**Internal distribution code:**

(A) [ - ] Publication in OJ
(B) [ - ] To Chairmen and Members
(C) [ - ] To Chairmen
(D) [ X ] No distribution

# Datasheet for the decision of 12 June 2024

**Case Number:** T 1975/19 - 3.3.07

**Application Number:** 12193597.7

**Publication Number:** 2599475

**IPC:** A61K9/00, A61K31/535, A61K31/5575, A61K31/542, A61K45/06, A61K31/215

**Language of the proceedings:** EN

**Title of invention:**
Pharmaceutical composition having desirable bioavailability

**Patent Proprietor:**
Alcon Research, Ltd.

**Opponents:**
Alfred E. Tiefenbacher (GmbH & Co. KG)
Generics [UK] Limited (trading as Mylan)

**Headword:**
Travoprost composition / ALCON

**Relevant legal provisions:**
EPC Art. 100(a), 100(b), 100(c), 56, 87(1)
RPBA Art. 12(4) (2007)

**Keyword:**

Late-filed objection - admitted (no)
Appeal examination - res judicata (no)
Priority - presumption of entitlement rebutted (no)
Amendments - added subject-matter (no)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

**Decisions cited:**

G 0001/22, G 0002/22, T 2431/17, T 0051/08, T 0167/93, T 2004/21

Europäisches Patentamt
European Patent Office
Office européen des brevets

**Beschwerdekammern**

**Boards of Appeal**

**Chambres de recours**

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

**Case Number: T 1975/19 - 3.3.07**

# D E C I S I O N
# of Technical Board of Appeal 3.3.07
# of 12 June 2024

| | |
|---|---|
| **Appellant:** (Opponent 1) | Alfred E. Tiefenbacher (GmbH & Co. KG)<br>Van-der-Smissen-Straße 1<br>22767 Hamburg (DE) |
| **Representative:** | Hamm&Wittkopp Patentanwälte PartmbB<br>Jungfernstieg 38<br>20354 Hamburg (DE) |
| **Appellant:** (Opponent 2) | Generics [UK] Limited (trading as Mylan)<br>Building 4<br>Trident Place<br>Mosquito Way<br>Hatfield<br>Hertfordshire AL10 9UL (GB) |
| **Representative:** | Gill Jennings & Every LLP<br>The Broadgate Tower<br>20 Primrose Street<br>London EC2A 2ES (GB) |
| **Respondent:** (Patent Proprietor) | Alcon Research, Ltd.<br>6201 South Freeway, Mail Code TB4-8<br>Fort Worth, TX 76134-2099 (US) |
| **Representative:** | Elkington and Fife LLP<br>Prospect House<br>8 Pembroke Road<br>Sevenoaks, Kent TN13 1XR (GB) |
| **Decision under appeal:** | **Decision of the Opposition Division of the European Patent Office posted on 7 May 2019 rejecting the opposition filed against European patent No. 2599475 pursuant to Article 101(2) EPC.** |

**Composition of the Board:**

| | |
|---|---|
| **Chairman** | A. Usuelli |
| **Members:** | E. Duval |
| | A. Jimenez |

## Summary of Facts and Submissions

I. Two oppositions were filed against European patent 2 599 475 on the grounds that its subject-matter lacked inventive step, it was not sufficiently disclosed and it extended beyond the content of the (earlier) application as filed. The ground of lack of novelty was mentioned but not substantiated.

II. The appeals were filed by both opponent 1 (appellant 1) and opponent 2 (appellant 2) against the decision of the opposition division to reject the oppositions.

III. Claim 1 of the patent as granted reads as follows:

"An aqueous ophthalmic pharmaceutical composition, comprising:
a pharmaceutical vehicle suitable for topical application to an eye of a human;
travoprost;
a polymeric quaternary ammonium compound as preservative;
one or more polyols selected from mannitol, glycerin, xylitol, sorbitol and propylene glycol; and
a surfactant wherein the surfactant is ethoxylated and hydrogenated castor oil at a concentration in the composition of less than 0.3 w/v %, wherein
i. the ethoxylated and hydrogenated castor oil surfactant is entirely or substantially entirely the only surfactant in the composition; and
ii. the composition is free of any benzalkonium chloride."

IV. The following documents were cited in the appealed decision:

D1: US6743439 B1
D2: WO 00/03736
D6: WO 97/29752
D11: Application as filed
D12: WO 02/38158 A1
D13: WO 00/04898
D14: Yee 2007
D15: US 61/037117 (1st priority doc)
D16: US 61/111920 (2nd priority doc)
D20: EP1321144 A1
D26: TRAVATAN-Z - Pharmacology Review
D34: Experimental Report
D35: Camber 1987
D36: Lewis 2007
D39: TRAVATAN-Z - Clinical Pharmacology and Biopharmceutics Review HW6
D41b: Declaration from Prof Reichl
D46: Burstein 1989
D49: WO 2009/117316

V. The opposition division decided the following:

(a) The ground for opposition of lack of novelty raised by opponent 1 had not been substantiated and was disregarded.

