BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [X] To Chairmen and Members
(C) [ ] To Chairmen

D E C I S I O N
of 26 February 1999

Case Number: T 0317/95 - 3.3.2

Application Number: 88200397.3

Publication Number: 0282132

IPC: A61K 33/24

Language of the proceedings: EN

Title of invention:
Compositions and their use for treating gastrointestinal disorders

Patentee:
The Procter & Gamble Company

Opponent:
01: Glaxo Group Limited
02: SmithKline Beecham plc.

Headword:
Gastrointestinal compositions/PROCTER & GAMBLE

Relevant legal provisions:
EPC Art. 52(1), (4), 54(1), (2), (5), 56

Keyword:
"Novelty and patentability under Article 52(4) EPC: (questionable)"
"Inventive step: (no), obvious modification in relation to simplification and patient's compliance"

Decisions cited:
G 0001/83, G 0005/83, G 0006/83, T 0069/83

Headnote:
Use claims directed to the second medical use of two known drugs - treatment by concurrent administration differing from treatment in the prior art by the prescribed regimen (see reasons No. 4).

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0317/95 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 26 February 1999

Appellant: (Proprietor of the patent)
The Procter & Gamble Company
One Procter & Gamble Plaza
Cincinnati
Ohio 45202 (US)

Representative:
Lawrence, Peter Robin Broughton
Gill Jennings & Every
Broadgate House
7 Eldon Street
London EC2M 7LH (GB)

Respondent: (Opponent 02)
SmithKline Beecham plc, Corporate Intellectual Property, SB House
Great West Road
Brentford, Middx. TW8 9BD (GB)

Representative:
Thompson, CLive Beresford
SmithKline Beecham plc
Corporate Intellectual Property
Two New Horizons Court
Brentford, Middlesex TW8 9EP (GB)

Other party: (Opponent 01)
Glaxo Group Limited
Berkeley Avenue
Greenford,
Middlesex, UB6 ONN (GB)

Representative:
Caffin, Lee
Glaxo Holdings plc
Glaxo House
Berkeley Avenue
Greenford,
Middlesex UB6 ONN (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 23 February 1995 revoking European patent No. 0 282 132 pursuant**

to Article 102(1) EPC.

Composition of the Board:

Chairman: P. A. M. Lançon
Members: G. F. E. Rampold
R. E. Teschemacher

Summary of Facts and Submissions

I. The appellants are the proprietors of European patent No. 0 282 132 granted in response to European patent application No. 88 200 937.3.

Both respondents (opponents) 01 and respondents (opponents) 02 filed oppositions to the patent as a whole on the grounds that the subject-matter of the patent opposed was not patentable under Article 100(a) EPC, because it was not new (Articles 52(1) and 54 EPC) and it did not involve an inventive step (Articles 52(1) and 56 EPC).

II. In the proceedings before the opposition division the appellants requested maintenance of the patent in amended form either on the basis of the main request comprising 21 claims filed on 17 November 1994 or, alternatively, on the basis of the auxiliary request comprising 17 claims filed on the same date.

The independent claims of the main request read as follows:

"1. Pharmaceutical compositions useful for treating or preventing gastrointestinal disorders, said compositions comprising:

(a) a bismuth-containing agent, or a pharmaceutically acceptable salt thereof;

(b) an H_2-receptor blocking anti-secretory agent; and

(c) a pharmaceutically acceptable carrier."

Claim 1 is followed by dependent claims 1 to 9 and 18 to 21 relating to specific embodiments of the pharmaceutical compositions according to claim 1.

"10. The use of a bismuth-containing agent and an H_2-receptor blocking anti-secretory agent for the manufacture of a medicament for the treatment or prevention of gastrointestinal disorders in humans or lower animals, said treatment or prevention comprising administering to said human or lower animal a composition comprising, by weight, from 0.1 to 99.8% of the bismuth-containing agent, and administering to said human or lower animal a safe and effective amount of an H_2 receptor blocking anti-secretory agent, **the administration of the said two agents being effected within 5 minutes of each other."**

Claim 10 is followed by dependent claims 11 to 17 relating to specific embodiments of the use according to claim 10.

The independent claims of the auxiliary request read as follows:

"1. Pharmaceutical compositions useful for treating or preventing gastrointestinal
disorders, said compositions comprising:

(a) a bismuth-containing agent, or a pharmaceutically acceptable salt thereof;

(b) an H_2-receptor blocking anti-secretory agent **which is ranitidine**; and

(c) a pharmaceutically acceptable carrier."

Claim 1 is followed by dependent claims 1 to 7 and 14 to 17 relating to specific embodiments of the pharmaceutical compositions according to claim 1.

"8. The use of a bismuth-containing agent and an H_2-receptor blocking anti-secretory agent for the manufacture of a medicament for the treatment or prevention of gastrointestinal disorders in humans or lower animals, said treatment or prevention comprising administering to said human or lower animal a composition comprising, by weight, from 0.1 to 99.8% of the bismuth-containing agent, and administering to said human or lower animal a safe and effective amount of an H_2 receptor blocking anti-secretory agent **which is ranitidine, the administration of the said two agents being effected within 5 minutes of each other."**

Claim 8 is followed by dependent claims 9 to 13 relating to specific embodiments of the use according to claim 8.

