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D E C I S I O N
of 22 June 1998

Case Number: T 0264/95 - 3.3.2

Application Number: 86304408.7

Publication Number: 0206626

IPC: A61K 33/00

Language of the proceedings: EN

Title of invention:
Use of Bismuth for the manufacture of a medicament for the treatment of gastrointestinal disorders induced by Campylobacter polyridis

Patentee:
Marshall, Barry James, Dr.

Opponent:
Glaxo Group Limited
Dr. Falk Pharma GmbH

Headword:
Campylobacter pyloridis/MARSHALL

Relevant legal provisions:
EPC Art. 54, 113(1), 114(1), 111(1), 123(2), (3)

Keyword:
"New facts submitted at the oral proceedings - accepted (Article 114(1) EPC)
"Party absent at the oral proceedings (Article 113(1) EPC) - remittal - (yes)"

Decisions cited:

G 0004/92, T 0019/86, T 0893/90

Catchword:

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0264/95 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 22 June 1998

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 9 February 1995 concerning maintenance of European patent No. 0 206 626 in amended form.**

Composition of the Board:

Chairman: U. Oswald
Members: C. Germinario
R. E. Teschemacher

Summary of Facts and Submissions

I. European Patent No. 0 206 626 was granted in response to European patent application No. 86 304 408.7 on the basis of five claims. Claim 1 reads as follows:

The use of bismuth for the manufacture of a medicament for the treatment of a disorder of the upper gastrointestinal tract of a human or other animal subject in which the disorder is caused or mediated by Campylobacter pyloridis, and wherein is excluded the use of bismuth in the form of bismuth subsalicylate.

II. Notice of opposition was filed by opponent I, who was a non-appealing party to the proceedings until his withdrawal of the opposition during the appeal proceedings, and opponent II (appellant II). Revocation of the patent in its entirety was requested on the grounds of lack of novelty, lack of inventive step, insufficiency of disclosure and on the grounds of Article 52(2)(a) EPC.

The following documents, cited during the proceedings, are relevant to the present decision:

(G1) Martin et al., The Lancet, 3 January 1981, pages 7 to 10

(G2) Marshall et al., The Medical Journal of Australia, Vol. 142, 15 April 1985, pages 439 to 444

(G3) Hislop et al., Gastroenterological Society of Australia, December 1984, page 907

(G4) WO-A-86/05981

(F1) EP-A-0 075 992

(F2) US-A-3 577 533

(F4) FR-A-6 197 M

(F7) "Pharmakologie", Knud O. Möller, Schwabe & Co. Verlag Busel-Stuttgart, 1966, pages 789 to 791

(F8) A. C. G. Borges et al. "The Lancet", 12 May 1984, pages 1068 to 1069

(F14) Pharmacology of Peptide Ulcer Disease- Springer-Velag (1991), Chapter 5, Helicobacter pylori, pages 107 to 147.

III. In its interlocutory decision, the opposition division held that the patent could be maintained in amended form.

Having concluded that the main request was not allowable for lack of novelty of claim 1 over the teaching in document (G4), and the first auxiliary request for lack of inventive step in the light of document (G2), the opposition division recognised the patentability of the second auxiliary request, which was limited to the use of bismuth in the form of

bismuth aluminate, bismuth subcarbonate, bismuth subnitrate or mixtures thereof, and to the therapeutic treatment of peptic ulcer disease only.

The opposition division held that the use of the three specific salts cited in claim 1 was not previously disclosed in connection with peptic ulcer disease caused by CLO (*Campylobacter pyloridis* organism) and that the skilled person could not predict from document (G2) or any other prior document the efficacy of these specific salts against CLO mediated disorders.

IV. Both appellant I (patentee) and appellant II (opponent II) lodged an appeal against this decision.

V. Appellant II submitted prior art documents disclosing bismuth salts for use in the treatment of gastritis or ulcer disease. He argued that, since gastrointestinal disorders were mainly caused by *Campylobacter pyloridis*, the prior therapeutic use of said bismuth compound necessarily covered the use according to the invention, even if said prior documents did not recognise *Campylobacter pyloridis* as a cause of the disorders. For this reason, the claimed subject matter had to be regarded as lacking novelty.