(b) The subject-matter of the main request did not extend beyond the content of the application as filed or the earlier application as filed.

(c) The criteria of sufficiency of disclosure were met.

(d) Regarding inventive step, starting from D26 as closest prior art, the differentiating features were the surfactant concentration of less than 0.3 w/v% and the presence of polymeric quaternary ammonium compounds (PQAC) in the absence of benzalkonium chloride (BAC). The technical problem was the provision of a stable, preserved aqueous ophthalmic composition of travoprost which is free from BAC but which has improved bioavailability. The claimed solution involved an inventive step.

Alternatively, starting from D2 or D1 as closest prior art, the claimed compositions differed by the PQAC, the absence of BAC, and the hydrogenated surfactant. The technical problem was the provision of an aqueous ophthalmic composition with improved bioavailability of travoprost. The claimed solution involved an inventive step.

VI. With their respective statements setting out the grounds of appeal, appellants 1 and 2 filed D50-D52 and D81, contested the validity of the priority for lack of entitlement, and raised objections of lack of novelty over D81 and lack of inventive step in view of D51.

D50: assignment declaration
D51: WO2008/052031
D52: Decision of the Opposition Division revoking EP3042646
D81: WO 2009/117242 A2

VII. With their reply to the appeals, the respondent filed auxiliary requests 1-6 and documents D54-D62.

D54: Employment Contract - Bhagat (Redacted)
D55: Employment Contract - Chowhan (Redacted)

D56: Employment Contract - Dahlin (Redacted)
D57: Employment Contract - Gan (Redacted)
D58: Employment Contract - Jani (Redacted)
D59: Employment Contract - Kabra (Redacted)
D60: Change of name AUL AI
D61: 2008-01-01 License Agreement (Redacted)
D62: Witness Statement of David O. Taylor

VIII. On 13 July 2021, the Board issued summons to oral proceedings scheduled for 25 October 2022.

By letter dated 28 February 2022, the respondent requested that the proceedings be stayed in view of referrals G 1/22 and G 2/22 if the Board would intend to admit the appellants' new allegations and evidence with respect to priority and inventive step.

On 22 March 2022, the Board cancelled the oral proceedings.

By letter dated 5 May 2022, appellant 2 requested that the oral proceedings be rescheduled as soon as possible, and that the proceedings be not stayed.

The Board addressed appellant 2's submission in a communication dated 18 May 2022, stating in particular that the scheduling or cancelling of a date for oral proceedings was an administrative measure within the discretionary power of the Board, and that, considering the potential relevance of referrals G 1/22 and G 2/22 to the case at hand and thus the possibility that no final decision be announced at the end of the oral proceedings, the Board had considered it appropriate to cancel the oral proceedings.

IX. The Board issued on 4 October 2023 new summons to oral proceedings scheduled for 12 June 2024.

The Board then set out their preliminary opinion in a communication under Article 15(1) RPBA.

The oral proceedings were held before the Board as planned on 12 June 2024.

X. The parties' requests were the following:

(a) The appellants requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

(b) The respondent requested that the appeals be dismissed and the patent be maintained as granted, or, alternatively, that the patent be maintained on the basis of one of auxiliary requests 1-6 filed with their reply to the appeals. The respondent further did not consent to the introduction of lack of novelty as a ground of opposition, and requested that neither the issue of entitlement to priority nor any of D81, D50 and D51 be admitted into proceedings.

XI. The appellants' arguments may be summarised as follows:

(a) Admission of the objections as to entitlement to priority and documents D81, D50 and D51

D51 and D81 had been considered in opposition proceedings against the divisional patent EP 3 042 646 and were both highly relevant in the present case. Decision T 2431/17, in which the priority had been found invalid for the parent

case, had *res judicata* effect for the patent family (T 51/08) and was thus binding for the present case. Furthermore, the evidence showed *prima facie* that the right to priority had not been transferred.

(b) The main request introduced added subject-matter in view of the lack of basis for an ethoxylated and hydrogenated castor oil, the selection of travoprost, the selection of the upper limit of 0.3 w/v % for the surfactant concentration and its isolation from the surfactant lower limits or amount of therapeutic agent, the selected polyols in the absence of boric acid, the absence of benzalkonium chloride (BAC), or the omission of further features pertaining e.g. to pH.

