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**Datasheet for the decision
of 22 March 2012**

Case Number: T 0107/08 - 3.3.02

Application Number: 99909930.2

Publication Number: 1071403

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Language of the proceedings: EN

Title of invention:

Pharmaceutical composition containing a statin and aspirin

Patentee:

Bristol-Myers Squibb Company

Opponent:

Bayer Health Care AG

Headword:

Pharmaceutical composition containing a statin and
asprin/BRISTOL-MYERS SQUIBB COMPANY

Relevant legal provisions:

EPC Art. 56

Keyword:

"All requests - inventive step (no): problem not solved over
the whole scope"
"Reformulation of the problem"

Decisions cited:

-

Catchword:

-



Case Number: T 0107/08 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 22 March 2012

Appellant:
(Opponent)

Bayer HealthCare AG
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Respondent:
(Patent Proprietor)

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Representative:

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Decision under appeal:

Decision of the Opposition Division of the
European Patent Office posted 5 November 2007
rejecting the opposition filed against European
patent No. 1071403 pursuant to Article 101(2)
EPC.

Composition of the Board:

Chairman: U. Oswald
Members: D. Boulois
D. Prietzel-Funk

Summary of Facts and Submissions

- I. European patent No. 1 071 403 based on application No. 99 909 930.2 was granted on the basis of a set of 23 claims. Independent claim 1 read as follows:
- "1. A pharmaceutical composition comprising a statin cholesterol lowering agent and aspirin in a formulation designed to minimize statin:aspirin interaction, wherein
- (i) the statin cholesterol lowering agent and the aspirin are formulated in a single bilayered tablet and wherein the aspirin is present in a first layer, and the statin cholesterol lowering agent is present in a second layer; or
- (ii) the pharmaceutical composition is in the form of a capsule containing both aspirin granules and statin cholesterol lowering agent granules."
- II. An opposition was filed against the granted patent. The patent was opposed under Article 100(a) EPC for lack of inventive step.
- III. The documents cited during the opposition and appeal proceedings included *inter alia* the following:
- (1) EP 336 298 A1
 - (2) WO97/38694
 - (3) US 5225202
 - (7) Dr W.A. Ritschel, Die Tablette, pages 22-,29,34-37, 41-48, 60-63, 77-80, 85, 191, 369-371
 - (8) Kurt H. Bauer, Karl-Heinz Frömming, Claus Führer, "Pharmazeutische Technologie", 1989, pages 138-141, 374-379, 384-387, 412-425, 546-553

(9) Rudolf Voigt, "Pharmazeutische Technologie", 1995, pages 127-130, 187-189, 261, 274-275, 283-286, 306-308

IV. The opposition division rejected the opposition (Article 102(2) EPC 1973). It considered that the ground of opposition mentioned in Articles 100(a) and 56 EPC did not prejudice the maintenance of the patent as granted.

It assumed that the cited prior art did not allow to predict that statins cannot be formulated together with aspirin in a solid formulation because of chemical incompatibility, and that the patentee has identified a new technical problem and a solution to it.

According to the opposition division only document (2) refers to solid formulation, while documents (1) and (3) are related to the problem of stability of the statins

in aqueous mediums. Document (2) does not hint to the presence of any problem when formulating a statin and an acid like folic acid in a solid form.

The opposition division was of the opinion that a new problem can be recognised only if one actually carries out the operation that unveils it, but this does not detract from the fact that the problem is in itself new.

V. The opponent (appellant) lodged an appeal against that decision.

VI. The respondent-proprietor filed a letter dated 23 September 2008 as a response to the grounds of

appeal. Additionally, the respondent filed two auxiliary requests.

Claim 1 of auxiliary request 1 reads as follows:

"1. A pharmaceutical composition comprising a statin cholesterol lowering agent and aspirin in a formulation designed to minimize statin:aspirin interaction, wherein

(i) the statin cholesterol lowering agent and the aspirin are formulated in a single bilayered tablet and wherein the aspirin is present in a first layer, and the statin cholesterol lowering agent is present in a second layer; or

(ii) the pharmaceutical composition is in the form of a capsule containing both aspirin granules and statin cholesterol lowering agent granules, and wherein the statin cholesterol lowering agent is pravastatin, fluvastatin, atorvastatin or cerivastatin."

Claim 1 of auxiliary request 2 reads as follows:

"1. A pharmaceutical composition comprising a statin cholesterol lowering agent and aspirin in a formulation designed to minimize statin:aspirin interaction, wherein

(i) the statin cholesterol lowering agent and the aspirin are formulated in a single bilayered tablet and wherein the aspirin is present in a first layer, and the statin cholesterol lowering agent is present in a second layer; or

(ii) the pharmaceutical composition is in the form of a capsule containing both aspirin granules and statin cholesterol lowering agent granules,

and wherein the statin cholesterol lowering agent is pravastatin."

