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) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

Datasheet for the decision of 23 November 2006

Case Number: T 0059/04 - 3.3.02

Application Number: 96919679.9

Publication Number: 0825860

IPC: A61K 31/43

Language of the proceedings: EN

Title of invention:
Use of a composition comprising amoxycillin and clavulanic acid for the manufacture of a medicament for the treatment of bacterial infections on paediatric patients

Patentee:
SMITHKLINE BEECHAM PLC, et al

Opponents:
Grünenthal GmbH
LEK Pharmaceutical and Chemical Company d.d.

Headword:
Pharmaceutical compositions/SMITHKLINE BEECHAM PLC

Relevant legal provisions:
EPC Art. 54, 56, 84, 123(2)
EPC R. 57(a)

Keyword:
"Novelty (yes): the combination of features was not specifically disclosed in the prior art"
"Inventive step (no): no non-obvious effect; the comparative tests do not concern the closest prior art"

Decisions cited:
T 0197/86, T 0344/99

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0059/04 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 23 November 2006

Appellant: (Patent Proprietor)
SMITHKLINE BEECHAM PLC
New Horizons Court
Brentford,
Middlesex TW8 9EP (GB)

Representative:
Connell, Anthony Christopher
GlaxoSmithKline
Corporate Intellectual Property (CN9.25.19)
980 Great West Road
Brentford,
Middlesex TW8 9GS (GB)

Respondent 1: (Opponent 01)
Grünenthal GmbH
Postfach 500444
D-52088 Aachen (DE)

Representative:
Kutzenberger, Helga
Kutzenberger & Wolff
Theodor-Heuss-Ring 23
D-50668 Köln (DE)

Respondent 2: (Opponent 02)
LEK Pharmaceutical and Chemical Company d.d.
Verovskova 57
SI-1526 Ljubljana (SI)

Representative:
TBK-Patent
Bavariaring 4-6
D-80336 München (DE)

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 30 December 2003 revoking European patent No. 0825860 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: J. Riolo
Members: A. Lindner
J. Seitz

Summary of Facts and Submissions

I. European patent No. 0 825 860 based on application No. 96 919 679.9 was granted on the basis of a set of six claims.

Independent claim 1 reads as follows:

"1. The use of amoxycillin trihydrate and potassium clavulanate in combination, in a weight ratio of 7:1, the weights being expressed as the free parent acids amoxycillin and clavulanic acid, for the manufacture of a paediatric medicament for treating bacterial infections in paediatric patients which medicament is administered twice daily (bid), at a dosage of between 20 and 70 mg/kg/day of amoxycillin and a *pro rata* amount of clavulanic acid."

II. Two oppositions were filed against the granted patent. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step, under Article 100(b) EPC for insufficiency of disclosure and Article 100(c) EPC for added matter over the application as originally filed.

III. The following documents *inter alia* were cited during the opposition and appeal proceedings:

(D1) Drugs, 1990, 39(2), pages 264-307, P.E. Todd and P. Benfield, "Amoxycillin/Clavulanic Acid; An Update of its Antibacterial Activity, Pharmaco-kinetic Properties and Therapeutic Use"

(D2) Eur. J. Clin. Microbiol. Infect. Dis., 1993, 12(5), 319-324, S. Jacobsson et al., "Evaluation of Amoxycillin Clavulanate Twice Daily versus Thrice Daily in the Treatment of Otitis Media in Children"

(D3) WO 95/28927

(D4) Repertorio Farmaceutico Italiano, 1989, pp. A-106-A-108

(D13) Antimicrobial Agents and Chemotherapy, 1982, 22(2), pages 346-349, F. Crokaert et al., "Activities of Amoxicillin and Clavulanic Acid Combinations against Urinary Tract Infections"

(D14) Ann. Pediatr. (Paris), 1992, 39, no. 2, pages 142-148, J. Astruc, "Efficacité et tolérance d'une nouvelle formulation d'amoxicilline 100 mg - acide clavulanique 12,5 mg dans les otites aiguës du nourrisson"

(D21) J. Drug Dev., 1989, 2 (Suppl. 1), pages 67-69, P. Croydon, "A Worldwide Survey of Clinical Experiences with Augmentin"

(D23) New Formulation of Augmentin® enhances Convenience and Tolerability for Children, GlaxoSmithKline press release, 19 September 1995

(D24) Austria-Codex Fachinformation 1994/95, pages 316-319.

