in terms of yield, for the preparation of amlodipine benzenesulphonate.

As the solution to this problem the patent in suit proposes the use of amlodipine salt and an alkali metal benzenesulphonate as starting materials.

3.3 In order to demonstrate that this problem has been solved the Respondent relied on the examples of the patent in suit, Annex IV filed during examination proceedings and, in particular, on the experimental report (document (15)) submitted in reply to the Board's observations, the results of which are reproduced below.

Experiment No.	Starting materials		Solvent	Yield [%]	HPLC purity [%]
	Amlodipine compound	Benzenesulphonate compound			
1 (= Ex. 5 of D1)	Amlodipine base	Ammonium benzenesulphonate	Industrial methylated spirit	67.1	98.51
2 (invention)	Amlodipine hydrochloride	Sodium benzenesulphonate	Industrial methylated spirit	85.7	99.49
3 (invention)	Amlodipine hydrochloride	Sodium benzenesulphonate	Water	96.7	99.77
4 (invention)	Amlodipine acetate	Sodium benzenesulphonate	Industrial methylated spirit	86.0	99.28
5 (invention)	Amlodipine acetate	Sodium benzenesulphonate	Water	92.7	99.34

The Board notes that Experiment No. 1 truly reflects example 5 of document (1) with a yield of 67.1% as compared to 70% in document (1). Experiments 2-5 are examples according to the invention, which have been carried out under the same experimental conditions regarding reaction temperature, reaction time, work-up procedure and molar amounts of the starting material as in example 5 of document (1). The experimental report therefore allows a fair comparison of the claimed process with the prior art. As is apparent from the table above, in the experiments according to the invention carried out in either methylated spirit, which may contain up to 10% of water, or water, the amlodipine benzenesulphonate was obtained in significantly higher yield than in the prior art. These results confirm the comparative test data of Annex IV carried out in water on which the Opposition Division relied in the decision under appeal. They also confirm the high yield obtained in the examples of the patent in suit, which have been carried out in water or a water-ethanol (1:1) mixture.

3.4 According to the Appellant the improvement in yield should not be taken into consideration when determining the problem underlying the invention for the purpose of assessing inventive step. The Appellant argued that the application as originally filed as well as the patent in suit already acknowledged document (1) and referred with respect to this document solely to the elimination of hazards and difficulties relating to the starting materials and reagent used therein. Improvements in yield were not mentioned in this context.

The Appellant acknowledged that, according to EPO case law (T 13/84, T 386/89 and T 184/82 were cited in this context) a reformulation of the problem was appropriate under certain circumstances, in particular, if (a) the objective assessment of inventive step relied on newly introduced prior art, which was closer to the invention than that cited in the application or the granted patent, or (b) an alleged effect of a described feature could be deduced by the skilled person from the application in the light of the prior art or (c) new effects submitted subsequently during the proceedings were implied by or related to the technical problem initially suggested. In relation to new effects it was not permissible to change the nature of the invention (T 344/89). The Appellant argued, however, that none of these circumstances applied in the present case. Document (1) as the closest prior art was mentioned in the patent in suit. The technical problem in the patent was formulated in comparison with document (1) and did not concern an improvement in yield. Neither was such an improvement deducible from the patent application. The Appellant pointed out that of the seven examples

given in the application as filed only three described a process with a yield greater than in the prior art. Examples 4, 6 and 7 showed yields which were lower than the yield of example 1 of document (1). Finally, the Appellant argued that the effect of increased yield, allegedly shown by the comparative examples in Annex IV, were not implied by or related to the technical problem originally suggested, which was the provision of a further process avoiding the use of hazardous solvents or starting materials. A skilled person who wished to avoid hazardous solvents and starting materials may tolerate decreased yields.