(c) The criteria of sufficiency of disclosure were not met, because the patent did not teach how a composition comprising only a polymeric quaternary ammonium compound (PQAC) as preservative in the absence of borate would be useful as a pharmaceutical composition, or would exhibit the level of stability required by the expression "pharmaceutical composition" of claim 1 of the main request.

(d) The main request did not meet the requirements of inventive step.

Starting from D26, the differences were the use of PQ-1 as preservative, and the lower amount of surfactant of less than 0.3 w/v %. The technical problem was to provide an alternative BAC-free composition for travoprost with an acceptable level

of bioavailability. The claimed solution did not involve an inventive step in view of D2, D6 or D20.

Alternatively, starting from D2 or D1, the replacement of BAC with PQ-1 was obvious in light of D7, D8, D14 and Dl8. The use of an ethoxylated and hydrogenated castor oil as claimed was not associated with any technical effect and was likewise not inventive.

XII. The respondent's arguments may be summarised as follows:

(a) Admission of the objections as to entitlement to priority and documents D81, D50 and D51

The appellants could, and should, have raised the issue of priority before the opposition division. The objection of lack of priority, D50, D51 and D81 were inadmissible under Article 12(4) RPBA.

(b) The main request did not introduce added subject-matter. In the (earlier) application as filed, the claimed features were disclosed as preferred, neither the presence of borate nor a lower limit to the surfactant concentration were required, the relatively low concentration of surfactant was not linked to particular travoprost concentrations, and the feature regarding the claimed surfactant being the only one in the composition was not inextricably linked to travoprost being the sole therapeutic agent.

(c) The criteria of sufficiency of disclosure were met. There was nothing to suggest that the claimed

compositions would not be suitable for use as pharmaceutical compositions.

(d) The main request met the requirements of inventive step.

The Travatan®-Z formulation of D26 was the closest prior art. The differences were the use of PQAC as preservative, and the lower amount of surfactant of less than 0.3 w/v %. The technical problem was the provision of a stable, preserved aqueous ophthalmic composition of travoprost which was free from benzalkonium chloride but which has improved bioavailability. The claimed solution involved an inventive step.

D1 and D2 were not realistic candidates as the closest prior art. If D2 was taken as starting point, the differences were the presence of PQAC, the absence of BAC, and the hydrogenated surfactant. The technical problem was the provision of preserved aqueous ophthalmic compositions comprising travoprost as the active ingredient which were free from harmful BAC yet still provided adequate prostaglandin bioavailability and stability. The claimed solution was not obvious. The same applied if starting from D1.

## Reasons for the Decision

The present decision is taken on the basis of the respondent's main request, i.e. the patent as granted (see III. above).

1. Admission of the objection regarding entitlement to priority and of documents D81, D50 and D51

1.1 In their respective statements setting out the grounds of appeal, both appellants submitted, for the first time, that the priority was invalid because the applicant, now patent proprietor and respondent, was not the successor in title to the applicants for the priority applications. The appellants filed the assignment D50 and the opposition division's decision D52 taken in a related case as evidence.

Based on this premise, the appellants cited in appeal new documents D51, as prior art under Article 54(2) EPC, and D81, as prior art under Article 54(3) EPC, and raised objections of lack of inventive step in view of D51 and lack of novelty over D81.

The respondent contested the admittance of these new submissions.

1.1.1 The assertion that the right to priority was not validly transferred, as well as D50, D51 and D81, represent new evidence and allegations of facts first submitted together with the appellants' respective statements of grounds of appeal, both filed in 2019. Following the transitional provisions set out in Article 25(2) RPBA 2020, the question as to whether these new submissions should be admitted must be decided on the basis of Article 12(4) RPBA 2007, which gives the Board discretion not to admit, on appeal, facts and evidence that could have been presented in the first instance proceedings.

The submissions on the validity of the priority, and D50, D51 and D81, were not filed in reaction to

developments in the previous proceedings, nor are they intended to fill in gaps in the appellants' cases presented in first instance. Instead, these submissions amount to bringing a fresh case in appeal. The fact that these submissions have also been made in a related case, namely the divisional case which gave rise to decision D52 in opposition proceedings, does not justify their admission in the separate case at hand. The appellants not only could but also should have introduced these facts and evidence in first instance, especially considering that the issue of entitlement to priority was raised in these related opposition proceedings well before the oral proceedings before the opposition division in the case at hand.

1.1.2 *Prima facie* relevance

The appellants expressed the view that the new submissions are *prima facie* relevant.