IV. By its decision pronounced on 14 November 2003, the opposition division revoked the patent under Article 102(1) EPC, because the main request contained added matter and the auxiliary request did not meet the requirements of inventive step. Its principal findings were as follows:

(1) As far as the main request (claims as granted) is concerned, the opposition division came to the conclusion that *acute otitis media* is only disclosed in specific examples which cannot be generalised. As a consequence, the requirements of Article 123(2) EPC had not been met.

(2) In connection with the auxiliary request (claims 1-6 filed with the letter of 11 September 2003), the opposition division was of the opinion that the requirements of Articles 123(3) and 83 EPC had been met. Moreover, it was held that the subject-matter claimed therein was novel, as (D1) did not specifically disclose the combination of all the features of claim 1, (D3) did not specifically relate to paediatric patients and (D14) did not disclose a ratio of 7:1 for the combination of amoxycillin and clavulanate.

(3) As for inventive step, the opposition division regarded document (D2) as representing the closest state of the art. In its opinion the only distinguishing feature over said disclosure was the ratio of 7:1 for the combination of

amoxycillin and clavulanate. Since it was known from (D1) to use amoxycillin and clavulante in a ratio of 7:1 for b.i.d. administration in adults and since it was further known from (D1) that the pharmacokinetic profile of amoxycillin and clavulanate in children parallels that in adults, it would appear obvious to use a ratio of 7:1 for b.i.d. administration in paediatric therapy.

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

VI. With his letter of 9 November 2006, the appellant filed a main request as well as three auxiliary requests.

(1) Independent claim 1 of the main request reads: "The use of amoxycillin trihydrate and potassium clavulanate in combination, in a weight ratio of 7:1, the weights being expressed as the free parent acids amoxycillin and clavulanic acid, for the manufacture of a paediatric medicament for treating bacterial infections in paediatric patients which medicament is in the form of a liquid aqueous suspension containing 150-450 mg amoxycillin per 5 ml liquid aqueous suspension and 25-75 mg clavulanic acid per 5 ml liquid aqueous suspension, or a dry powder or granule formulation for reconstitution into such a suspension, and is orally administered twice daily (bid), at a dosage of between 20 and 70 mg/kg/day of amoxycillin and a *pro rata* amount of clavulanic acid."

(2) Independent claim 1 of the first auxiliary request is identical to claim 1 of the main request,

except that the dosage for amoxycillin has been changed from "between 20 and 70 mg/kg/day" to "45 or 70 mg/kg/day".

(3) Independent claim 1 of the second auxiliary request is identical to claim 1 of the main request, except that the dosage for amoxycillin has been changed from "between 20 and 70 mg/kg/day" to "45 mg/kg/day".

(4) Independent claim 1 of the third auxiliary request is identical to claim 1 of the main request, except that the dosage for amoxycillin has been changed from "between 20 and 70 mg/kg/day" to "45 mg/kg/day" and the treatment from "bacterial infections" to "otitis media".

VII. At the oral proceedings of 23 November 2006, the appellant filed an amended main request as well as amended auxiliary requests 1-3 in replacement of the previous requests. These requests correspond to the previous main request and auxiliary requests 1-3, wherein the range "150 - 450 mg of amoxycillin" was replaced by "200 or 400 mg of amoxycillin".

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

(1) As regards the clarity objections raised by the board at the oral proceedings in connection with the main request as filed with the letter of 9 November 2006, the appellant held that if there was a contradiction between a ratio of 7:1 and the concentration ranges of amoxycillin and clavulanic acid in the liquid aqueous suspension, the person

skilled in the art would immediately identify the ratio of 7:1 as the governing feature. He would only take into account compositions that respect all the features of claim 1. As a consequence, he would restrict the concentration ranges of amoxycillin and clavulanic acid rather than change the ratio of 7:1.

(2) In connection with the admissibility of the requests filed at the oral proceedings of 23 November 2006, he argued that these new requests were the reaction to the objections raised by the board for the first time at the oral proceedings. As a consequence, these requests could not have been filed earlier.