VII. Oral proceedings took place on 22 March 2012.

VIII. The appellant's arguments can be summarised as follows:

Document (2) should be considered as the closest prior art and discloses single dosage forms comprising a statin, folic acid and an additional active agent such as aspirin (page 9, lines 9-25, page 14, lines 5-10; claims 25 and 29). The dosage form can be a tablet or a capsule (page 12, lines 14-15).

The difference over document (2) is the formulation in the form of bi-layer tablets, or in the form of capsule comprising different granulates.

According to the patent, the technical effect is an improved stability, which is not shown by any data or evidence. In particular, the data filed with the letter dated 14 June 2004 cannot provide any evidence regarding inventive step, since the tablet comprises an intermediary separating layer. There is no data shown for the capsule form.

In consequence, there is no technical effect provided by the difference.

Bi-layer tablets are known from document (7) (see page 41), document (8) (see page 377) or document (9) (see page 307). The skilled person knows this particular dosage form and would be able to formulate it, especially for incompatible drugs.

Moreover, the problem raised by present patent is a common problem and belongs to routine for a skilled person. The skilled person would put the two drugs together and analyze the existence of possible incompatibilities. If the drugs are compatible, they can be formulated together. Otherwise, the skilled person would choose a bi-layer tablet as well-known option.

Furthermore, even if the skilled person would not have known anything about the stability problem of the composition, he would have found *indicia* through the teaching of documents (1) and (3). Document (1) relates to the stabilization of statins at low pH environment (see page 2, lines 2-4), and document (3) mentions the acid-labile character of the statins (see column 2, lines 8-11).

IX. The respondent's arguments can be summarised as follows:

Document (2) should be considered as the closest prior art.

The problem vis-à-vis document (2) is the provision of a dosage form comprising aspirin and statin minimizing the interactions between the two drugs, for use in lowering cholesterol and reducing the risk of a myocardial infarct.

A first experimental report was filed with a letter dated 14 November 2003 before the examining division to show the incompatibility of the drugs.

A second experimental report was filed with the letter dated 14 June 2004 before the examination division, to

show that a layered tablet would solve the problem. This experiment showed that there was no interaction between aspirin and statin. The presence of an inert intermediate layer must be seen only as an optimal solution of separation of the drugs. A simple bi-layered tablet would also have provided a minimal interaction between aspirin and statin. These experimental reports show that the problem has been solved.

Although Document (2) shows a possible association between a statin, folic acid and aspirin, the document does not give any indication regarding a possible incompatibility. According to document (2), there is no stability problem. Folic acid is a weak acid, as aspirin is, and the compositions may even comprise products such as citric acid, without envisaging any stability problems. The problem was therefore unknown from document (2).

Consequently, in view of the teaching of document (2), the skilled person would not have been incited to take any measure to separate aspirin from the statin, and would not have consulted any of the documents (7), (8) or (9).

This problem could further not be deduced from documents (1) or (3). Document (1) deals with the stability of a pharmaceutical composition to a low pH environment, which can only be the stomach environment. Document (3) relates explicitly to the stability of the statin in the low pH environment of the stomach (see column 2, lines 26-27).

- X. The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 1 071 403 be revoked.

- XI. The respondent (patentee) requested that the appeal be dismissed, or, auxiliarily, that the decision under appeal be set aside and the patent be maintained in amended form on the basis of auxiliary request 1 or auxiliary request 2, both submitted with the letter dated 23 September 2008.

Reasons for the decision

- 1. The appeal is admissible.

- 2. Main request - Inventive step:

The present invention relates to a pharmaceutical composition which includes a statin cholesterol lowering agent and aspirin designed in a manner to minimize interaction of aspirin with the statin, including physical and chemical incompatibility (see paragraphs [0001], [0003] of the contested patent).

- 2.1 Document (2), which constitutes the closest prior art is concerned with a combination therapy comprising an HMG-CoA reductase inhibitor, namely a statin, and folic acid. The combination therapy is formulated as a single dosage formulation, in particular under the form of a tablet or a capsule (see page 9, lines 9-25; page 12, lines 14, 15). The formulation may comprise an additional active agent which can be aspirin, chosen

from a list (see page 9, line 24; page 14, line 10; claim 29).