III. Of the 12 citations relied on by the respondents in the course of the first instance opposition proceedings, the following are referred to in this decision:

(1) Digestion, Vol. 37, Supplement 2, 1987, S. Karger, Basel

(6) P. R. Salmon, Combination Treatment: Colloidal Bismuth Subcitrate with H_2-Antagonists; excerpt from (1) corresponding to pages 42 to 46 of (1)

(1/6) Reference number used in this decision for quoting the Salmon paper contained in (1) and (6)

(2) R. E. Pounder, Duodenal ulcers that will not heal; Gut, 1984, **25**, 697-702

(3) R. E. Pounder, Histamine H_2-receptor antagonists and gastric acid secretion, Pharmac. Ther. Vol. 26, 1984, 221-234

IV. In its decision dated 23 February 1995 the opposition division held that the novelty of the subject-matter of all claims of the contested patent had to be acknowledged.

In particular, it found that none of the citations made available in the proceedings disclosed a pharmaceutical composition according to claim 1 comprising both a bismuth containing agent and an H_2-receptor blocking anti-secretory agent.

As far as the use of said two active agents for the preparation of a medicament for the specified therapeutic treatment according to claim 10 (second or further medical indication) was concerned, the opposition division considered that the reference in the fourth full paragraph on page 699 of the Pounder paper (2) to the **"simultaneous treatment"** of patients suffering from gastrointestinal disorders with a bismuth containing agent and an H_2 receptor blocking anti-secretory agent could not necessarily be interpreted as meaning **"simultaneous administration"** of said two agents to an individual patient.

It took the view that the novelty of the claimed second medical use over the Salmon paper (1/6) or the Pounder paper (2) resided in the limitation of the use claims during opposition proceedings to **concurrent or simultaneous administration** ("within 5 minutes of each other") of both the bismuth containing agent and the H_2 receptor blocking anti-secretory agent, since treatment or prevention of gastrointestinal disorders in humans or animals comprising concurrently or simultaneously administering said two active agents could not be derived from the cited prior art.

The opposition division saw the technical problem vis-à-vis the state of the art according to citations (1/6) or (2) as that of simplifying the known treatment of gastrointestinal disorders which could readily be achieved by formulation of the two medicaments into a combined product or by their simultaneous application to a patient in need of them. In contrast to the appellants' (proprietors') allegations, it was unable to recognise in the state of the art the existence of a prejudice against the combined or simultaneous application of a bismuth containing agent and an H_2-receptor blocking anti-secretory agent in the treatment of gastrointestinal disorders.

The further restriction of the claims of the auxiliary request to the specific use of ranitidine as the H_2-antagonist was in the opinion of the opposition division an obvious selection from a limited number of options.

The patent was therefore revoked under Article 102(1) EPC on the ground of the lack of inventive step of both

the main request and the auxiliary request.

V. The appellants lodged an appeal against the decision of the opposition division and submitted a statement of grounds.

Both respondents filed their observations in response to the grounds of appeal. By letter dated 18 December 1998, respondents 01 withdrew the opposition.

VI. Of the documents submitted during the appeal proceedings, the following are referred to in this decision:

(16) L. Wallin et al., Scand. J. Gastroent., 1979, 14, 349-353

(17) D. M. Parkin et al., Deviation from prescribed drug treatment after discharge from hospital; Brit. Med. Journal, 1976, 686-688

VII. Oral proceedings were held on 26 February 1999. The appellants' submissions, both in the written procedure and at the oral proceedings, can be summarised as follows:

The opposition division correctly concluded that there was no lack of novelty for the reasons set out in points 2.1 to 2.3 on pages 4 to 5 of the impugned decision and referred to in paragraph IV above.

On the other hand, contrary to the view adopted by the opposition division, the skilled man at the priority date had reason to believe that it would be better to

administer the two active agents at different moments, even when a course of "combination therapy" according to citation (1/6) or "simultaneous treatment" according to citation (2) was followed. In particular, the following reasons diverted the skilled person away from in fact combining the two agents or administering them simultaneously:

At the priority date of the invention in 1987, the effectiveness of the bismuth agent in gastrointestinal therapy was believed to be dependent on

(i) ensuring that the coating was precipitated before the agent passed beyond the relevant portion of the gastrointestinal tract, eg an ulcer crater, and

(ii) ensuring that the coating adhered strongly and for a long time to that portion.

One of the prime factors believed to govern the speed of precipitation and the adherence of the coating was the pH. Thus, the median intra gastric pH of an ulcer patient was about 1.4. In citation (1/6) and similarly in citation (2) it had been stated that the optimum pH in the stomach for the precipitation of bismuth from the bismuth-containing agent was between 2.5 and 3.5. H_2-receptor blocking agents, such as cimetidine or ranitidine, were known to raise the intragastric pH, but it was only after a latency period of about 40 minutes following the administration of cimetidine that a pH of over 2 was attained, as evidenced by Figure 2 on page 352 of citation (16). In the case of ranitidine this latency period was even extended.

In view of the foregoing, the appellants concluded that, while raising the pH might seem to suggest the possibility of a course of treatment in which both a bismuth compound and an H_2-blocker were used, administration of either agent at different times to compensate for the latency period required for raising the pH, as suggested in (1/6), had been considered by the skilled person preferable over simultaneous administration.

For therapeutic efficacy the bismuth coating should adhere as tightly as possible to the mucous layer of the ulcer or other lesion. It was known that, in order to favour this, the pH should not be raised significantly, because it was believed that at a higher pH the binding was rapidly weakened and most of the coating would therefore be lost. This knowledge militated against administering a bismuth agent in conjunction with anything, such as an H_2-blocker, which would tend to raise the pH. If at all, it rather suggested to a person skilled in the art the administration of the two agents to be widely spaced in time.