(3) As for the objections of the respondents raised under Article 123(2) EPC in connection with the requests filed at the oral proceedings of 23 November 2006, it was argued that all the features of claim 1 had their basis in the claims as originally filed. Therefore, there was no new combination of features taken from several lists. As far as the feature "paediatric medicament" is concerned, it was emphasised that the application as originally filed solely disclosed paediatric medicaments. Reference was made to page 3, line 27 and page 4, line 11 of the application as originally filed. Finally, the appellant contested the respondents' objection that specific values (200 mg/5 ml and 400 mg/5 ml of amoxycillin and 28.5 mg/5 ml and 57 mg/5 ml of clavulanate) are not specifically disclosed if they are accompanied

by a tolerance range (± 10%) by citing decision T 344/99.

(4) It was also held that the inclusion of "dry powder and granule" into claim 1 was in accordance with Rule 57(a) EPC. Claim 1 as granted related to paediatric medicaments in general and the restriction to "liquid suspensions, dry powders or granule formulations for reconstitution" was a reaction to the respondents' objection concerning the validity of the first priority.

(5) Moreover, the claims were clear, as the person skilled in the art could readily recognise that the claims comprised three alternatives, namely suspensions, dry powders or granules and that the latter two forms must be suitable for reconstitution into suspensions.

(6) In connection with novelty, the appellant emphasised that D1 did not disclose paediatric medicaments having a weight ratio of amoxycillin to clavulanic acid of 7:1 for b.i.d. administration. The tablets comprising 875 mg amoxycillin and 125 clavulanic acid were only for adults. Moreover, D1 was a review of a large number of scientific articles. As their content was not always accurately summarised, it was necessary to turn to the original articles where the lack of novelty destroying disclosure was even more apparent than in D1.

(7) With regard to inventive step, D2 was considered to represent the closest prior art. D2 disclosed two different treatment schemes for *otitis media* in children: a composition comprising amoxycillin and clavulanic acid 4:1 for t.i.d. application, and a composition comprising slightly higher amounts of amoxycillin and clavulanic acid 4:1 for b.i.d. administration. In view of the fact that b.i.d administration in D2 resulted in higher incidences of diarrhoea as an unwanted side effect, the composition for t.i.d. administration was considered to represent the closest prior art. As compared to the closest prior art, the subject-matter of the present main request solved three problems: better compliance, less severe side effects in the form of diarrhoea and no diminution of the therapeutic efficacy. Reference was made to clinical trials A and B of the patent in suit where these effects were clearly shown. The lower incidence of diarrhoea for the b.i.d. regimen as evidenced in the patent in suit was in contrast to the teaching of D2. Moreover, there was a prejudice against applying a b.i.d regimen for the treatment of severe infections such as *otitis media*, as D4 clearly indicated an increase in the posology from twice per day to three times per day if severe infections were to be treated.

With regard to auxiliary request 1 the appellant held that D2 was now even less pertinent, as there was no reason for the person skilled in the art to increase the dosage of amoxycillin from 33.2 mg/kg/day (D2) to 45 or 70 mg/kg/day. The US formulation serving as reference in clinical trial

A of the patent in suit (40 mg/kg/day of amoxycillin, ratio 4:1, administered three times per day) now represented the closest prior art, and the subject-matter of auxiliary request 1 involved an inventive step in the light of the non-obvious effects shown in clinical trials A and B.

With regard to auxiliary request 2, the appellant additionally pointed out that the subject-matter as claimed now more or less corresponded to clinical trial A where, in contrast to clinical trial B, a clear reduction in the incidence of diarrhoea was demonstrated.

As for auxiliary request 3, it was held that claim 1 was now limited to the treatment of *otitis media* which belonged to the severe bacterial infections for which there existed a prejudice as far a b.i.d. regimen of the combination of amoxycillin and clavulanic acid was concerned. Reference was made to (D4) in this context.

IX. The respondents' arguments can be summarized as follows:

(1) As far as the clarity objections raised in connection with the main request as filed with letter of 9 November 2006 are concerned, the respondents contested that the ratio of 7:1 was the governing feature. Claim 1 was contradictory in itself and therefore not in accordance with the requirements of Article 84 EPC.

(2) In connection with the admissibility of the sets of claims filed at the oral proceedings of 23 November 2006, it was held that they were late-filed and should therefore not be admitted. Although it was true that the specific objections under Article 84 EPC were raised for the first time at the oral proceedings, the appellant had already amended the claims several times in the course of the appeal procedure. Each set of claims filed in the course of the appeal procedure had been formally deficient. The appellant could be expected to file a formally correct set of claims in due time so that the respondents were in a position to properly prepare their case.