The Board may consider the aspect of *prima facie* (high) relevance under Article 12(4) RPBA 2007, not as a sufficient justification, but as an additional condition for the admittance of the new submissions (see Case Law of the Boards of Appeal, 10th edition, 2022, V.A.5.13.2).

But, in any case, considering the change in jurisprudence brought about by decision G 1/22 on the issue of entitlement to priority, none of the new submissions, which are all conditional on the priority being found invalid at least in respect of the earliest priority application D15, are *prima facie* relevant, for the following reasons:

The patent (filed as a divisional by Alcon Research, Ltd., i.e the respondent) claims priority from the applications D15 (filed on 17 March 2008 by Kabra, Jani, Gan, Bhagat, Chowhan and Dahlin) and D16 (filed on 6 November 2008 by Bhagat, Carreras, Chowhan, Cuchi, Dahlin, Galán, Gan, García, González, Jani, Jiménez, Kabra and Martínez).

Under Article 87(1) EPC, the right of priority belongs to the person who has duly filed D15 and D16 or his successor in title.

However, following G 1/22, there is a rebuttable presumption under the autonomous law of the EPC that the applicant claiming priority in accordance with Article 88(1) EPC and the corresponding Implementing Regulations is entitled to claim priority. The party challenging the subsequent applicant's entitlement to priority has to prove that this entitlement is missing (see point 110 of the reasons). The presumption that the subsequent applicant is entitled to the priority right is a strong presumption under normal circumstances. The party challenging the entitlement to priority cannot just raise speculative doubts but must demonstrate that specific facts support serious doubts about the subsequent applicant's entitlement to priority.

Here, the evidence on file does not establish that the priority applicants did not allow the subsequent applicant to rely on the priority.

The appellants firstly allege that the assignment by Ms N. Jiménez was only signed after filing of the subsequent application on 13 March 2009 (see D50, page 15). However, this allegation, which is not clearly

supported by the signature date on this document (which appears to be 2 March 2009), is in any case not relevant for the earliest priority D15 for which Ms N. Jiménez is not an applicant.

To support this *prima facie* relevance, the appellants further relied on the different parties involved in the transfers shown in D54-D62 and on the expression "license" used in D61, combined with the lack of evidence of a transfer to the subsequent applicant.

However, in the Board's view, considering that G 1/22 establishes a strong presumption of validity and places the burden on the opponents to prove the contrary, the lack of evidence of a transfer of the right to priority to the subsequent applicant cannot be equated with a proof that this transfer did not take place. Absent any further circumstances, evidence of a transfer of the right to priority to a third party other than the subsequent applicant, such as to Alcon Inc. (see T 2431/17, point 1.5.5 of the reasons, third paragraph), does not amount either to a proof that this right to priority was not, in turn, further transferred to the subsequent applicant. Indeed, as explained in G 1/22 (see point 106 of the reasons), the presumption also applies if the title to the subsequent application has not been acquired from the priority applicant but from a third party having the right to the invention in the respective territory. This presumption applies all the more in the case at hand considering that all parties involved are legal persons belonging to the same group and their employees. Lastly, considering the low standards applicable under the autonomous law of the EPC, in which even informal or tacit transfers of priority rights are normally accepted (see G 1/22, points 99-100 of the reasons), the fact that document

D61 is entitled "License agreement" does not *prima facie* demonstrate either that the transfer to the subsequent applicant did not take place.

Accordingly, the appellants' late submissions are not *prima facie* convincing.

Under these circumstances, none of these newly filed documents and objections were admitted under Article 12(4) RPBA 2007.

1.1.3 Binding effect of T2431/17 - *res judicata*

The patent in suit derives from a divisional application. The present Board issued decision T 2431/17 in respect of the patent deriving from the parent application. In this decision, the Board, following the established case law at the time, which placed the burden of proof on the applicant asserting that priority is rightly claimed (see point 1.5.3 of the reasons), found the priority to be invalid because the succession in title had not been credibly established.

The appellants invoke a binding effect of this earlier decision. The Board does not agree.

No binding effect from this earlier decision in respect of a different case can be derived from Article 111(2) EPC. At most, the principle of *res judicata* may be applicable, though some Boards have questioned whether a final decision taken in opposition appeal proceedings could have any "cross-procedural" *res judicata* effect at all on separate opposition (or opposition appeal) proceedings concerning a patent granted on a divisional

(see the Case Law of the Boards of Appeal, 10th edition, 2022 II.F.2.4.3.c)).