These observations were consistent with the advice on page 61 of citation (1) to avoid "the taking of antacids too closely to doses of De-Nol", ie colloidal bismuth subcitrate (hereinafter referred to as CBS), and were also consistent with the statement at the same place that the "cytoprotective properties of De-Nol in animals decline when the luminal pH is raised".

Having regard to the foregoing points, the appellants maintained that the climate of opinion at the priority

date was certainly not in favour of simultaneous administration. Rather, there existed a certain prejudice in the state of the art against the concurrent administration of a bismuth-containing agent and an H_2-receptor blocking anti-secretory agent in the treatment of gastrointestinal disorders.

The results in the declaration by Dr Carryl provided, in the appellants' opinion, evidence that there was unexpectedly a clear clinical advantage in administering the bismuth-containing agent and the H_2-receptor blocking agent simultaneously in comparison with administering them at widely separated times. In particular the increased levels of bismuth and its longer residence in the stomach obtained by simultaneous administration, as shown in the declaration, allowed greater and more effective attack on **H. pylori** which resided in the stomach region and, accordingly, more effective treatment of gastrointestinal disorders.

The skilled person in the present case was therefore a clinical pharmacologist aiming to provide improved treatments rather than a general practitioner or hospital doctor aiming simply to improve compliance. A clinical pharmacologist would not consider modification of a regimen by administering an H_2-blocker at the same time as another agent to be risk-free and obvious.

VIII. The respondents' submissions can be summarised as follows:

The novelty of claim 10 over the explicit disclosure of the Salmon paper (1/6) was alleged by the opposition

division to be based on the concurrent administration of the two active agents. Since this limitation related to a method of treatment of the human or animal body, it could not serve to distinguish the invention over the prior art. If the limitation to concurrent administration in claim 10 was disregarded, all of the features of the claim were disclosed in citation (1/6).

The opposition division was correct in its finding that all the claims of the main request and of the auxiliary request lacked inventive step over (1/6) and (2). The prior art clearly contemplated combined treatment of patients suffering from gastrointestinal disorders with a bismuth-containing agent and an H_2-receptor blocking anti-secretory agent.

The problem to be addressed by the skilled worker was the self-evident one of how to simplify the combined treatment. The solution was to formulate the two drugs in a single pharmaceutical composition or to administer them within 5 minutes of each other, for example, concurrently.

The appellants' arguments in support of inventive step were based on their allegation that there was at the priority date a prejudice against simultaneous administration. This view clearly misinterpreted the prior art, since citation (1/6) expressly stated in the right-hand column on page 43 that optimal precipitation of bismuth from CBS occurred when the intragastric pH was between 2.5 and 3.5, whilst the median 24-hour intragastric pH was 1.4 in untreated duodenal ulcer cases and that, precisely for this reason, the use of CBS and an H_2- antagonist in combination appeared

particularly attractive for short term results.

The appellants' argument that the skilled person seeking optimum pH conditions for bismuth precipitation had not chosen simultaneous administration to avoid precipitation taking place during the latency period required for raising the intragastric pH under the influence of the H_2-antagonist, did not support the existence of a prejudice. Any benefit in spacing apart the administration of the two drugs as regards bismuth precipitation could only be marginal given that bismuth was known to precipitate satisfactorily and rapidly at pH 1.4. Any such marginal benefit would, however, be far outweighed by the simplification afforded by simultaneous administration.

The further argument put forward by the appellants that at the higher pH to be expected following simultaneous administration of the H_2 receptor blocking anti-secretory agent the binding of the bismuth coating would be lost did not support the existence of a prejudice either. This further alleged reason for a prejudice assumed that the bismuth-containing agent would at the priority date of the patent in suit have been supposed to work by forming a coating, ie the so-called "Band-Aid" effect. While this was a theory put forward at an earlier date with regard to the mechanism of action of the particular bismuth compound CBS, at the priority date in 1987 it had already been recognised that bismuth compounds had a campylobacter-inhibiting antimicrobial action which made them effective in the treatment of gastrointestinal disorders and people skilled in the art would not have supposed at the priority date of the patent in suit

that this action was dependent upon the "Band-Aid" effect.

The appellants had not succeeded in finding a single reference in the prior art to the existence of a prejudice against simultaneous administration. The nearest to such a statement of prejudice to which the appellants had been able to refer was the advice in citation (1) at page 61 against the taking of antacids too closely to CBS. It was, however, an undisputed fact that antacids had different effects compared to H_2-receptor blocking anti-secretory agents upon administration. Antacids neutralised the pH in the gastrointestinal tract very quickly, while in contrast there was a latency period of at least 30 minutes in the case of H_2-receptor blockers. It therefore could not be assumed that what applies for antacids also applies for H_2-receptor blockers.

During oral proceeding respondents 02 raised doubts in several respects about the possible value and reliability of the results reported in the declaration by Dr Carryl for the assessment of inventive step. Thus, apart from the fact that, in contrast to the state of the art according to citation (1/6), ranitidine was used as the H_2-receptor blocking anti-secretory agent in place of cimetidine, they criticised in particular the fact that, for whatever reason, the course of administering the two active agents described in (1/6) had not been followed in the comparative tests. Whereas in (1/6) the bismuth-containing agent CBS was given before the H_2 receptor blocker cimetidine was administered, CBS and ranitidine were administered in the comparative tests in reverse order. Moreover,

the finding of increased levels of bismuth or its longer residence in the stomach of animals was, in the respondents' opinion, not indicative of any improvement in reducing the relapse rate of ulceration in humans.