VI. Other arguments were presented by opponent I. Among other objections, the relevance of document G2 was emphasised, whose teaching was not limited to disclosing the anti-*Campylobacter pyloridis* activity of tripotassium dicitrate bismuthate (De-Nol), since it also disclosed the same activity for bismuth citrate.

The repeatability of the invention was also questioned, since no evidence was given in the patent disclosure that the three bismuth salts cited in the claim maintained by the opposition division had ever been tested for any activity.

VII. With the statement setting out the grounds of appeal, and, later, as a reaction to the opponents' arguments, appellant I filed several amended versions of the main and auxiliary requests. Claims 1 and 2 of the main request submitted on 15 June 1998 for consideration at the oral proceedings read as follows:

1. The use of bismuth for the manufacture of a medicament for the treatment of a peptic ulcer disease of a human or other animal subject in which the disease has been diagnosed as being caused or mediated by Campylobacter pyloridis, and wherein the bismuth in the medicament to be administered is not in the form of bismuth subsalicylate or in the form of tripotassium dicitrate bismuthate.

2. The use of bismuth according to claim 1 wherein the bismuth is selected from bismuth aluminate, bismuth subcarbonate, bismuth citrate, bismuth subgallate, bismuth subnitrate, bismuth tartrate and mixtures thereof.

VIII. Oral proceedings were held on 22 June 1998. As previously announced, appellant II failed to appear at the hearing, though duly summoned.

IX. Before opening the discussion on the matter of the novelty and inventive step of the subject-matter claimed in the latest version of the claims, the board felt the need to clarify some preliminary aspects of the claimed invention. The board expressed doubts as to the compliance with the requirements of Article 84 and 123 EPC of the feature "*in the medicament to be administered*", newly introduced into the claim in relation to the bismuth forms excluded from the scope of claim 1. However, the appellant filed during the proceedings new main and auxiliary requests from which the expression was deleted.

A further point was the exclusion from the scope of claim 1 of bismuth in the form of "tripotassium dicitrate bismuthate" and the inclusion of bismuth in the form of bismuth citrate in claim 2. Considering appellant I's contention that the two salts, once in solution, are indeed the same compound, this seemed to be an apparent contradiction. The appellant argued that bismuth citrate, being insoluble in water, could only be solubilized in ammonia solution. However, when solubilised in ammonia solution, the citrate is converted into subcitrate. For this reason, document G2, while formally citing both bismuth compounds, actually refers to only one, namely the subcitrate (De-Nol). However, according to the appellant, this situation, did not apply to the patent under appeal, since claim 2 referred to the use of bismuth citrate as such, thus in insoluble form, for the preparation, for example, of a suspension.

X. As to the novelty of the claimed subject-matter, appellant I argued that not all the patients suffering from gastrointestinal disorders were found to be infected by *C. pyloridis*. Since patients suffering similar symptoms could not be treated in the same way if their symptoms have different causes, a preliminary step of diagnosis, now integrated into the wording of the claim, is always necessary to allow the identification of a specific novel **sub-class** of patients among all the patients who suffer from GI disorders. Since, according to the invention, only this newly identified sub-class is to be subjected to bismuth treatment, the novelty of the therapeutic treatment and, accordingly, of the claimed use of the bismuth should be recognised.

XI. Bearing in mind that the use of the bismuth derivatives of the present invention in the treatment of gastrointestinal disorders such as ulcer disease or gastritis was known long before the relevant date of the patent at issue, as proved by documents cited during the proceedings (see F2, F4 and F7), the board drew appellant I's attention to the difference between the present situation and the situation considered in the prior decisions T 19/86 (OJ EPO 1989, 25) and T 893/90 (22 July 1993, not published in OJ EPO), both relevant to the present case. In these decisions, the competent boards had recognised that, if the use of a compound was known in the treatment of a disease, the treatment of the same disease with the same compound could nevertheless represent a novel therapeutic

application when the treatment was carried out on a **novel** group of patients **not-overlapping** the group of patients treated according to the prior art (see sero-positive versus sero-negative piglets or haemophilic versus non-haemophilic patients). On the contrary, according to the present invention, the treatment of ulcer disease with the known bismuth derivatives was performed, as admitted by appellant I during the oral proceedings, on a sub-class of the same patient group which had been subjected to the treatment according to the prior art documents, this sub-class being distinguished from the broader group by way of a preliminary diagnostic step. For this reason, the board questioned the novelty of claim 1 according to all requests.