3.5 However, in the Board's judgement, the technical effect of providing amlodipine benzenesulphonate in high yield is already deducible from the application as filed and not a new effect, even if it has not been explicitly mentioned in the discussion of document (1) in the introductory part of the application as filed. The yields are indicated in all but one examples of the application as filed and example 5 of document (1) mentions the yield as well. Examples 1, 2, 4-6 and 7 (erroneously also called example 6) of the patent application, which are identical to examples 1, 2, 4-7 of the patent in suit, display a yield of 81% and higher, compared to 70% in example 5 of document (1). Thus, by simply comparing the yield of the examples of the application as filed and the yield obtained in the prior art process, the skilled person will notice that the yield obtained in the process according to the invention is considerably higher than the yield obtained in the prior art. The skilled person will also notice that in the prior art processes such high yield can only be achieved by using the hazardous free

benzenesulphonic acid and that the use of ammonium benzenesulphonate instead of the free acid considerably reduces the yield of amlodipine benzenesulphonate (cf. example 1 and 5 of document (1)). Thus, although the examples in the patent in suit may not be seen as an entirely proper comparison with the example 5 of document (1), it is nevertheless readily deducible for the skilled person that providing amlodipine benzenesulphonate with high yield, which does not rely on the use of corrosive benzenesulphonate, is one of the technical effects aimed at by the invention vis-à-vis document (1). The Appellant's comparison with example 1 of document (1) is erroneous, as the process illustrated by example 5 and not example 1 of document (1) is considered to be the closest prior art.

3.6 In conclusion, contrary to the Appellant's view, the objective problem to be solved in the light of the prior art (example 5 of document (1)) may be seen in the provision of a process for the preparation of amlodipine benzenesulphonate with increased yield.

3.7 The next step is to examine whether or not the technical problem defined above is solved over the whole claimed area.

3.7.1 According to the experimental data submitted by the Respondent (document (15)) the use of amlodipine hydrochloride and amlodipine acetate as starting material in either water or methylated spirit results in a considerable increase in yield compared to example 5 of document (1) (see point 3.3 above). These results confirm the high yields obtained in the patent in suit for the same salts (examples 1 and 4 with

yields of 88% and 83%). It is also apparent from the patent in suit that the use of amlodipine formate, amlodipine chloroacetate, amlodipine methansulphonate or amlodipine nitrate (examples 2, 5, 6 and 7) achieves comparable high yields (81% to 90%). Document (14), which is a repetition of example 3 of the patent in suit, which, according to the Respondent, contained an error (see point 3.10.3 below), would appear to confirm that the same also applies, if amlodipine hydrobromide is used as starting material. In the absence of any evidence to the contrary, it is reasonable to assume that the use of any of the amlodipine salts as defined in claim 1, which correspond to the salts used in the examples of the patent in suit, and sodium benzenesulphonate leads to an increase in yield.

3.7.2 With regard to the use of alkali metal benzenesulphonates other than sodium benzenesulphonate as starting material, the Board, in the absence of evidence to the contrary, has no reason to doubt that other salts with elements from the same group of the periodic table, i.e. other alkali salts, solve the technical problem as defined above. The Appellant has not raised any objections concerning this issue.

3.8 The Board is thus satisfied that the objective technical problem as defined in point 3.6 above is credibly solved over the whole claimed area.

3.9 According to the Appellant the technical problem was not solved over the whole scope of the claims for essentially the following reasons:

3.9.1 An increase in yield was not achieved in all the examples of the patent in suit. The yield in examples 4, 6 and 7 of the patent in suit was lower than in example 1 of document (1). This was confirmed by comparative example II (of Annex IV), which was based on example 1 of document (1). Accordingly, the high yield in comparative examples III and IV of Annex IV might not be due to the use of the claimed starting materials but rather to some other technical feature not present in claim 1.

3.9.2 Document (1) did not aim at an optimisation of yield and purity, but was mainly directed to the advantages of amlodipine benzenesulphonate in pharmaceutical formulations together with processes for its preparation. The skilled person would therefore understand that it might be possible with different reaction conditions to achieve high yield and purity using the processes disclosed in document (1).

3.9.3 The yields reported in the examples of the patent in suit as well as the comparative examples in Annex IV could not be trusted, since the examples were carried out in water and could have resulted in the formation of hydrates, thereby leading to an artificially increased yield. This would also explain the yield of 105% in example 3 of the patent in suit.

3.9.4 Furthermore, any comparison between the examples of the patent in suit or the comparative examples of Annex IV and example 5 of document (1) was flawed, because the former described only part of the overall process, by which amlodipine benzenesulphonate was made from the free base. The amlodipine salt starting material must

be made from the free base, but there was no disclosure of the yield achieved in this reaction.