IX. The appellants (proprietors) requested that the decision under appeal be set aside and the patent be maintained

- **as the main request** on the basis of claims 1 to 21 filed by fax on 17 November 1994;

  alternatively, they requested that the patent be maintained

- **as the first auxiliary request** on the basis of claims 1 to 17 filed by fax on 26 January 1999 (corresponding to the auxiliary request in the first instance opposition proceedings with a minor editorial amendment to claim 8); or

- **as the second auxiliary request** on the basis of claims 1 to 9 and 18 to 21 of the set of claims according to the main request; or

- **as the third auxiliary request** on the basis of claims 1 to 7 and 14 to 17 of the set of claims according to the first auxiliary request.

X. Respondents (opponents) 02 requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Amendments (Articles 84, 123(2) and (3) EPC)*

The claims as amended by the appellants during the opposition or opposition appeal proceedings comply with the provisions of Articles 84 and 123(2) and (3) EPC. Since the admissibility of the requests on file in these formal respects was not disputed by the respondents, there is no need for further detailed substantiation of this matter.

3. *Publication date of citations (1), (6), (1/6); state of the art (Article 54(2) EPC)*

It is undisputed that the patent in suit enjoys the priority of an earlier application in USA on 9 March 1987. Citation (1) is entitled "De-Nol^{R}: Mucosal Protection and Peptic Ulcer Disease; Proceedings of the De-Nol Symposium, 8 September 1986, The World Congress of Gastroenterology, Sao Paulo"; it bears in the top left-hand corner of the front page the remark "Released June 1987".

It has, however, never been contested by the appellants during the entire proceedings that citation (1) and, accordingly, citations (6) and (1/6) represent a true

and authentic account of the earlier oral disclosure during the symposium mentioned above. The content of the above mentioned citations is therefore considered as comprised in the state of the art within the meaning of Article 54(2) EPC.

4. *Novelty (Article 54(1) EPC); patentability under the terms of Article 52(4) EPC*

4.1 Lack of novelty of **claim 10 of the main request** over the disclosure of citation (1/6) is one of the grounds on which the oppositions are based and which was brought up by respondents 02 during oral proceedings before the board. The opposition division explicitly acknowledged the novelty of claim 10 in point 2 of the reasons for the decision (see paragraph IV above).

The respondents' objection to the lack of novelty of claim 10 is based, *inter alia*, on the argument that the limitation introduced in said claim during opposition proceedings to **concurrent administration** of both the bismuth-containing agent and the H_2-receptor blocking agent related to a **method of treatment of the human or animal body by therapy** and that, according to the established case law of the boards of appeal, subject-matter excluded from patentability under Article 52 EPC could not be relied upon to distinguish the alleged invention over the cited prior art according to (1/6).

4.2 Indeed, citation (1/6) already describes the possible benefit of the combined therapy of a bismuth-containing agent, more specifically CBS, and an H_2-receptor blocking anti-secretory agent, more specifically

cimetidine, in the treatment of gastrointestinal disorders. According to the **drug regimen** prescribed for the treatment disclosed in citation (1/6), CBS tablets were given as 2 tablets twice a day, the first half an hour to 1 hour before breakfast, and the second half an hour before the last meal of the day; cimetidine was given as 2 tablets at bedtime (see page 44, right hand column, first full paragraph).

If this disclosure of the state of the art is compared with the claimed subject-matter in the contested patent, it is found that the combined **use** of the two active agents, ie CBS and cimetidine, disclosed in citation (1/6) does **not** differ from the **use** claimed in claim 10 of the main request (see paragraph II above) with regard to the combination of the two single active agents used **and** the therapeutic application of the medicament for the treatment or prevention of gastrointestinal disorders in humans or animals. Claim 10 is in no way restricted to the medicament being manufactured in any particular concentration, dosage or formulation either.

Hence, the sole difference between the prior art of (1/6) and the subject-matter of claim 10 resides in the **prescribed treatment regimen** used for administering the bismuth-containing agent on the one hand, and the H_2-receptor blocking anti-secretory agent, on the other, to an individual patient in need of them. The regimen in (1/6) comprises administering said bismuth-containing agent half an hour before the last meal of the day and said H_2-receptor blocking anti-secretory agent at bedtime, whereas according to present claim 10 these two active agents are administered within 5

minutes of each other, e.g. concurrently.

4.3 Therefore, the issue of novelty raised by the respondents essentially concerns the question of whether the mere difference in the course of the administration of the two drugs or, expressed differently, the difference in the prescribed regimen, could indeed confer novelty on claim 10.
Moreover, the respondents' objections to claim 10 appear to imply the issue of the patentability of the subject-matter of claim 10 under the terms of Article 52(4) EPC.

In the parallel decisions G 1/83, G 5/83 and G 6/83 (OJ ECO 1985, 60, 64, 67, cited in the following as G 5/83), relied on for the assessment of novelty of claim 10 by the appellants in their submissions and the opposition division in its decision, the Enlarged Board of Appeal allowed claims in a specific format for a **further medical indication**. According to Order no. 2 of the above decisions, an European patent may be granted with claims directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application.

In the context of the question of law referred to the Enlarged Board for appeal in the above decisions (*"Can a patent directed to the use be granted for the use of a substance or composition for the treatment of the human or animal body by therapy ?"*; see summary, paragraph I) the Enlarged Board of Appeal considered as a **further medical indication** the use of a substance, already known as a medicament, to treat an illness or disease not previously treated by means of that

substance (see G 5/83, especially reasons, point 17, 2nd paragraph). While the treatment of a different illness or disease, was specifically recognised in decision G 5/83 to represent a new therapeutic application (further medical indication) of a medicament known per se, this does not yet exclude the possibility of deriving a second or further medical indication (a new therapeutic application) of a substance or composition, already known as a medicament, likewise from some other, previously unknown feature or embodiment (than treatment of a different illness or disease) associated with the use of that substance or composition in a method for the medical treatment of the human or animal body. In this respect reference is made to the boards of appeal case law, for example, as summarized in "Case Law of the Boards of Appeal of the European Patent Office", 3rd edition, 1998, section I.C. 6.2.2; "Novelty of the new therapeutical application."