(3) In connection with the requirements of Article 123(2) EPC, the respondents essentially argued that the present claims were the result of selections from several lists. Moreover, it was held that the application as originally filed did not specifically disclose paediatric medicaments. This objection was particularly pertinent for the dry powder and the granule formulation which in the application as originally filed had to be suitable for being transformed into a paediatric suspension but were not paediatric *per se*. The respondents held that there was no basis for the features 200 mg/5 ml and 400 mg/5 ml of amoxycillin and 28.5 mg/5 ml and 57 mg/5 ml of clavulanate, as in the application as originally filed these figures were disclosed with a tolerance range of ± 10%. A further objection under Article 123(2) EPC was raised as regards the change of wording from "..when reconstituted"

(claim 12 as originally filed) to "...for reconstitution" (claim 1 of main and auxiliary requests 1-3) in connection with the dry powder and granule formulation).

(4) The introduction of the features "dry powder" and "granule formulation" was not occasioned by a ground for opposition and, as a consequence, not allowable under Rule 57(a) EPC.

(5) As for the clarity of the claims as filed at the oral proceedings of 23 November 2006, respondent 2 argued that the unit "per 5 ml liquid aqueous suspension" is not clear in connection with dry powder or granule formulation. Further problems were seen in the fact that claim 1 now contained three alternatives in the form of one finished product (suspension) and two preforms (dry powder and granules).

(6) The respondents held that (D1) destroyed the novelty of claim 1 of the main request as filed at the oral proceedings of 23 November 2006. In connection with the dry powder or granule formulation he argued that any powder or granule composition including tablets or capsules comprising amoxycillin and clavulanate in a 7:1 ratio destroyed the novelty of the said claim.

(7) As far as the inventive step of the main request as filed at the oral proceedings of 23 November 2006 is concerned, the respondents defined D2 as closest prior art and argued that the ratio of 7:1 was the only distinguishing feature. The problem

to be solved by increasing the ratio of amoxycillin to clavulanate from 4:1 to 7:1 could be defined as follows: increase in the antibacterial activity. The solution was obvious as it was known that the antibacterial effect was obtained from amoxycillin, whereas the clavulanate served a different purpose, namely the prevention of the formation of beta-lactamase. The person skilled in the art would select a 7:1 ratio, because this ratio had already been used for oral b.i.d. administration in adults.

X. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or of one of auxiliary requests 1-3 as filed at the oral proceedings of 23 November 2006.

The respondents (opponents) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. The main request and auxiliary request 1-3 submitted during the oral proceedings of 23 November 2006 replace the requests as filed with letter of 9 November 2006.

3. Admissibility of the requests filed at the oral proceedings of 23 November 2006:

It is well-established by the jurisprudence of the boards of appeal that, in considering the admissibility of late-filed submissions, account is to be taken, *inter alia*, of whether they could have been filed earlier. The board came to the conclusion that it was not possible for the appellant to file his new sets of claims earlier for the following reasons: together with the statement of the grounds of appeal dated 7 May 2004, the appellant filed a new main request which was identical with auxiliary request 1 of the decision under appeal as well as three auxiliary requests. It was only then that respondent 1 contested the validity of the first priority for the first time with his letter of 27 December 2004 although the claims to which the objections were directed had already been on file at the proceedings of the first instance. The appellant then filed amended claims with his letter of 15 July 2005 as a reaction to respondent 1's new objections. Then, in his letter of 20 October 2006, respondent 1 raised new objections under Article 84 and 123(2) EPC to which the appellant reacted again by filing further amended claims with his letter of 9 November 2006. Finally, the appellant was confronted with fresh clarity objections at the beginning of the oral proceedings of 23 November 2006. As a consequence, taking into consideration the procedural steps taken by the parties up to the oral proceedings of 23 November 2006, the appellant had to be given the opportunity to further amend his claims in the interest of procedural fairness. Moreover, the amendments made were predictable and could therefore not take the respondents by surprise. As a consequence, the amended main request as well as auxiliary requests 1-3 filed at

the oral proceedings of 23 November 2006 were admitted into the procedure.