*Res judicata* is a matter finally settled by a court of competent jurisdiction, rendering that matter conclusive as to the rights of the parties and their privies, such a final judgment constituting an absolute bar to a subsequent legal action involving the same claim, demand or cause of action, and the same parties or their privies (Case Law of the Boards of Appeal, 10th edition, 2022, V.A.10.1). As explained in T 167/93 (see point 2.5 of the reasons), this principle is of extremely narrow scope and supposes, among others, not only that the parties are the same but also that the issues of fact are the same. This is however not the case here, considering at least that the claim requests are different (in which the present case differs from T 51/08 cited by the appellants) and that the admittance of the priority issue was not under debate in the parent case T 2431/17. For these reasons already, the Board considers that the principle of *res judicata* is not applicable, i.e. that it neither precludes the respondent from pursuing the present different claim requests in the divisional case at hand, nor mandates that the issue of priority entitlement be admitted in the present appeal proceedings, and even less that it be considered settled.

1.1.4 For the above reasons, the Board did not admit any of the late filed submissions into the appeal proceedings, namely the issue of entitlement to priority, D50, D51 and D81.

The objection of lack of novelty over D81 is additionally a fresh ground for opposition submitted

for the first time in appeal. The respondent explicitly disagreed with the introduction of this new ground. Considering the non-admission of D81, the issue of whether this new ground should be introduced is moot.

2. Article 100(c) EPC, added subject-matter

2.1 The patent in suit derives from a divisional application. In the following, compliance with Article 76(1) EPC is discussed. References to passages of the parent application as filed are meant to refer to the parent application as published under the PCT as D49.

For the following reasons, the main request does not introduce matter extending beyond the content of the parent application as filed (D49).

Claim 1 of the main request relates to an aqueous ophthalmic pharmaceutical composition comprising in combination:

- a pharmaceutical vehicle suitable for topical application to an eye of a human;
- travoprost;
- a polymeric quaternary ammonium compound (PQAC) as preservative;
- one or more polyols selected from mannitol, glycerin, xylitol, sorbitol and propylene glycol; and
- a surfactant

  wherein the surfactant is ethoxylated and hydrogenated castor oil

  at a concentration in the composition of less than 0.3 w/v %,

  wherein the ethoxylated and hydrogenated castor oil surfactant is entirely or substantially

entirely the only surfactant in the composition; and

- the composition is free of any benzalkonium chloride (BAC)

The combination of travoprost as therapeutic agent with ethoxylated and/or hydrogenated vegetable oil surfactants is disclosed on page 3 (line 23), page 10 (lines 29-35) and page 11 (lines 8-10) of the parent application as filed. A pointer to the choice of travoprost is furthermore derivable from the fact that it is singled out as highly preferred on page 4 (lines 28-31) and is used in all examples.

As vegetable oil that has been ethoxylated *and/or* hydrogenated, castor oil is emphasized in claim 7 (see also page 8, lines 31-32) of the parent application as filed. In other words, the parent application discloses the general use of ethoxylated *and/or* hydrogenated castor oil, and thus also, in one alternative, of ethoxylated *and* hydrogenated castor oil. The fact that the surfactants of choice (HCO-40, HCO-60 and HCO-200) are all well-known examples of ethoxylated and hydrogenated castor oil (see page 10, lines 32-35, and the use of HCO-40 all examples) particularly points to this alternative.

The feature that this preferred surfactant be entirely or substantially entirely the only one in the composition is also disclosed on page 10 (lines 35-37). This passage indicates that the surfactant "can" be entirely or substantially entirely one or more ethoxylated and/or hydrogenated vegetable oils, and continues on page 11 by stating that the therapeutic agent "can" be entirely or substantially entirely one or more prostaglandins. Considering this wording, i.e.

the repetition of the expression "can", the two features are not seen as inextricably linked.

Claim 1 of the main request further mandates that the composition comprise one or more polyols selected from mannitol, glycerin, xylitol, sorbitol and propylene glycol, without specifying their amount. This list of polyols recited in claim 1 is disclosed as preferred on page 13 (lines 35-36) and does not involve a selection. It is furthermore not apparent that the parent application as filed discloses the use of borates or boric acid as essential, either generally or in the context of using these polyols. On the contrary, page 13 (line 20, "When used") clarifies that the presence of these borates is optional. This conclusion is not modified by the fact that borates are used in all examples comprising PQ-1, because the disclosure of the parent application as filed is not limited to these examples. Lastly, the first paragraph on page 14 indicates that "when used", the polyols are "generally", i.e. ordinarily, used in certain amounts, but does not describe these amounts as essential. Hence this feature relating to the polyols requires neither a selection nor an isolation from further unclaimed features.