4.4 When applying the criteria set forth above to the present case it is found that both the cytoprotective agent BNS, on the one hand, and the acid-suppressing agent cimetidine, on the other, were at the priority date well-known and widely used commercially available drugs which had already been administered for years by doctors to patients for the treatment of duodenal ulcer and other gastrointestinal disorders [cimetidine, for example, had been introduced in 1976, see (3), top of page 221] and the activities, effects and possible side-effects of which had already been exhaustively documented [see, as examples only, citations (1), (3) and (16)].

In the context of the present case it appears particularly important to note that the **combined or simultaneous therapy** of both CBS and cimetidine in the treatment of patients suffering from duodenal ulcer had also already been initiated before the priority date by a hospital doctor specialised in gastroenterology, namely Dr P. R. Salmon (see 1/6), as a pure therapeutic method with the aim to provide an improved treatment of gastrointestinal disorders. This combined therapy involves separately administering both the commercially available drugs BNS and cimetidine to patients in need of them, using a certain prescribed regimen referred to by Dr Salmon in citation (1/6) and mentioned in point 4.2 (above).

The invention as such which forms the subject-matter of claim 10 in fact involves the treatment of exactly the same category of patients by separately administering to them exactly the same two commercial drugs in the same concentration, dosage and formulation (see page 3, line 56 to page 5, line 25 of the contested patent) for the treatment of **entirely the same illness or disease,** with the sole exception that the prescribed regimen for this treatment is slightly modified (BNS and cimetidine are administered to the patient within five minutes of each other). It appears therefore difficult to recognise in the present invention a new field of therapeutic application or any further medical indication in general associated with the claimed combined use of the bismuth-containing agent and an H_2-receptor blocking anti-secretory agent.

4.5 In considering of whether the instruction in claim 10 concerning the particular course of the administration

of the two known drugs (ie the prescribed regimen) for the treatment of gastrointestinal disorders may be regarded as relating to a further medical indication, sight should not be lost of the reasons for which the Enlarged Board of Appeal allowed claims for a second or further medical indication in analogy to the fiction of novelty for first medical indications laid down in Article 54(5) EPC. The Enlarged Board stated that it is the purpose of the exclusion of medical treatments from patentability according to Article 52(4) EPC to free from restraint non-commercial and non-industrial medical and veterinary activities. To prevent the exclusion in Article 52(4) EPC from going beyond its proper limits it seemed appropriate to take a special view of the concept of the state of the art for second and further medical indications. It was apparently the intention of the Enlarged Board of Appeal to allow claims directed to a further medical indication, in order to provide a certain compensation for the restriction on patent rights in the industrial and commercial field resulting from Article 52(4) EPC, first sentence (see G 5/83, especially reasons, point 22).

This suggests that, when it comes to the assessment of the possible limits of what could indeed be recognised to be a further medical indication (new therapeutic application) within the meaning of decision G 5/83, it appears appropriate to consider the question of whether the sole distinguishing feature, which was introduced in the claim directed to a further medical use for the purpose of delimiting the claimed subject-matter from the prior art, relates to non-commercial and non-industrial medical activities.

The board has no reason to question the appellants' submission that the pharmaceutical industry, too, is engaged in optimizing the use of drugs and medicaments by investigating the optimum regimen for their administration to achieve the maximum possible therapeutic effect. Notwithstanding this, determination of the best individual treatment schedule, in particular the prescribing and modification of drug regimens used for administering a particular medicament, so as to comply with the specific needs of a patient, appear to be in the first place part of the typical activities and duties of the doctor in attendance in exercising his professional skills of curing, preventing or alleviating the symptoms of suffering and illness. These are, however, typical non-commercial and non-industrial medical activities which Article 52(4) EPC intends to free from restraint.

In any case, before the priority date of the contested patent, the medical practitioner was in the present case aware of the possibility of treating gastrointestinal disorders using the particular combination of drugs defined in claim 10. He was similarly in a position to prescribe an effective regimen for treating each patient according to his individual needs (see citation (1/6), *loc. cit*.)

In view of the preceding it appears questionable to the board whether the feature in the last half-sentence of claim 10, which in fact relates to the prescribing of a specific drug regimen for a basically known medical treatment, more specifically, to the concurrent administration of both the bismuth-containing agent and the H2-receptor blocking agent for the treatment of

gastrointestinal disorders, could indeed be considered to represent a further medical indication from which novelty could be derived on the basis of the principles set out in decision G 5/83.

It appears questionable, too, whether this feature indeed reflects a medical activity in the industrial and commercial field not excluded from patentability within the terms of Article 52(4) EPC, as maintained by the appellants.

4.6 Since the main request and similarly the auxiliary requests have in any case to be dismissed on the ground to be dealt with in point 5 (below), there is no need to give a decision on the respondents' objections to claim 10 on the ground of lack of novelty and non-patentability under the terms of Article 52(4) EPC.

The novelty of claim 1 of the main request and the second auxiliary request was not contested and can, in the board's judgment, be acknowledged, as can the novelty of the claims of the first and third auxiliary requests, since neither the formulation of a bismuth-containing agent and an H_2-receptor blocking agent into a single combined product, nor the administration of ranitidine as the specific H_2-receptor blocking agent in combination with a bismuth-containing agent for the treatment of gastrointestinal disorders can be derived from the cited state of the art. The issue in the present case is therefore that of inventive step.

5. *Inventive step (Articles 52(1) and 56 EPC)*

5.1 With respect to inventive step the opposition division

referred in point 3.1 of the reasons for the impugned decision to citation (1/6) and equally to citation (2) as the most relevant state of the art. The Pounder paper (2) likewise discloses the use of cytoprotective bismuth-containing agents and acid-suppressing H_2-receptor blocking anti-secretory agents, eg cimetidine and ranitidine, in the treatment and prophylaxis of duodenal ulceration. In the fourth full paragraph on page 699, citation (2) provides the skilled reader with the conclusive teaching that maximal "Band-Aid" activity might occur during **simultaneous treatment** of ulcer patients with tripotassium dicitrato bismuthate and an H_2-antagonist without giving any further details about the conditions or methods used in this simultaneous treatment, for example, as far as the prescribed regimen for the administration of these two active agents is concerned.

The board concurs with the opinion of the opposition division that the expression **"simultaneous treatment"** used in (2) necessarily includes the option of **concurrently or simultaneously administering** the said two active agents to an individual patient but does not exclude any other possible treatment regimens for the combined therapy, for example, administration of the two active agents more or less widely spaced apart in time.

Since citation (1/6) does not only disclose the possibility of treating patients suffering from gastrointestinal disorders with a bismuth containing agent and an H_2- receptor blocking anti-secretory agent simultaneously, but also furnishes the skilled reader with certain details as to the combination of the

specific medicaments administered and, in particular, the regimen used in said treatment (see point 4 above), it is considered to be closer to the subject-matter of the invention than citation (2). Moreover, the results of the combined therapy reported in (1/6) already indicate a significant increase in the short term (4 weeks) healing rate of ulcer patients compared to the treatment with CBS or cimetidine alone (see especially page 45, Table VI; Conclusion).

5.2 In submitting at the appeal stage some comparative tests in the declaration by Dr Carryl, the appellants apparently wanted to take account of the fact that in the present case the state of the art according to citation (1/6) approaches the subject-matter of the patent in suit so closely that it is necessary to submit an indication of inventive step. The comparative tests submitted purport to demonstrate that the problem which had been solved by the claimed invention was the provision of **a more effective therapy** for gastrointestinal disorders mediated by the microorganism **H. pylori** (formerly known as **Campylobacter pyloridis**).

If comparative tests are chosen to demonstrate an inventive step on the basis of an unexpected effect, such tests must meet certain criteria. These include the maximum possible adherence to the instructions, parameters and conditions used in the closest state of the art to make sure that the tests provide **a true and**

reliable account of the results achieved when carrying out the teaching of the state of the art and that the claimed effect has indeed its origin in the distinguishing feature of the invention over **what is in fact disclosed in the closest state of the art.**

The requirements set forth above are not met in the present case since in the comparative tests submitted the course of administering CBS and cimetidine disclosed in citation (1/6) has not been followed. In spite of the fact that in the context of the present invention the course of administration appears crucial to the definition of the problem to be solved, no reasonable explanation could be provided on the part of the appellants during oral proceedings why in the comparative tests a CBS solution was administered to the test animals 4 hours after the H_2- receptor blocker ranitidine was given, whilst in the prior art of (1/6) the active drugs were administered in reverse order, ie CBS was given before the H_2-receptor blocker cimetidine was administered.

For other reasons, too, it appears in the board's opinion questionable whether the comparative evidence provided could indeed support the appellants' allegation that the claimed invention would provide a more effective therapy for gastrointestinal disorders mediated by the microorganism **H. pylori**. This allegation is effectively based on the finding that simultaneous administration resulted in increased levels of bismuth and its longer residence in the stomach of animals and the as yet unproven conclusion that an increased cytoprotective effect of the bismuth agent found in animal experiments would indeed result

in a more effective therapy for gastrointestinal disorders.

At the top of the right-hand column on page 61 of (1) it is, however, stated that the cytoprotective effects of CBS seen in animal experiments and the actual ulcer-healing properties of the drug are believed to be **unconnected**, since cytoprotection constitutes the mechanism by which damage is prevented while healing is the process of repairing damage already done.

Consequently, the alleged but only insufficiently supported advantageous effect cannot be taken into consideration for the determination of the problem underlying the claimed invention and hence also not for the assessment of the inventive step.

5.3 Given (1/6) as representing the closest state of the art the technical problem the invention sets out to solve may therefore be seen as that of simplifying the combined treatment of gastrointestinal disorders with a bismuth-containing agent and an H_2- receptor blocking anti-secretory agent to improve compliance without impairing the beneficial therapeutic effect achieved by the combined therapy. Simplification is in any case a reasonable and desirable objective which the skilled person would obviously seek to achieve. In the particular field of therapeutic treatment simplification of the patient's regimen affords, *inter alia*, the advantage of minimising the permanent risk of deviation from the prescribed drug treatment which may cause total or partial failure of the therapy (see in this respect, as an example only, citation (17), especially page 688: discussion).

The solution to this problem suggested in the contested patent is to combine the bismuth-containing agent and the H_2-receptor blocking agent in a single pharmaceutical composition (claim 1 of all requests on file) or to administer these two active agents separately within 5 minutes of each other (claim 10 of the main request, claim 8 of the first auxiliary request). It has not been contested by the respondents and the board has no reasonable doubts that the combined formulation or concurrent administration plausibly solves the technical problem defined above.

5.4 With reference to the observations in the foregoing points and the state of the art according to (1/6) and (2) the board is of the opinion that the skilled person in the present case is a specialist in gastroenterology or a team of specialists of that skill aiming to simplify the known combined therapy and to improve compliance. The appellants' allegation that there was at the priority date a certain concern about possible detrimental interactions between the two particular kinds of drugs used in the present simultaneous treatment requiring the assistance of a clinical pharmacologist does not find any support in the cited state of the art and has likewise not been substantiated in the appellants' submissions.

As is stated at page 43, right-hand column of (1/6), the aims of the combined therapy in (1/6) were to compare the efficacy of CBS alone, or cimetidine alone *versus* that of the combination of CBS and cimetidine in the treatment of duodenal ulcer, in order to improve the medical treatment of peptic ulceration. Under these

circumstances it appears reasonable that Dr. Salmon adhered in his study for the purpose of comparison to the conventional course used for administering the single active agents in order to obtain reliable results on the possible benefit of the combined therapy.

However, the specialist who was interested in taking advantage of the benefits achieved by using the combined therapy disclosed in (1/6) in his daily practice and whose principal aim is treatment would obviously attempt to make his patients' regimen as simple as possible, in order to improve patient compliance. Compliance is known to be a particular problem in out-patient populations where the prescribed drug regimen does not come under the permanent observation of a medical practitioner. It should be noted that non-compliance represents several risks and is a major cause of failure of treatment regimens.

In this context, the skilled person would have felt at the priority date of the contested patent a strong incentive to solve the problem defined above by administering the bismuth-containing agent and the H_2-receptor blocking anti-secretory agent concurrently, preferably simultaneously, as for the reasons given above concurrent administration may have certain benefits that even outweigh theoretical disadvantages.

Having learned from (1/6) the advantages of the combined therapy, the skilled formulator in the pharmaceutical industry would obviously have deemed the provision of a single pharmaceutical preparation for co-administration of the two active agents to represent

a particularly convenient and attractive pharmaceutical dosage form to facilitate implementation of the combined therapy.

5.5 The appellants' arguments in support of inventive step are essentially based on the allegation that there existed at the priority date a prejudice against simultaneous administration of a bismuth-containing agent and an H_2-receptor blocking anti-secretory agent. It is accepted that inventiveness could sometimes be established by demonstrating that a known prejudice, ie a widely held but incorrect opinion of a technical fact, needed to be overcome.

The burden is on the appellants to demonstrate that the alleged prejudice really existed. The existence of a prejudice should normally be demonstrated by reference to handbooks representing the general, commonly accepted specialist knowledge and encyclopaedias published before the priority date. Any prejudice which might have developed after the priority date is of no concern in the judgment of inventive step.

Contrary to the requirements set forth above, there was no evidence provided to adequately support the appellants' contention that in the present case at the priority date of the claimed invention a prejudice existed in the state of the art which would have diverted the skilled person away from simultaneous or common administration of the two active agents. It rather appears that, in the absence of a real prejudice in the sense outlined above, the appellants made in their submissions **an *ex post facto* attempt to create a prejudice, which in fact did not exist,** by more or less

arbitrarily selecting certain isolated disclosures from the state of the art and purposively combining them with the benefit of hindsight.

In fact, contrary to there being a prejudice against simultaneous administration, the Pounder paper (2) refers in full paragraph 4 on page 699 to possible advantages of **simultaneous treatment** which clearly includes the obvious option of **simultaneously administering** both the bismuth-containing agent and the H_2-antagonist. The appellants allegation that a prejudice had existed is therefore not readily understood, because both citation (1/6) - see especially top right-hand column on page 43 - and likewise citation (2) - see lines 1 to 3 of paragraph 4 on page 699 - underline the fact that optimal precipitation of bismuth in the stomach occurred when the pH was between 2.5 and 3.5, whilst the median 24-hour intragastric pH was 1.4 in untreated duodenal ulcer cases and that, **precisely for this reason**, the combined use of a bismuth-containing agent and an H_2-receptor blocking anti-secretory agent having the capability of raising the pH to the desired level was recommended as particularly attractive for short term healing.

The appellants provided no evidence in support of their assertion that the effectiveness of the bismuth agent in gastrointestinal therapy was indeed believed to be reduced or to deteriorate by the concurrent administration of an H_2-receptor blocking anti-secretory agent or that simultaneous administration was indeed believed to bear any risk due to potential interactions between the two drugs.

The appellants' reference in this respect to Prof. Konturek's advice in citation (1) at page 61 (see especially right-hand column, second paragraph) against the taking of antacids too closely to doses of CBS is similarly not of any help in supporting the existence of a prejudice. It is an undisputed fact that antacids have different effects compared to H_2-receptor blocking anti-secretory agents upon administration. While antacids neutralise the pH in the gastrointestinal tract immediately after ingestion as a result of interaction between the antacid and the hydrochloric acid in the stomach, H_2-receptor blockers are systemic drugs and do not cause a significant rise in the intragastric pH for a latency period of 30 minutes or more - see citation (3). Hence, in the absence of any evidence to the contrary, the skilled person would not assume that the advice given in (1) applies to the administration of H_2-receptor blockers as well.