4. Rule 57(a) EPC:

Claim 1 as granted was directed to a second medical use claim directed to paediatric medicaments in general. The board agrees with the appellant's argumentation that the replacement of "paediatric medicaments" by "liquid aqueous suspensions ..., or a dry powder or granule formulation for reconstitution into such a suspension" was an appropriate reaction to respondent 1's objection concerning the validity of the first priority. It is noted that a valid first priority was of paramount importance for novelty and inventive step due to the existence of pertinent intermediate documents (D3; D23). As a consequence, the subject-matter of the main request and auxiliary requests 1-3 as filed at the oral proceedings of 23 November 2006 is in accordance with the requirements of Rule 57(a) EPC.

5. Article 123(2) EPC:

5.1 Claim 1 of the main request as filed at the oral proceedings is based on original claim 12 and its dependent claims, in particular claims 14, 15, 19 and 25 which all refer back to independent claim 12. As a consequence, present claim 1 cannot be considered as a new combination of hitherto unconnected features as alleged by the respondents. For completeness's sake, it is noted that claim 12 and its dependent claims do not specifically mention the treatment of bacterial infections. However, this feature can be found on page 1, lines 3-6, which is a general statement

applicable to all embodiments of the patent in suit. In addition, the board is of the opinion that specific values are specifically disclosed even if they are accompanied by a tolerance range.

5.2 With regard to auxiliary request 1, the basis for the amendment (45 or 70 mg/kg/day of amoxycillin) can be found in claims 19 and 21 of the application as originally filed.

5.3 With regard to auxiliary request 2, the basis for the amendment (45 mg/kg/day of amoxycillin) can be found in claim 21 of the application as originally filed.

5.4 With regard to auxiliary request 3, the basis for the amendment (treatment of *otitis media*) can be found on page 2, lines 19-22 of the application as originally filed.

5.5 As a consequence, the subject-matter of the main request and auxiliary requests 1-3 meets the requirements of Article 123(2) EPC. In view of the subsequent decision concerning inventive step (cf. paragraph 10 below), a more detailed discussion concerning the basis for the amendments is not needed.

6. Clarity:

The subject-matter of the main request and of auxiliary requests 1-3 is clear, as the person skilled in the art can readily recognise that the claims comprise three alternatives, namely suspensions, dry powders or granules and that the latter two forms must be suitable for reconstitution into suspensions. Moreover, it is

clear for the person skilled in the art that the feature "per 5 ml liquid aqueous suspension" does not refer to the dry powder and the granule formulation. As a consequence, the requirements of Article 84 EPC are met. In view of the subsequent decision concerning inventive step (cf. paragraph 10 below), a more detailed discussion concerning the clarity of the claims is not needed.

7. Insufficiency:

The objections concerning insufficiency were not upheld by the respondents. In view of the fact that the cause for this objection (upper limit of 70 mg/kg/day of amoxycillin in claim 1 and 70 ± 10 mg/kg/day of amoxycillin in a dependent claim) was no longer present in the claims filed at the oral proceedings, the board has no reason to further investigate this matter. As a consequence, the subject-matter of the main request and auxiliary requests 1-3 meets the requirements of Article 83 EPC.

8. Priority:

The validity of the first priority was not discussed in connection with the claims as filed at the oral proceedings. In view of the fact that all the documents subsequently used in connection with novelty and inventive step were published before the first priority date of 3 May 1995, the board has no reason to further investigate this matter.

9. Novelty:

9.1 Main request:

(D1) discloses on page 266 (paragraph titled "Therapeutic Trials") the use of amoxycillin and clavulanic acid in the range 250/125 to 875/125 mg two or three times daily for the treatment of bacterial infections in adults and bodyweight-adjusted dosages for children. On page 267 (paragraph "Dosage and Administration"), it is further noted that the recommended dosage for children is in the range 20-40 mg/kg. Page 281 (first complete paragraph of the left-hand column) discloses the fact that a regimen of 875 to 125 mg of amoxycillin to clavulanic acid which corresponds to a ratio of 7:1 was administered twice per day. On page 296 (first paragraph of the left-hand column) it is again emphasized that the dosage comprising 875 to 125 mg is administered two or three times per day, depending on the severity of the infection and finally, in the second paragraph of the same column, suspensions and syrups are recommended for oral administration in paediatric patients.

Although, as can be seen from the previous paragraph, (D1) discloses all the individual features of present claim 1, the board came to the conclusion that the combination of all these features is not specifically disclosed in (D1). This concerns in particular the combination of the 7:1 ratio amoxycillin to clavulanic acid **plus** paediatric application **plus** b.i.d administration **plus** liquid aqueous suspension or galenic form suitable for reconstitution into such a suspension.

In view of the subsequent decision concerning inventive step (cf. paragraph 10 below), a more detailed discussion concerning novelty is not needed. As a consequence, the subject-matter of the main request as filed at the oral proceedings of 23 November 2006 is novel (Article 54 EPC).

9.2 Auxiliary requests 1-3:

This finding applies *mutatis mutandis* to auxiliary requests 1-3.

10. Inventive step:

10.1 Main request:

10.1.1 The patent in suit relates to the use of a combination of the antibiotic amoxycillin trihydrate and the beta-lactamase inhibitor potassium clavulanate, in a weight ratio of 7:1 for the manufacture of a paediatric medicament for treating bacterial infections, in particular *otitis media*, in paediatric patients such medicament being administered twice daily at a dosage of between 20 and 70 mg/kg/day of amoxycillin and a *pro* rata amount of clavulanate (page 1, lines 43-47 and 51 of the patent specification). The medicament is to be provided in the form of a liquid aqueous suspension or of a dry powder or granule formulation for reconstitution into a liquid aqueous suspension (page 3, lines 2-4 of the patent specification).

10.1.2 (D2) concerns a comparative study of a b.i.d. and t.i.d administration of the 4:1 combination of amoxycillin to clavulanate for the treatment of *otitis media* in children. As far as the b.i.d. administration in D2 is concerned, the combination was administered in the form of a suspension comprising 50 mg/ml amoxycillin (= 250 mg/5ml). The daily dosage of amoxycillin was in the range of 26.6-33.2 mg/kg/day. For the t.i.d. administration, slightly different concentrations were used: there, the suspension contained 25 mg/ml amoxycillin (125 mg/5 ml) and the daily dosage of amoxycillin was in the range of 20.0-25 mg/kg/day (page 320, paragraph "Dosage and Duration of Therapy"). (D2) represents the closest prior art.

10.1.3 In fact, there was agreement between the parties to the extent that (D2) represents the closest prior art; there was disagreement, however, as to whether the b.i.d or the t.i.d administration should be used as the basis for inventive step. The appellant defined the t.i.d. administration of (D2) as closest prior art in view of the technical problem to be solved by the present invention. He argued that it is established practice to select as closest prior art a document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention. The invention of the contested patent addressed three interconnected problems: (a) reduction of diarrhoea commonly observed after paediatric application of amoxycillin and clavulanate, while (b) not worsening the therapeutic efficacy, and (c) better compliance. In view of this problem, and in particular in view of aspect (a), the person skilled in the art would not select the b.i.d. administration as disclosed

in (D2), as there the incidence of diarrhoea was shown to be higher than for the t.i.d. administration. Reference was made to table 3 of (D2).

The board cannot agree to this reasoning. As far as aspect (a) of the problem defined above is concerned, reference is made to (D2), page 322, paragraph bridging columns 1 and 2, where it is stated that a slightly higher incidence of adverse reactions in the b.i.d. group was not statistically significant. In other words, the incidence of diarrhoea is roughly the same in both groups. As for patient compliance, however, it goes without saying that the b.i.d. regimen is clearly preferable to t.i.d. administration. Taking into consideration that the therapeutic efficacy in (D2) is the same for b.i.d. and t.i.d. administration, the b.i.d. regimen of (D2) represents the closest prior art.

10.1.4 As can be seen from paragraph 10.1.2 above, there are the following two differences between (D2) and the subject-matter of present claim 1: (a) the concentrations of active agent in the suspension are different: 250 mg of amoxycillin per 5 ml of suspension in (D2) vs. 200 or 400 mg in present claim 1 and corresponding *pro rata* amounts of clavulanate; and (b) in (D2) the ratio of amoxycillin to clavulanate = 4:1 rather than 7:1.

With regard to the concentration of active agent in the suspension (difference (a)), it is noted that this feature has no influence on the therapeutic performance. It only determines the volume of suspension that has to be administered in order to

obtain a certain dosage. No particular effect can be attributed to changing the concentration of amoxycillin from 250 to 200 mg/5ml.

As far as the difference in the ratio of amoxycillin to clavulanate is concerned, the board notes that there is no evidence of a non-obvious effect based on changing the ratio from 4:1 to 7:1. It is true that the patent in suit contains comparative tests (clinical trial A) which demonstrate a lower incidence of diarrhoea for the ratio 7:1, but as the opposition division had already correctly pointed out in the decision under appeal, these tests cannot be taken into consideration, as the comparison was made with a 4:1 t.i.d. regimen which does not represent the closest prior art. In this context, it is emphasised that it has been established case law at the EPO that if comparative tests are chosen to demonstrate an inventive step on the basis of an improved effect, the nature of the comparison with the closest state of the art must be such that the said effect is convincingly shown to have its origin in the distinguishing feature of the invention (T 197/86, OJ 1989, 371).

In the absence of any non-obvious effects, the technical problem has to be defined as follows: using an alternative amoxycillin/clavulanate composition for the paediatric treatment of bacterial infections by means of b.i.d. oral administration. The problem was solved by the use as claimed in present claim 1.

In the light of the working examples of the description of the patent in suit, the problem appears to be solved.

10.1.5 In the assessment of inventive step, it appears appropriate in this case to evaluate as a next step whether the person skilled in the art, starting from the b.i.d. regimen of (D2), had any motivation to look for alternatives. (D2) itself does not suggest changing the compositions described therein, but guidance can be found elsewhere: thus, in (D1) (page 295, last complete paragraph of the left-hand column) it is stated that the frequency of gastrointestinal adverse effects observed after administration of the combination of amoxycillin and clavulanate appears to be related to the dosage of clavulanate administered and may occur more often in children. From this passage, the person skilled in the art not only gets a clear motivation to look for an alternative, but he is also told which direction to take: he should keep the concentration of clavulanate as low as possible and this can be achieved conveniently by increasing the ratio of amoxycillin to clavulanate.

10.1.6 In the last step it has to be determined whether the solution of the problem, i.e. the selection of a 7:1 ratio, was obvious. In this context, the board wants to draw the attention to (D1) (page 281, first complete paragraph of the left-hand column), which discloses compositions comprising 875 mg of amoxycillin and 125 mg of clavulanic acid (ratio = 7:1) for the b.i.d. treatment of bacterial infections in adults. Furthermore, as was already indicated by the opposition division in the decision under appeal, (D1) contains the teaching that the pharmacokinetic profile of amoxycillin and clavulanic acid in children parallels that in adults and that mean pharmacokinetic variables

are the same as in adults, indicating similar patterns of absorption and excretion (D1, page 279, second complete paragraph of the left-hand column). In the light of this teaching, the person skilled in the art, trying to find an alternative composition for the b.i.d. treatment of paediatric patients would clearly rely on a composition whose suitability for b.i.d treatment in adults was already known rather than experiment with other ratios. As a consequence, the subject-matter as claimed in the present main request does not involve an inventive step over (D2) in combination with (D1).

10.1.7 Arguments of the appellant:

(1) There is a prejudice to apply the b.i.d. regimen in the treatment of *otitis media*. (D4) contains the teaching to increase the dosage regimen of the combination of amoxycillin and clavulanate from b.i.d. to t.i.d. when the infections in question are severe. In view of the fact that *otitis media* is a severe infection, a b.i.d. regimen is counter-indicated. The board cannot follow this reasoning for the simple reason that (D2) clearly shows that *otitis media* can successfully be treated by means of a b.i.d. regimen.

(2) Although there is no direct comparative test to show that the incidence of diarrhoea is lower with a b.i.d. regimen of the 7:1 combination of amoxycillin and clavulanate than with a b.i.d. regimen of the 4:1 combination of amoxycillin and clavulanate, such an effect can at least qualitatively be deduced by combining the results of the comparative tests of (D2) with the clinical

trials of the patent in suit: (D2) compares a t.i.d. 4:1 regimen with a b.i.d. 4:1 regimen and finds a worsening in the incidence of diarrhoea. Clinical trials A and B of the patent in suit compare a t.i.d. 4:1 regimen with a b.i.d. 7:1 regimen and find an improvement in the incidence of diarrhoea. The conclusion to be drawn from these tests is the following: b.i.d. 4:1 is worse than t.i.d. 4:1 which is worse than b.i.d. 7:1. It can clearly be deduced therefrom that b.i.d. 4:1 is worse than b.i.d. 7:1 and as a consequence, the objective problem with regard to (D2) is an improvement in terms of the incidence of diarrhoea rather than a simple alternative.

The board does not agree for the following reasons: as far as the comparison between b.i.d 4:1 and t.i.d 4:1 in (D2) is concerned, reference is again made to (D2), page 322, paragraph bridging columns 1 and 2, where it is stated that a slightly higher incidence of adverse reactions in the b.i.d. group was not statistically significant. If it is not statistically significant, then it cannot be taken into account. However, even if a slight tendency towards an improvement in the incidence of diarrhoea were acknowledged for the t.i.d 4:1 regimen, then its cause could easily be explained by the different amounts of active agents used in the comparative test: for the b.i.d. 4:1 regimen a dosage between 26.6 and 33.2 mg/kg/day of amoxycillin was used, as compared to 20.0-25.0 mg/kg/day for the t.i.d. 4:1 regimen (D2, page 320, last three lines of the left-hand column). It stands to reason that a

higher concentration of active agent causes more severe side effects. There is no evidence at all that the same results would have been obtained by using equal amounts of active agent in both regimens. An additional complication is the fact that the results of one set of tests were combined with the results of a different set of tests where different conditions prevailed so that it is next to impossible to draw even qualitative conclusions. As a consequence, in the absence of any direct comparative tests between b.i.d. 7:1 and b.i.d. 4:1, the board cannot discern any improvement over the closest prior art in the assessment of inventive step.

10.2 Auxiliary request 1:

10.2.1 Claim 1 of auxiliary request 1 is now further characterised by a dosage of 45 or 70 mg/kg/day of amoxycillin and a *pro rata* amount of clavulanate.

10.2.2 Again, (D2) represents the closest state of the art and now the problem to be solved with regard to (D2) has to be defined as follows: increase in the antibacterial activity. The problem was solved by increasing the amount of active agent from 33.2 mg/kg/day of amoxycillin (highest dosage for the b.i.d. regimen of (D2)) to 45 and 70 mg/kg/day, respectively, with the corresponding amounts of clavulanate.

10.2.3 The board is of the opinion that increasing the antibacterial activity by increasing the dosage of the antibacterial agents is an obvious step for the person skilled in the art. In addition, dosage adjustment of

the combination of amoxycillin and clavulanate to the severity of the bacterial infections had already been disclosed for a 4:1 t.i.d. regimen. Reference is made to (D24) (page 317, paragraph "Augmentin 312,5 mg-Pulver zur Sirupbereitung") where it stated that the daily dosage is within the range of 37.5-75 mg/kg/day depending on the nature of the infection and the responsiveness of the pathogen to the active agent. In the absence of any further effects, it is obvious to select daily dosages from this range for the b.i.d. regimen. As a consequence, the subject-matter as claimed in auxiliary request 1 does not meet the requirements of Article 56 EPC.

10.2.4 The appellant argued that the person skilled in the art would not increase the dosage of (D2), as (D2) is of Scandinavian origin where in contrast to countries like Germany or Italy antibacterial dosages were traditionally kept rather low. The board does not agree. The person skilled in the art is not bound by certain cultural traditions but takes note of the state of the art in its entirety. Thus, he is aware of document (D24) and knows that higher dosages than those of (D2) exist which can be applied if the severity of the infection so demands. As a consequence, this argument cannot succeed.

10.3 Auxiliary request 2:

10.3.1 As compared to auxiliary request 1, claim 1 of auxiliary request 2 is now further limited to a dosage of 45 mg/kg/day of amoxycillin and a *pro rata* amount of clavulanate. The second alternative of auxiliary request 1 (70 mg/kg/day) was deleted. In view of the

fact that present claim 1 is identical to the first alternative of auxiliary request 1, the requirements of Article 56 EPC are not met for the same reasons as outlined in paragraph 10.2.3 above.

10.3.2 The appellant argued that claim 1 is now limited to the example of clinical trial A where a clear reduction of the incidence of diarrhoea was observed. This argument cannot succeed, as the comparison was not made with the closest prior art (cf. paragraph 10.1.4 above).

10.4 Auxiliary request 3:

As compared to auxiliary request 2, claim 1 of auxiliary request 3 is now further limited to the treatment of *otitis media*. In view of the fact that D2 is also concerned with the treatment of *otitis media*, the subject-matter of auxiliary request 3 does not meet the requirements of Article 56 EPC either, for the reasons outlined above in paragraphs 10.1.4 and 10.3.2.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Sánchez Chiquero J. Riolo