The upper limit of 0.3 w/v % for the surfactant concentration is shown in the parent application as filed on page 11 (lines 14-18), not as part of a range, but in a list of preferred upper limits given separately from the list of typical lower limits. The upper limit chosen in claim 1 can be isolated from these lower limits. In this respect, the Board does not share the appellants' view that, because no minimal amount is specified, claim 1 covers compositions without surfactant at all. Claim 1 relates to a

"composition, comprising [...] a surfactant". The further definition of the amount of surfactant by an upper limit and no lower limit does not mean that claim 1 extends to compositions comprising no surfactant.

Appellant 2 further objected that the amount of surfactant cannot be isolated from the amount of therapeutic agent. However, in the Board's view, the parent application does not describe such a link as essential. In particular, page 4 of the parent application (see lines 28-31) does not specify any relative amounts of travoprost and surfactant, but solely mentions the presence of travoprost in combination with a "relatively low amount" of surfactant, which is defined in claim 1 by the upper limit of 0.3 w/v %. The parent application as filed nowhere defines the amount of surfactant by reference to the amount of travoprost.

The absence of BAC is disclosed in the parent application as filed as the preferred option, and not, as alleged by appellant 1, as a mere alternative to its presence (see page 14, lines 11-14).

Appellant 1 further criticised the absence in claim 1 of further features shown in the parent description, namely the pH of 4-9 (page 12, paragraph 2) and the amount of borate (page 13, paragraph 3). However none of these further features is described as essential in the parent application as filed. The expression "typically" (page 12, line 13) does not mean that the pH range is mandatory. And the optional nature of the borate is made clear by the expression "when used" on page 13, as explained above.

Accordingly, the main request does not extend beyond the content of the parent application as filed.

2.2 The divisional application as filed (published under the EPC as D11) incorporates all the subject-matter of the parent application, i.e. it incorporates the parent description (as pages 1-27 of the divisional description), figures 1 to 6, and the subject-matter of all parent claims 1-41 as embodiments on pages 28-32 of the divisional description. Consequently, the main request does not extend beyond the content of the divisional application as filed either.

3. Article 100(b) EPC, sufficiency of disclosure

According to appellant 1, the criteria of sufficiency of disclosure are not met. The expression "pharmaceutical composition" of claim 1 of the main request would mandate that the composition exhibits a required level of stability, which would not be shown to be achieved in the patent. The patent would also fail to show that a composition comprising only a polymeric quaternary ammonium compound (PQAC) as preservative in the absence of borate would be useful as a pharmaceutical composition.

In the Board's view, the expression "pharmaceutical composition" of claim 1 does not imply a specific minimum level of stability. Additionally, the appellants did not provide evidence that, in the absence of boric acid, the exemplified compositions would not be suitable for use as ophthalmic pharmaceutical compositions.

Accordingly, the requirements of sufficiency of disclosure are met.

4. Articles 100(a) and 56 EPC, inventive step

4.1 According to the patent (see paragraph [0002]), the invention relates to ophthalmic compositions having relatively low concentrations of surfactant that promote the bioavailability of a therapeutic agent (i.e. travoprost). The patent further indicates that the use of the amounts of surfactant specified herein can increase bioavailability in a manner that can at least partially or substantially entirely offset losses in bioavailability that may occur when benzalkonium chloride (BAC) or other such ingredient are not present (see paragraph [0044]). As a further possible objective (see paragraphs [0003] and [0017]), achieving a desired degree of stability is mentioned.

The appellants contest that the claimed subject-matter involves an inventive step starting from the Travantan®-Z composition of D26, from example 2 of D2, or from example 5 of D1.

4.2 Starting from D26 / Travatan®-Z

4.2.1 D26 discloses Travatan®-Z, a BAC-free travoprost-containing ophthalmic formulation. D26 addresses both the need for avoiding BAC due to its ocular toxicity and the resulting loss in bioavailability as compared with the BAC-containing product Travatan® (see section 2.6.4 of D26).

Travatan®-Z contains in particular travoprost, the surfactant polyoxyl 40 hydrogenated castor oil (HCO-40), propylene glycol, sorbitol and boric acid (see page 5 of D26). It was common ground among the parties that the concentration of HCO-40 in the known

Travatan®-Z formulation is 0.5 w/v% (see the respondent's reply dated 3 February 2020, page 27).

4.2.2 The differentiating features identified in the appealed decision are undebated, namely:
(i) the surfactant concentration is less than 0.3 w/v% and
(ii) the composition contains a polymeric quaternary ammonium compound (PQAC) as preservative.