5.6 It was further asserted on the part of the appellants that, in order to achieve effective bismuth precipitation, it was believed at the priority date to be necessary or at least advantageous to have raised the intragastric pH [from pH 1.4 in untreated ulcer patients to pH 2.5 to 3.5 for the bismuth agent CBS, see point 5.5 above]. For this reason the skilled practitioner seeking optimum pH conditions for bismuth precipitation would, in the appellants' opinion, not have chosen simultaneous administration to avoid precipitation taking place during the latency period of the H_2-receptor blocker with the pH being below the optimum range but would have given preference to administration of the two active agents at different times.

This argument is not convincing. Firstly, bismuth preparations have for years successfully been administered as the sole active agent for the treatment of ulcer patients and were thus known to exhibit their beneficial therapeutic effect equally at a lower pH in the absence of an H_2-receptor blocker (see in this respect Table VI at page 45 in (1/6); (2), especially page 697, line 5 from the bottom to page 698, line 9 from the bottom). Secondly, the results of the combined therapy provided in the Salmon paper (1/6) indicate a significantly increased early (4 weeks) healing of duodenal ulcers **in spite of the fact that** the bismuth agent was given prior to raising the intragastric pH by the administration of the H_2- receptor blocker.

Accordingly, in contrast to the appellants' allegations, the skilled person would have reasonably concluded that any beneficial effect which could possibly be achieved by spacing apart the time of administration of the two drugs to allow raising the intragastric pH at the time of bismuth ingestion, would, if at all, only be marginal and would be outweighed by the simplified regimen afforded by simultaneous administration.

The appellants also relied on the argument that according to the prevailing expert's opinion at the priority date a significant rise in intragastric pH and, accordingly, the administration of an H_2-receptor blocking anti-secretory agent, which would tend to raise the pH, should be avoided in connection with the administration of a bismuth agent, in order to favour tight adherence of the bismuth coating to the mucous layer of the ulcer or other lesion, because it was

believed that at a higher pH the adherence was rapidly weakened and most of the coating would therefore be lost.

Apart from the fact that this argument, too, is unsubstantiated and entirely unsupported by any disclosure in the state of the art, it appears to be in contradiction with the appellants' assertion referred to in the foregoing two paragraphs that it would be beneficial to have raised the intragastric pH at the time of bismuth administration in order to achieve effective bismuth precipitation. Moreover, the appellants' view was at the priority date clearly obsolete in view of the fact that the beneficial results of the combined therapy reported in the Salmon paper (1/6) were achieved in spite of using a treatment regimen which involved ingestion of the H_2-receptor blocker subsequent to bismuth administration.

5.7 All in all, having carefully studied the cited state of the art and the parties' submissions in the proceedings, the board cannot recognise a real prejudice or at least a good reason which would possibly have prevented the skilled person from the obvious solution of the problem defined above by combining a bismuth-containing agent and an H_2-receptor blocking anti-secretory agent in a single pharmaceutical composition or by administration of said two agents simultaneously. Therefore, the board considers for the reasons given above that the main request and the second auxiliary request do not involve an inventive step.

5.8 In the claims of the first and third auxiliary requests

the H_2-receptor blocking anti-secretory agent was restricted to ranitidine which is likewise a well-known H_2-receptor blocking anti-secretory agent, commercially available for years- see (3). Ranitidine is, for example, specifically referred to in citation (2) as an alternative to cimetidine and is said to have a greater ant-secretory effect than cimetidine (see page 699, lines 4 to 20). Ranitidine of course belongs to the class of H_2-antagonists which are recommended at page 699 of (2) to be combined with tripotassium dicitrato bismuthate for **simultaneous treatment** of ulcer patients.

By reference to section 5.9 on page 225 of citation (3), the appellants themselves have admitted that cimetidine and ranitidine have remarkably similar absorption, distribution and elimination characteristics (see appellants' letter dated 26 January 1999, paragraph 4.20). It follows that on the basis of the disclosure of citations (2) and (3) the skilled person would consider ranitidine as an obvious alternative to cimetidine for the combined therapy of gastrointestinal disorders.

The appellants argued that, following the ingestion of ranitidine, the latency period required for raising the intragastric pH was longer than the corresponding period following administration of cimetidine and implied that this was a reason for a particular prejudice against simultaneous application of ranitidine and a bismuth agent. However, apart from the fact that this prejudice similarly finds no adequate support in the cited documents, it has already been noted in the foregoing point 5.6 that bismuth

precipitation apparently takes place sufficiently and quickly at the untreated, normal intragastric pH of ulcer patients.

The further argument that, at the higher pH in the stomach resulting from the greater anti-secretory activity of ranitidine compared to cimetidine, the binding of the bismuth coating to the mucous layer was believed to be rapidly weakened with the consequence of detrimental effects in the treatment of gastrointestinal disorders is likewise entirely unsubstantiated. Moreover, with reference to what has been said in the last paragraph of point 5.6 above, this argument does not appear to be a good reason for the existence of a prejudice either.

5.9 In conclusion, the board cannot recognise a real prejudice or at least a good reason which would possibly have prevented the skilled person from the similar obvious solution of the problem defined above by combining a bismuth-containing agent and ranitidine in a single pharmaceutical composition or administration of said two agents simultaneously. Therefore, the board considers for the reasons given above that the first auxiliary request and the third auxiliary request do not involve an inventive step either.

5.10 Since for the reasons given in this decision it was, in the board's opinion, obvious for the skilled person to arrive at the proposed solution of the technical problem concerned, none of the requests could be considered to be acceptable under the terms of Article 52(1) in conjunction with Article 56 EPC, even

if it were accepted that a more effective therapy for gastrointestinal disorders could possibly be achieved as an extra effect caused by the combined or simultaneous administration of the two active agents (see decision T 69/83, OJ EPO 1984, 357).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Martorana P. A. M. Lançon