XII. Following this discussion, appellant I filed a new version of the main and auxiliary requests.

The text of claim 1 of the main request reads as follows:

"*The use of bismuth for the manufacture of a medicament for the treatment of a peptic ulcer infectious disease of a human or other animal subject in which the disease has been diagnosed as being caused or mediated by Campylobacter pyloridis, and terminating the treatment after the diagnosis is negative, and wherein the bismuth is not in the form of bismuth subsalicylate or in the form of tripotassium dicitrate bismuthate".*

Claim 2 remained unchanged and the auxiliary requests

were modified along the same lines as in the main request.

XIII. The appellant argued that the treatment according to the invention was intended to eradicate the *C. pyloridis* infection, not merely to heal the ulcer, and that the successful achievement of this target could take much longer than simply healing the ulcer. The therapeutic result obtained by the method of treatment of the invention, when compared to treatment regiments known in the prior art, was a lower relapse rate of peptic ulcer diseases. This result was highlighted in the description of the filed application on page 2, last three lines from the bottom.

XIV. Appellant I (patentee) requested that the decision under appeal be set aside and the case be referred to the first instance for further examination on the basis of the requests (one main and three auxiliary requests) as submitted during the oral proceedings.

Appellant II (opponent II) had requested in writing that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

1. The appeal is admissible.

2. *Late filed claims*

At the oral proceedings, the board cast doubts about the novelty of claim 1 of the main request (in the version submitted just before the oral proceedings) on the basis of the prior art documents (F2), (F4) and (F7), describing the prior use of some bismuth derivatives of claim 1 in the treatment of ulcer disease (or gastritis) (see (F2), column 4, lines 53 to 71, (F4), page 1, right-hand column, lines 26 to 31, and example 1 and (F7), page 790). The reading of these documents by the board was substantially different from the interpretation given by the opposition division. In fact, in the board's judgement, the definition of the cause or mediating agent of the disease did not contribute significantly to the recognition of the novelty of the therapeutic treatment provided in the claim and thus to the novelty of the claimed use of bismuth.

The board considered it legitimate for appellant I to try to overcome this novelty problem, which was not apparent before, by filing new sets of claims.

3. *Article 123(2) and (3) EPC*

Claim 1 of the present main and first to third auxiliary requests have all been amended in the same way. The new feature ".. infectious disease" is disclosed eg in original claim 3. The further new features "..in which the disease has been diagnosed as being ..." and ".. and terminating the treatment after the diagnosis is negative,.." are disclosed in the original application on page 6, lines 16 to 20. The bismuth forms excluded from the scope of the claim, namely bismuth subsalicylate and tripotassium dicitrate bismuthate, are both cited in the original application, on page 5, lines 11 to 13. The requirements of Article 123(2) EPC are therefore fulfilled.

Moreover, claim 1 according to the present main and auxiliary requests is limited in scope over the granted claim 1. The treatment of "a disorder of the upper gastrointestinal tract", cited in granted claim 1, has been limited to the treatment of "peptic ulcer infectious disease". Besides, the whole treatment is, after amendment, more strictly defined in that at least two additional essential steps have been introduced into it, ie the diagnostic steps performed prior to administering bismuth and later on to decide, on the basis of a negative result, the end of the treatment. For this reason the protection conferred by the granted claims is not extended by the amendments.

4. Although allowable pursuant to Article 123(2) and (3) EPC, claim 1 of all the main and auxiliary requests

filed during the oral proceedings is substantively different from the claims considered by the opposition division, and by the other parties in the written phase of the appeal.

In fact, the text of the claims considered by the opposition division, specifically the wording "The use of bismuth ... for the manufacture of a medicament for the treatment of a ... disorder (or disease) ... **caused** or **mediated** by *Campylobacter pyloridis"* does not necessarily imply any anti-*C. pyloridis* activity of the bismuth compounds. Different bismuth salts, such as the aluminate, the nitrate, the subnitrate or the carbonate, were indeed already known in the broadest treatment of gastritis or peptic ulcers for their anti-acid or anti-pepsin properties as disclosed in (F2), column 4, lines 53 to 71, (F4), page 1, right-hand column, lines 26 to 31 and example 1 and (F7), page 789 ff. Therefore, such compounds, though not provided with any antibacterial activity, would, nevertheless, contribute to the treatment of the ulcer or other gastrointestinal diseases regardless of whether or not caused or mediated by *C. pyloridis*.

The same considerations also apply to all the preceding versions of the claims considered by the parties in the written phase of the appeal.

Unlike all the previous versions, the claims filed during the oral proceedings define a treatment in which the term of reference is no longer the healing of the evident disease (ulcer) but the detection and the

eradication of the *C. pyloridis* infection. In this case, therefore, the claim seems to be directed to the anti-bacterial (*C. pyloridis*) activity of the bismuth, and to an antibacterial treatment which may last longer than the healing of the ulcer or other gastrointestinal diseases.

5. In consideration of the substantive difference between the latest version of the main and auxiliary requests and all the previous ones, the board is of the opinion that these new claims raised new questions of fact for the first time during the oral proceedings, on which the other party, having failed to appear at the oral proceedings, has had no opportunity to present their comments.

6. According to decision G 4/92 (OJ EPO 1994, 149), a decision against a party who has been duly summoned but who has failed to appear at the oral proceedings may not be based on facts put forward for the first time during those oral proceedings, since this would infringe the fundamental right of the parties stipulated in Article 113(1) EPC.

7. In consideration of the requests of appellant II that the decision under appeal be set aside and that the patent be revoked, which requests are still valid, any final decision of the board of appeal other than the revocation of the patent, for instance a decision simply recognising the novelty of the subject-matter of any one of the main or auxiliary requests filed at the oral proceedings, would be a decision **against** an absent

party, namely appellant II.

8. Nevertheless, a preliminary substantive consideration of the new claims is necessary in order to assess the course of the further prosecution of the appeal. The board notes that none of the prior art documents (F2), (F4) and (F7), anticipating the use of the bismuth derivatives according to the invention in the treatment of ulcer disease, has recognised the contribution of *Campylobacter pyloridis* to the manifestation and further relapse of ulcer disease. For this reason, the factor indicating the beginning and the termination of the treatment according to this prior art must necessarily be the detection and healing of the ulcer itself. The traditional treatments are characterised by a very high (80-90%) rate of ulcer relapse as reported in many pre-and late-published documents such as (G1), page 9, right-hand column, lines 3, 4 and last paragraph of the same column, and (F14) "Effect of Relapse Rates of Duodenal Ulcer" and "Effect of Relapse Rates of Gastric Ulcer", pages 132 to 135. Unlike in the prior treatment, in the regimen of bismuth administration according to the invention, the factor determining the termination of the treatment is the negative diagnosis of *Campylobacter pyloridis*. However, the eradication of the infection is not necessarily concomitant with the healing of the ulcer and, in appellant I's contention, it takes longer than the simple healing of the ulcer. This is confirmed by (F8), page 1069, in which the author observed that patients recovered from ulcer disease nevertheless remained infected by the CLO bacteria. As indicated in the

original description (page 2, last complete sentence), and as confirmed by the late published document (F14), page 134, lines 3 to 8 the continuation of the bismuth treatment until the eradication of the infection is not neutral, but entails the technical effect of a decreased rate of ulcer relapse as compared with the treatment known in the prior art.

On the other hand, documents (F1) and (G2), cited during the proceedings against the novelty of the claimed subject-matter, concern the use of bismuth subcitrate, which is excluded from the scope of claim 1 of all the main and auxiliary requests.

9. Therefore, on the basis of the facts on file, the board's view is that a direct revocation of the patent for lack of novelty cannot be considered at this stage of the appeal proceedings. However, not being in a position to take any other decision without violating appellant II's right to be heard in the interpretation of decision G 4/92 (supra), the board can decide only whether to prosecute the appeal in writing or to remit the case to the first instance.

10. Considering the request of appellant I to remit the case to the opposition division and taking into account the amendments requiring substantial further examination, the board considers it appropriate that the new facts be examined by two instances. Therefore, the board makes use of the power conferred to it by Article 111(1) EPC and remits the case to the first instance for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside

2. The case is remitted to the first instance for further prosecution.

The Registrar: The Chairman:

E. Görgmaier U. Oswald