4.2.3 Technical effect of the claimed reduced amounts of surfactant:

Tables B-D of the patent, and the *in vivo* experimental evidence shown in paragraphs (199)-(203) of the reply dated 3 February 2020, compare compositions which differ only by the amount of surfactant. This evidence shows a statistically significant effect on bioavailability, both in the context of composition lacking PQAC (tables B-D of the patent), or containing PQAC as required by claim 1 (see the data in the reply). In particular, formulations 2 to 4 of the reply, comprising respectively 0.5 w/v% HCO-40 as in Travatan®-Z or 0.2 or 0.1 w/v% as claimed, exhibit bioavailabilities ($AUC_{0-4\ hours}$ in ng.hr/mL) of resp. 31.7, 36.3 and 47.4 with standard deviations below the differences between these values, namely ±1.0, ±2.8 and ±4.5. These comparisons with a modified variant of the prior art D26 convincingly demonstrate that the effect on bioavailability has its origin in the distinguishing feature pertaining to surfactant amount.

The appellants emphasized the differences in other parameters, and their potential effect on bioavailability, between Travatan®-Z and the composition used by the respondent for comparison

(formulation 2), in particular regarding zinc content. However the relevant question is not which technical effects can be expected from these other parameters, but whether the nature of the comparison is such that an effect is convincingly shown to have its origin in the distinguishing feature, here the amount of surfactant.

Secondly, this effect is illustrated by formulations with 0.2 and 0.1 w/v% surfactant and can be accepted for the claimed range of less than 0.3 w/v% in comparison with the further removed value of 0.5 w/v% of the prior art Travatan®-Z formulation.

The above data also show that the lower amount of surfactant thus allows to offset the loss in bioavailability caused by the omission of BAC in the composition (compare formulations 1 and 2, showing a decrease in $AUC_{0-4\ hours}$ from 39.9 to 31.7 upon replacement of BAC with PQ-1 in compositions comprising 0.5 w/v % HCO-40).

Appellant 1 contests the effect of the claimed surfactant amounts on bioavailability based on the *in vitro* experiments D34, wherein no significant difference in permeation properties was apparently detected between compositions 426 and 430 with 0.2 and 0.6 w/v % macrogolglycerol hydroxystearate (see page 5 of D34 and the opinion D41b). The Board agrees with the opposition division that, considering that the other concentrations tested in D34 rather confirm the trend observed in the respondent's *in vivo* experiments, the single data point for 0.6 w/v % in D34 in an *in vitro* model does not convincingly disprove the effect shown by the respondent *in vivo* tests.

Finally, the appellants's unsubstantiated criticisms of the broadness of claim 1 regarding the amounts of PQ-1, travoprost or surfactant do not call into question the achievement of the effect on bioavailability over the claimed scope.

4.2.4 Technical problem and obviousness:

Considering the effect of the claimed surfactant amounts on bioavailability, the technical problem is the provision of an aqueous ophthalmic composition of travoprost which is free from BAC but which has improved ocular bioavailability.

The claimed solution is not rendered obvious by any of D2, D6, D20 or D46, for the following reasons:

D2 relates to storage-stable prostaglandin formulations. The travoprost formulation of example 2 of D2 comprises 0.1 w/v % of a surfactant which is however not hydrogenated. Furthermore, D2 does not address the bioavailability of travoprost.

D6 (see page 9, second paragraph) mentions an adverse effect of polyethoxylated castor oil on prostaglandins activity. The surfactant is not hydrogenated, and no effect on bioavailability is mentioned.

D20 considers an upper limit of 0.5 w/v % for non-ionic surfactants, points to a surfactant concentration ten or more times that of the prostaglandin derivative to achieve desired water-solubility (see page 3, lines 46-52), or mentions a formulation comprising 0.01 w/v% HCO-60 (see table 1, page 4). However D20 is silent as to any effect on bioavailability of travoprost.

D45 and D46 relate to the effect of ethoxylated castor oil surfactants on protection from dry eyes.

None of these documents make the effect of the ethoxylated and hydrogenated castor oil surfactant concentration on the prostaglandin bioavailability obvious.

Hence the claimed invention is not obvious starting from D26.

4.3 Starting from D2 or D1

The appellants alternatively objected to lack of inventive step starting from D2. The respondent contested that D2 is suitable as starting point. In this respect, the opposition division expressed the view that D26 was a more suitable starting point than any of D1 or D2 because D26 related to the same purpose or effect as the contested patent. The appealed decision nonetheless sets out the opposition division's reasoning using the problem solution approach starting from D2/D1 before concluding that the criteria of inventive step are met. The Board follows the same approach below.

4.3.1 D2 aims at improving the storage stability of aqueous prostaglandin compositions, in particular for ophthalmic use, and addresses this problem by packaging the compositions in e.g. polypropylene containers. In example 2 (see page 13), D2 discloses an aqueous ophthalmic composition comprising travoprost (compound 32), 0.1 w/v% chremophor EL (an ethoxylated castor oil surfactant) and BAC.