- 2.2 The contested patent contains three examples. Examples 1 and 3 correspond to the claimed bi-layer tablets. None of the formulations disclosed in the examples of the contested patent were submitted to a stability test to show an improvement in the drug interactions.

Accordingly, the problem to be solved by the subject-matter of claim 1 of the main request against document (2) can only be seen as the provision of further dosage forms of aspirin and statin.

Having regard to the working examples of the patent in suit, the board is convinced that the problem has been credibly solved.

- 2.3 Thus, the question to be answered is whether the proposed solution(s) would have been obvious to the skilled person in the light of the prior art.

- 2.3.1 Documents (7), (8) and (9) represent documents of the general knowledge in the field of pharmaceutical technology.

The teaching of these documents appears to be relevant, since they show that the manufacture of bi-layer tablets were common practice for the skilled person. Document (7) discloses on page 41 (see paragraph 1.3.1.1.4.) the preparation of multi-layered tablets, as does document (8) on page 377 and document (9) on pages 307-308.

The provision of bi-layer tablets comprising a different drug in each distinct layer is therefore an obvious solution for the skilled person.

- 2.3.2 The respondent argued that the skilled person would not have associated the teaching of document (2) with the teaching of documents (7), (8) or (9). Starting from the teaching of document (2), the skilled person would indeed not have found any indication regarding a potential incompatibility between aspirin and the statin. The formulation disclosed in document (2) comprises further weak acids, such as folic acid or citric acid without envisaging dosage forms allowing a stabilisation thereof. In the absence of any incitation, the skilled person would not have envisaged the provision of a bi-layer tablet or a capsule with the different granules.

The board could however not follow this reasoning. The problem of incompatibility was indeed not mentioned or known from document (2). It remains that, for a problem be taken in account for the judgement of inventive step, the proposed solution must be credible. The board is however not convinced that the problem was solved by the subject-matter of claim 1 of the main request. Indeed, one of the claimed alternative is a bi-layer tablet which allows a direct contact between aspirin and the statin at its interface, since its subject-matter does not comprise any further technical feature allowing a physical separation between said layers or said actives. The same applies all the more to the claimed alternative in which aspirin and statin granules are mixed together in a capsule. In both claimed alternatives, the direct contact between the

drugs would lead unavoidably to a degradation and a storage instability.

The respondent relied additionally on two tests to demonstrate the claimed effect. It filed insofar a first experimental report with a letter dated 14 November 2003 before the examining division, and a second experimental report with the letter dated 14 June 2004 before the examination division.

The first test shows that both components degraded if they are stored in the form of a dry blend or a wet blend. The data illustrate the incompatibility between aspirin and statin.

The second test related to a layered tablet comprising a layer with aspirin and a layer with the statin separated by an inert intermediate layer. The product in which aspirin and statin are separated has showed to have a good stability.

The board does however not see in the said tests an evidence that the problem of interaction between aspirin and the statin has been solved by the claimed subject-matter. If tests are chosen to demonstrate a beneficial effect, the tested compositions representing the invention must correspond to the subject-matter as claimed. This is not the case with both respondent's experiments. The first test merely shows that a problem of incompatibility between aspirin and the statin exists, while the second test is performed on a tri-layered tablet, which is not encompassed by the subject-matter of claim 1. The subject-matter of claim 1 does indeed not comprise a further separating layer in the claimed bi-layer tablets.

2.4 Thus, the subject-matter of claim 1 of the main request is obvious vis-à-vis document (2). Consequently, the main request does not meet the requirements of Article 56 EPC.

3. Auxiliary requests 1 and 2 - Inventive step

3.1 The subject-matter of claim 1 of auxiliary request 1 differs from claim 1 of the main request in the further restriction to the preferred statins, namely "and wherein the statin cholesterol lowering agent is pravastatin, fluvastatin, atorvastatin or cerivastatin."

Document (2) envisages to use the same actives (see claim 11), so that the reasoning for inventive step used under point 2 applies mutatis-mutandis to claim 1 of auxiliary request 1. No inventive step can be seen with the further addition of this technical feature.

Consequently, the subject-matter of claim 1 of auxiliary request 1 is obvious. Thus, auxiliary request 1 does not meet the requirements of Article 56 EPC.

3.2 The subject-matter of claim 1 of auxiliary request 2 differs from the main request in the restriction to the preferred statin, namely "and wherein the statin cholesterol lowering agent is pravastatin".

Since the use of pravastatin is also envisaged in document (2), the reasoning used under point 2 applies mutatis-mutandis to claim 1 of auxiliary request 2. Consequently, auxiliary request 2 does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:

N. Maslin

U. Oswald