3.9.5 The Opposition Division based its finding that the technical effect of increasing yield and purity was linked to the modification in the starting materials on a single example, as comparative example IV of Annex IV was not an example falling within the scope of claim 1.

3.9.6 Finally, there was no example which demonstrated a higher yield than the prior art when using a water and C_1-C_2-alcohol mixture.

3.10 The Board is not convinced by the Appellant's arguments.

3.10.1 It has already been established in point 3.1 above that the process illustrated in example 5, not example 1, of document (1) represents the closest state of the art, serving as the starting point for assessing inventive step. An improvement in yield is already apparent by comparing the examples of the application as filed with example 5 of document (1), and document (15) confirms in a fair comparison that the effect is linked to the use of the different starting materials. The Appellant did not provide any comments or observations on the experimental evidence as shown in document (15).

3.10.2 The Appellant's arguments regarding a possible increase in yield, if different reaction conditions were to be used in the processes of document (1), is, in the absence of any data supporting this allegation, entirely speculative and must therefore be disregarded.

3.10.3 The same applies with regard to the alleged formation of hydrates of amlodipine benzenesulphonate. No evidence for such a formation was provided by the Appellant, who has the burden of proof for its allegation. Example 3 of the patent in suit cannot serve as evidence. Although the Appellant is correct in pointing out that the amount of the amlodipine benzenesulphonate corresponds to a yield of more than 100% (i.e. 104%), this on its own does not justify the conclusion that hydrates are formed or that in general the yields in the patent in suit or the comparative data cannot be trusted. This inconsistency can also be explained by some error in transcribing the results of the laboratory experiments, as pointed out by the Respondent. This also appears to be the more plausible explanation in view of the sharp melting point of the product in example 3, which is consistent with the literature data of the non-hydrated form, and the repetition of example 3 of the patent in suit by the Respondent (document (14)). Without any data or corroborating evidence the Appellant's arguments as to the formation of hydrates are mere speculation.

3.10.4 The fact that the patent in suit does not take into account the step of reacting the amlodipine free base with the acid to form the starting material is irrelevant, because as correctly stated by the Opposition Division, there appears to be no basis for requiring yields of any upstream processes to be included in any comparison, since any preceding steps do not form part of the subject-matter claimed and must, therefore, remain completely speculative.

3.10.5 The Appellant is also not correct in alleging that the Opposition Division based its conclusion for a link between the yield and the presently claimed starting materials on only one example. In the first place, example IV of Annex IV refers to the use of amlodipine chlorohydrate as starting material. The term "chlorohydrate" is, although incorrectly, often used to refer to a hydrochloride. Thus, example IV falls within the scope of the claims. Secondly, in addition to the two example in Annex IV, the Opposition Division also considered the examples in the patent in suit in order to come to its conclusion.

3.10.6 Finally, the Appellant's allegation that no example has been provided with a water alcohol mixture as solvent is inconsistent with the facts. Example 4 of the patent in suit uses a mixture of ethanol and water with yields comparable to the examples carried out in water alone.

3.11 It then remains to be decided whether or not the claimed solution is obvious.

3.11.1 In document (1) amlodipine benzenesulphonate has been prepared solely with amlodipine free base. Furthermore, the person skilled in the art would have noted that the use of benzenesulphonic acid ammonium salt (example 5 in document (1)) instead of the free acid (example 1 of document (1)) resulted in a significant decrease in the yield of the desired amlodipine benzenesulphonate (83.8% vs. 70%). Thus, from the teaching of document (1) alone the skilled person would not have inferred that the use of the claimed amlodipine salts in combination with a benzenesulphonic acid salt with a different

counter ion solves the objective technical problem as formulated in point 3.6 above.

There are also no reasons apparent as to why the skilled person searching for a solution to this technical problem should turn to any of the documents (3) to (4) or (6) to (8) as argued by the Appellant.

3.11.2 Document (3) and (4) are excerpts from basic textbooks and relate to simple precipitation and solubility rules for mostly inorganic salts and electrolytes in water, for example the reaction of potassium chromate with barium nitrate or the solubility of sodium chloride or silver chloride in water. They cannot help the skilled person in deciding how to alter the known process of example 5 of document (1) for the preparation of amlodipine benzenesulphonate in order to improve its yield.

3.11.3 Documents (6) to (8) are patent documents directed to compounds which are not even closely related to the amlodipine or amlodipine benzenesulphonate and methods for their preparation. For this reason it is already questionable whether the skilled person would have considered these documents at all, without the benefit of hindsight. In fact the only link between these documents and the patent in suit is the salt exchange reaction, which is the solution provided by the patent. A proper application of the problem-solution approach, however, requires that the prior art must be considered without the knowledge of the solution provided by the patent in suit in order to avoid an analysis based on hindsight. Furthermore, the mere fact that a salt exchange reaction has been used in these documents for

the preparation of very specific and structurally quite different salt derivatives, does not help the skilled person in deciding how he should modify the process in example 5 of document (1) in order to achieve the improvement he was searching for.

3.11.4 Document (2) referred to in the decision under appeal relates to 1,4-dihydropyridine derivatives, including amlodipine, and their pharmaceutically acceptable acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate or acid phosphates, acetate, etc. (page 2, lines 48-51). The salts were prepared by reacting a free base with a free acid (examples 12 and 22), similar to example 1 of document (1). The Board agrees with the Opposition Division's finding that the skilled person was not able to extract any valuable teaching from this document when faced with the problem of improving the yield of the process of example 5 of document (1).

3.12 According to the Appellant the presently claimed process was identical in terms of chemistry to the process of document (1) and was therefore immediately obvious for the skilled person. In particular, the Appellant argued that in example 5 of document (1) the benzene ammonium salt would dissociate into the corresponding ammonium cation and the benzenesulphonate anion. The ammonium cation would then react with water to produce ammonia and H_3O^+ ions. The latter would protonate amlodipine to obtain the protonated amlodipine cation. In support of its arguments the Appellant cited document (3). Thus, according to the Appellant, document (1) disclosed the bringing together of the protonated amlodipine cation and the

benzenesulphonate acid anion, which was exactly what was done in the patent in suit. The use of salts as starting materials in the presently claimed process was an obvious way of providing the ions required for the preparation of amlodipine benzenesulphonate. Furthermore, since amlodipine benzenesulphonate was the least soluble species, it would selectively precipitate out of a solution of amlodipine hydrochloride and amlodipine benzenesulphonate, which were both highly soluble.

3.13 In the Board's judgment, the Appellant's explanations regarding the alleged chemical mechanism is an attempt to interpret example 5 of document (1) with the knowledge of the present invention. The Appellant's explanations start from the hypothesis that the reaction is made in water with completely dissociated ions. The use of water is a feature of the patent in suit **but not of document (1)**. In document (1) the reaction is made in basically an organic solvent (industrial methylated spirit), which may contains **up to 10%** water. Depending on the producer, this amount could also be significantly lower. However, even if correct, these explanations fail to explain why the skilled person would have contemplated the use of a different benzenesulphonic acid salt and the use of an amlodipine salt when faced with the problem of improving the yield of the prior art process, particularly in view of the teaching in document (1) according to which free benzenesulphonic acid and free amlodipine base should be used in order to obtain a high yield.

3.14 Furthermore, the Appellant relied on the observations made by the examiner during examination of the patent application who initially formulated the problem to be solved as the provision of an alternative process avoiding the use of hazardous solvents and starting materials and considered that the solution was obvious because it was apparent that the process taught by document (1) could also be performed in water, if only the amlodipine base was converted into a water soluble form. To this the Appellant added that it is general knowledge that some salts of amlodipine would be more soluble in water than others. In particular the skilled person would learn from document (1) that amlodipine hydrochloride had good water solubility. In trying to avoid alcohol as a solvent the skilled person would therefore consider using a soluble salt of amlodipine.

3.15 The Appellant's line of arguments is based on the premise that the problem to be solved is a mere alternative. However, in view of the objective problem as formulated in point 3.6 above these arguments are unconvincing, as they fail to explain why the person skilled in the art would have modified the process of the prior art seeking to improve its yields. Moreover, in the Board's judgement, the examiner's initial "conclusion", which incidentally was not upheld, goes beyond what the skilled person would have objectively inferred from document (1) without the benefit of hindsight knowledge of the invention. Document (1) solely teaches the reaction of amlodipine base with ammonium benzenesulphonate or the free acid with amlodipine free base in industrial methylated spirit. The conclusion that the skilled person would have been prompted to investigate whether the process of document

(1) could be performed in water, **if an acid addition salt of amlodipine is used**, takes into account part of the solution of the present invention, which is at variance with a proper application of the problem-solution approach.

It is acknowledged that in the context of a better bioavailability, document (1) refers to the solubility of amlodipine benzenesulphonate as well as other amlodipine salts in water. However, without the knowledge of the invention, this passage cannot be interpreted as an indication for the skilled person to use a salt exchange reaction as presently claimed for the preparation of amlodipine benzenesulphonate. It merely helps to explain why the presently claimed process works.

3.16 Furthermore, the Appellant argued that if the problem to be solved was to provide an alternative process that avoids hazardous starting material, namely benzenesulponic acid, the use of an alkali metal salt of benzenesulphonic acid instead of the ammonium salt was obvious, because it avoided the undesirable evolution of the gaseous ammonia.

3.17 However, the problem to be solved is the provision of a process for the preparation of amlodipine benzenesulphonate with improved yield and, as has been established above (point 3.11 above) neither document (1) nor any of the other prior art documents provides the skilled person with a pointer how to solve this technical problem.

3.18 The Board is also not convinced by the Appellant's submission that the use of the presently claimed salt exchange reaction was obvious, because this reaction was by the priority date of the patent a well known and well understood chemical process as illustrated by documents (6) to (8). It has already been set out in point 3.11.3 above, why, in the Board's judgement, this line of argument must fail.

3.19 In support of its arguments, the Appellant also provided an affidavit of Mr. Pettman, a qualified expert (document (9)). According to Mr. Pettman moving from amlodipine base and ammonium benzenesulphonate to an acid addition salt of amlodipine and alkali metal benzenesulphonate was a matter of routine optimisation for any competent process chemist. Salt exchange reactions were well known to process chemists and represented, therefore, an obvious alternative. Furthermore, if water was to be used as the only solvent, replacing the poorly soluble amlodipine free base with a more soluble acid salt would have been a routine matter. It would also have been a routine matter to provide the necessary benzenesulphonate anion and to consider other salts than the ammonium benzenesulphonate to avoid the elimination of ammonia.

3.20 The Board observes that Mr. Pettman explains why, in his opinion, the presently claimed salt exchange reaction was an obvious **alternative** way of making amlodipine benzenesulphonate. The problem to be solved was, however, to provide an improved process for the preparation of amlodipine benzenesulphonate, an issue which Mr. Pettman does not address. Mr. Pettman's

affidavit is therefore not pertinent in the present case.

3.21 Finally, the Appellant relying on decisions T 21/81 and T 226/88 considered that the advantage provided by the claimed process was merely a bonus effect. According to this case law:

"If, having regard to the state of the art, it would already have been obvious for a person skilled in the art to arrive at something falling within the terms of a claim, because an advantageous effect could be expected to result from the combination of the teachings of the prior art documents, such claims lacks inventive step, irrespective of the circumstances that an extra effect (possibly unforeseen) is obtained."
(T 21/81, OJ EPO 1983, point 6 or the reasons, T 226/88, not published, point 3.5 of the reasons)

The Appellant argued that the advantageous effect of avoiding hazardous solvents and starting material would be immediately achievable for the skilled person given the understanding that the amlodipine base and the benzenesulphonic acid could be replaced by salts. In support the Appellant referred to his explanation of the general chemistry underlying the invention and document (1). Any improvement in yield was therefore merely a bonus effect.

3.22 According to the Board's judgment, the understanding implied by the Appellant relies on an analysis based on hindsight knowledge of the invention (see point 3.12 above) and cannot be used to conclude obviousness of

the invention. The case law cited by the Appellant is therefore not applicable.

3.23 In view of the above the Board concludes that the prior art taken as a whole would not have directed the person skilled in the art towards the claimed process for solving the technical problem defined in point 3.6 above. For this reason the subject-matter of Claim 1 of the patent as granted involves an inventive step in the sense of Article 56 EPC. This conclusion also applies to the preferred embodiments defined in Claims 2 to 6.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow P. Ranguis