4.3.2 The subject-matter of claim 1 of the main request differs from example 2 of D2 by the absence of BAC, the presence of PQAC as a preservative, and the fact that the surfactant is hydrogenated.

4.3.3 It is credible that the absence of BAC will at least lead to an improved safety of the composition, considering the well known irritant nature of BAC. Apart from this, no improvement is demonstrated to arise from the use of a hydrogenated and ethoxylated castor oil over the ethoxylated castor oil of D2. No evidence was adduced either as to an improvement of the bioavailability of the formulation associated with the differentiating features. Contrary to the situation when starting from D26, the surfactant concentration of less than 0.3 w/v% is not part of the differentiating features over D2, and the associated improved bioavailability cannot be taken into account.

However, considering the remoteness of the disclosure in D2 as regards the problem underlying the invention, this lack of demonstration of an improvement does not mean that the claimed invention should be assessed as to obviousness on the assumption that the skilled person does not need to be concerned at all with any of the properties of the formulation addressed in the patent, namely its bioavailability and stability, for the following reasons:

The patent in suit seeks to offset the loss in bioavailability caused by the omission of BAC in the composition (see 4.1 above). In contrast, the composition of example 2 of D2 contains BAC, and D2 is entirely silent about issues of travoprost bioavailability. In addition, the composition of example 2 of D2 proposed as starting point by the

appellants is the least stable composition of D2, i.e. of a document aiming at improving stability.

When assessing inventive step, an interpretation of the prior art documents as influenced by the problem solved by the invention, where the problem was neither mentioned or even suggested in those documents, must be avoided, such an approach being merely the result of an *a posteriori* analysis (see the Case Law of the Boards of Appeal, 10th edition, 2022, I.D.6).

In the circumstances of the present case, while the above shortcomings of D2 do not necessarily preclude an assessment of inventive step over this document, they must nonetheless be taken into account in the problem solution approach. These circumstances, and the silence of D2 as to any bioavailability concerns resulting from the omission of BAC or otherwise, means that the claimed formulations are not to be regarded as mere alternatives to the formulation of D2, because such an approach where the problems that the patent demonstrably addresses are ignored or considered implicitly solved in D2 would amount to an *ex post facto* analysis (see T 2004/21, points 3.11-3.16 of the reasons for analogous considerations).

The problem may accordingly be formulated, as proposed by the respondent, as the provision of preserved aqueous ophthalmic compositions comprising travoprost as the active ingredient which are free from harmful BAC yet still provide adequate prostaglandin bioavailability and stability.

4.3.4 Obviousness

The appellants' objection would firstly suppose that the skilled person start from the formulation of Example 2 of D2, despite this formulation being the least stable composition of D2, which is itself concerned with stability. It would additionally suppose that the skilled person modify this formulation by removing BAC therefrom, despite expecting from the prior art that such a modification would be detrimental to travoprost bioavailability. This disadvantage is observed *in vivo* in D26 (see §2.6.4.1): "Travatan® BAC-free formulation (Travatan® Z) provided lower intraocular concentrations and AUC values of active AL-5848 compared to Travatan®". The documents relied on by the appellants do not lead to a different conclusion, i.e. do not show that the skilled person would not expect this detrimental effect of BAC. D35 (see page 30-31; page 29, table 1) is not concerned with Travoprost. D36 (see page 102, par. 1) relates to efficacy, and D39 (see pages 3 and 6) mentions expectations as to systemic availability, which are different properties to bioavailability.

Accordingly, the skilled person seeking to provide a travoprost formulation with adequate bioavailability and stability would not arrive at the claimed subject-matter starting from D2 in an obvious manner. The appellants' objection is thus not convincing.

4.3.5 D1 relates to sulfonated styrene/maleic anhydride copolymers which enhance the preservation of ophthalmic compositions containing a cationic drug (see column 1, lines 48-67), travoprost being additionally present in some examples. Example 5 of D2 shows compositions comprising travoprost, BAC, as well as 0.2 w/v % HCO-40 and 0.05 w/v % N-lauroylsarcosine as surfactants (see column 6, example 5, compositions E and F). D1, like

D2, is silent about travoprost bioavailability. As with D2, example 5 of D1 does not disclose the absence of BAC and the presence of PQAC. Additionally, in example 5 of D1, the ethoxylated and hydrogenated castor oil surfactant is not entirely or substantially entirely the only surfactant in the composition. The assessment of inventive step starting from D1 is analogous to D2, such that the same conclusion applies.

Accordingly, the criteria of inventive step are met.

## Order

## For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated