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**Datasheet for the decision
of 20 August 2020**

Case Number: T 0277/17 - 3.3.01

Application Number: 06785533.8

Publication Number: 2035441

IPC: A61K31/714, A61K9/08, A61K47/10

Language of the proceedings: EN

Title of invention:
CYANOCOBALAMIN LOW VISCOSITY AQUEOUS FORMULATIONS FOR
INTRANASAL DELIVERY

Applicant:
Par Pharmaceutical, Inc.

Headword:
Cyanocobalamin/PAR

Relevant legal provisions:
EPC Art. 84, 123(2), 56
EPC R. 103

Keyword:

Clarity - main request and auxiliary requests 1, 2 and 4 (no)
Added subject-matter - auxiliary request 3 (yes)
Inventive step - auxiliary requests 5 and 6 (no)
Partial reimbursement of appeal fee - (no) - late withdrawal
of the request for oral proceedings



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Case Number: T 0277/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 20 August 2020

Appellant: Par Pharmaceutical, Inc.
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Representative: D Young & Co LLP
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Decision under appeal: **Decision of the Examining Division of the
European Patent Office posted on 31 August 2016
refusing European patent application No.
06785533.8 pursuant to Article 97(2) EPC**

Composition of the Board:

Chairman A. Lindner
Members: J. Molina de Alba
M. Blasi

Summary of Facts and Submissions

- I. By its decision announced on 28 June 2016 and posted on 31 August 2016, the examining division refused European patent application No. 06 785 533.8.

The decision was based on the claims of a main request and six auxiliary requests.

The examining division found that claim 1 of the main request and of each of auxiliary requests 1 to 5 was unclear, and also added subject-matter. Regarding auxiliary request 6, the examining division considered that the subject-matter of claim 1 lacked an inventive step over document D1 (WO 86/05987).

- II. The applicant (appellant) filed an appeal against that decision. With the statement of grounds of appeal, it filed seven claim sets as its main request and auxiliary requests 1 to 6.

Claim 1 of the main request reads as follows.

"1. A stable pharmaceutical aqueous solution of cyanocobalamin comprised of cyanocobalamin and water wherein said solution of cyanocobalamin is suitable for intranasal administration, has a viscosity less than about 1000 cPs, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least 5% relative to an intramuscular injection of cyanocobalamin,

wherein the solution contains no mercury or mercury-containing compounds."

Claim 1 of auxiliary requests 1 and 2, which are identical, reads as follows.

"1. A stable pharmaceutical aqueous solution for administering cyanocobalamin intranasally through an actuator tip as a spray, wherein the aqueous solution consists of:

cyanocobalamin;

a buffering agent comprised of citric acid and sodium citrate;

a humectant selected from the group consisting of: sorbitol, propylene glycol, and glycerin;

a preservative selected from the group consisting of: benzyl alcohol, chlorobutanol, and benzalkonium chloride; and

water,

wherein said solution of cyanocobalamin is suitable for intranasal administration, has a viscosity less than about 1000 cPs, wherein the spray has a spray pattern ellipticity ratio of from 1.0 to 1.4 when measured at a height of 3.0 cm from the actuator tip, and wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least 5% relative to an intramuscular injection of cyanocobalamin, wherein the solution contains no mercury or mercury-containing compound."

Claim 1 of auxiliary request 3 reads as follows.

"1. A stable pharmaceutical aqueous solution for use in treating vitamin B12 deficiency in a mammal, the use comprising elevating the vitamin B12 levels in the cerebral spinal fluid (CSF) by administering a sufficient amount of the stable pharmaceutical aqueous solution intranasally as a spray through an actuator tip so that the average ratio of vitamin B12 in the CSF to that in the blood serum (B12 CSF/B12 Serum x 100) is increased to at least 1.1, wherein said stable pharmaceutical aqueous solution is comprised of cyanocobalamin at a concentration of 0.5% of total weight of solution, a buffering agent consisting of citric acid at a concentration of 0.12% and sodium citrate at a concentration of 0.32%, glycerin at a concentration of 2.23%, benzalkonium chloride at concentration of 0.02%, and water wherein said stable pharmaceutical aqueous solution is suitable for intranasal administration."

Claim 1 of auxiliary request 4 is the same as claim 1 of auxiliary request 3, except that the following passage has been added at the end:

"has a viscosity less than about 1000 cPs, wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least 5% relative to an intramuscular injection of cyanocobalamin, wherein the solution contains no mercury or mercury-containing compound, and wherein the spray has a spray pattern ellipticity ratio of from 1.0 to 1.4 when measured at a height of 3.0 cm from the actuator tip."

Claim 1 of auxiliary request 5 reads as follows.

"1. A nasal spray consisting of an aqueous solution containing cyanocobalamin at a concentration of 0.5 wt% of total weight of solution, citric acid at a concentration of 0.12 wt%, sodium citrate at a concentration of 0.32 wt%, glycerin at a concentration of 2.23 wt%, 50 wt% benzalkonium chloride at a concentration of 0.04 wt% and water at a concentration of 96.79 wt%, wherein the solution contains no mercury or mercury-containing compounds."

Claim 1 of auxiliary request 6 derives from claim 1 of auxiliary request 5, from which the condition that the solution contains no mercury or mercury-containing compounds has been deleted.

III. The board scheduled oral proceedings in line with the appellant's request.

In a communication pursuant to Article 15(1) RPBA dated 27 January 2020, the board gave its preliminary opinion. Among other objections, the board stated that:

- the feature *"a viscosity less than about 1000 cPs"* in claim 1 of the main request and auxiliary requests 1, 2 and 4 rendered the claim unclear (Article 84 EPC);
- claim 1 of auxiliary request 3 added subject-matter (Article 123(2) EPC); and
- the subject-matter of each of the claim requests on file lacked an inventive step (Article 56 EPC) over document D1.

- IV. On 13 May 2020, the board issued a communication enquiring whether, in view of the COVID-19 pandemic, the appellant would attend the oral proceedings scheduled for 25 June 2020, either in person or if it were held as a videoconference. A response was requested as soon as possible.
- V. On 22 June 2020, the board's registrar telephoned the appellant's representative, and learnt that no one would attend the oral proceedings - whether held in person or as a videoconference - and that the representative was waiting for information from the client concerning withdrawal of the request for oral proceedings.
- VI. By a letter received on 24 June 2020, the appellant withdrew its request for oral proceedings and stated that it would not attend the oral proceedings, but wished to rely on its written submissions.
- VII. On the same day, the board cancelled the oral proceedings and the appeal proceedings continued in writing.
- VIII. The appellant's arguments, where relevant to the present decision, may be summarised as follows.

The feature in claim 1 of the main request and auxiliary requests 1, 2 and 4 that viscosity is less than about 1000 cPs is clear. Although claim 1 does not specify the temperature at which viscosity is to be measured, viscosity is a common physical property and its measurement is part of common general knowledge. When a viscosity value does not specify a temperature, the skilled person understands that the viscosity has been measured at 20°C.

Claim 1 of auxiliary request 3 is based on claim 31 and paragraphs [0022], [0060] and [0063] of the application as filed.

The nasal sprays in claim 1 of auxiliary requests 5 and 6 are inventive over those in document D1. The differences between the claimed sprays and those in D1 do not result from a simple routine optimisation but from a significant research effort. The claimed sprays are stable and provide good bioavailability of cyanocobalamin by intranasal administration.

- IX. The appellant requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request or, alternatively, one of auxiliary requests 1 to 6, all filed with the statement of grounds of appeal.

Reasons for the Decision

1. The appeal is admissible. It complies with the requirements pursuant to Articles 106 to 108 and Rule 99(2) EPC.
2. Main request - Clarity (Article 84 EPC)
 - 2.1 One of the features characterising the pharmaceutical aqueous solution of claim 1 of the main request is a viscosity of less than about 1000 cPs.
 - 2.2 It is part of the basic knowledge in thermodynamics that viscosity is a function of temperature and that, in liquids, viscosity usually increases as temperature

decreases. Thus, the characterisation of a liquid by a viscosity value without indicating the temperature at which viscosity has been measured makes little sense.

Claim 1 does not indicate the temperature at which its aqueous solution is characterised by having a viscosity of less than about 1000 cPs. This introduces a lack of clarity, since a solution that fulfils the viscosity condition of claim 1 at a given temperature could not do so at lower temperatures, and vice versa. Consequently, the fact that claim 1 does not give the temperature at which viscosity is measured renders the claim unclear.

- 2.3 The appellant has not disputed the relationship between viscosity and temperature. Its argument was, rather, that claim 1 was clear because, in the absence of a temperature being given, the skilled person would understand that this was 20°C.

The board cannot accept this argument, which is merely an unsupported assertion. To the board's knowledge, there is no convention in the scientific community that when the measuring temperature of a viscosity value is not given it should be understood that it is 20°C. The convention is, rather, that because of the dependency of viscosity on temperature a viscosity value must always be accompanied by the temperature at which it has been measured.

- 2.4 Hence, the board holds that claim 1 of the main request lacks clarity, contrary to Article 84 EPC.

3. Auxiliary requests 1, 2 and 4 - clarity
(Article 84 EPC)

Like claim 1 of the main request, claim 1 of each of auxiliary requests 1, 2 and 4 specifies that the claimed aqueous solution has a viscosity of less than about 1000 cPs but fails to specify a measuring temperature. Thus, for the reasons put forward in relation to the main request, claim 1 of each of auxiliary requests 1, 2 and 4 lacks clarity.

4. Auxiliary request 3 - added subject-matter
(Article 123(2) EPC)

- 4.1 The appellant filed a clean and a marked-up version of the claims of auxiliary request 3. These versions differ in that the passage *"has a viscosity less than about 1000 cPs, wherein said solution of cyanocobalamin has a bioavailability of cyanocobalamin when administered intranasally of at least 5% relative to an intramuscular injection of cyanocobalamin"* has not been deleted in the marked-up version of claim 1.

According to the appellant (see statement of grounds of appeal, page 9, title "Auxiliary Request 3") *"AR3 does not include the definition of the spray pattern ellipticity ratio, the viscosity, the bioavailability, or that the solution contains no mercury or mercury-containing compound"*. Thus, it is apparent that the correct version of the claims of auxiliary request 3 is the clean version.

Therefore, when referring to the set of claims of auxiliary request 3, the board refers to its clean version. If the marked-up version were considered, the

objection of lack of clarity raised in relation to claim 1 of the main request and auxiliary requests 1, 2 and 4 would also apply to claim 1 of auxiliary request 3.

- 4.2 With regard to the basis for the claims of auxiliary request 3 in the application as filed, the appellant referred to its submissions in the letter dated 28 April 2016 in relation to then auxiliary request 5 (see statement of grounds of appeal, page 9, title "Auxiliary Request 3"). It referred also to paragraph [0063] as the basis for medical use.

The basis for the aqueous solution of claim 1 mentioned in the appellant's letter of 28 April 2016 was formed by claim 31 and paragraphs [0022] and [0060] of the application as filed. Paragraphs [0022] and [0060] are not relevant to the case at issue, since they define ellipticity ratios and droplet sizes, which are features that are not specified in claim 1 of auxiliary request 3.

- 4.3 Claim 31 as filed discloses a method involving the use of an aqueous solution of cyanocobalamin which contains the same ingredients in the same amounts as defined in claim 1 of auxiliary request 3. However, claim 31 as filed contains additional restrictions, namely that the solution has a viscosity of less than about 1000 cPs and a bioavailability of cyanocobalamin when administered intranasally of at least about 5% relative to an intramuscular injection of cyanocobalamin. These additional restrictions have been deleted in claim 1 of auxiliary request 3.

The restrictions on viscosity and bioavailability in claim 31 as filed would be superfluous, and could then

be removed without adding subject-matter, if the aqueous solution were defined in a closed manner (i.e. as "consisting of" a specific combination of ingredients in given amounts), because in that case the properties of viscosity and bioavailability could be considered to be inherent in the solution. Otherwise, deletion of the restrictions would result in added subject-matter.

Claim 31 as filed and claim 1 of auxiliary request 3 define their aqueous solutions with the expression "comprised of". It is therefore essential to assess whether this expression defines a closed list of components (in the same way as "consisting of") or whether it is open to the addition of further ingredients (in the same way as "comprising").

Turning to the application as filed, the expression "comprised of" appears to be a synonym of "comprising". This is apparent from its use in claim 1 as filed, which discloses an aqueous solution comprised of cyanocobalamin and water but which, according to dependent claims 2, 4 and 8, may contain additional ingredients such as a buffer, a humectant or a preservative. Hence, the aqueous solutions of claim 31 as filed and claim 1 of auxiliary request 3 are not limited to the stated ingredients in the given amounts.

This means that the aqueous solution in claim 1 of auxiliary request 3 is open to the addition of ingredients such as a thickener giving the solution a viscosity above 1000 cPs. Such a composition is not supported by any of the passages referred to by the appellant or, in particular, by claim 31 as filed.

- 4.4 Hence, the board concludes that claim 1 of auxiliary request 3 adds subject-matter which goes beyond the content of the application as filed, contrary to Article 123(2) EPC.
5. Inventive step (Article 56 EPC) - claim 1 of auxiliary request 5
- 5.1 The application is directed to the formulation of aerosol sprays for the intranasal administration of vitamin B₁₂, in particular cyanocobalamin.
- 5.2 The appellant regarded document D1 as the closest prior art. The board agrees with that view.

D1 deals with the formulation of an aerosol spray for the intranasal administration of vitamin B₁₂ which provides contact between the vitamin and the nasal mucosa for an extended period of time (see page 1, lines 5-8, and page 3, lines 1-17). The spray is an isotonic aqueous solution having a pH of 4 to 6 which ensures a shelf life of at least one year and minimises nasal mucosa irritation (see page 4, lines 4-10). Optionally, it may also contain a humectant such as glycerin to inhibit drying of the mucous membrane and prevent irritation (see page 4, lines 17-20). A preservative such as benzalkonium chloride is added to increase shelf life (see page 5, lines 1-4). In its examples (see pages 6 and 7), D1 discloses three compositions containing vitamin B₁₂ in the form of cyanocobalamin at 0.2, 0.5 and 1.0 wt.%, an acetic acid/sodium acetate buffer, preservatives including benzalkonium chloride, mercury-containing compounds and boric acid, and water.

5.3 The nasal spray of claim 1 of auxiliary request 5 differs from those in document D1 in three respects:

i) the buffer is citric acid/sodium citrate rather than acetic acid/sodium acetate;

ii) it contains glycerin; and

iii) it does not contain mercury-containing compounds.

5.4 There is no evidence on file showing that there is an interaction among these differences to produce a combined or synergistic technical effect. Nor has the appellant argued that this is the case. Therefore, an analysis of the technical effect that these differences bring about needs to be carried out individually for each of the differences.

Difference i) does not produce any technical effect. The citric acid/sodium citrate buffer of claim 1 provides the same pH as the acetic acid/acetate buffer of D1, namely 4 to 6 (see claim 2 of the application as filed, and page 4, lines 4-10 of D1).

Regarding difference ii), the application explains (see paragraph [0068]) that humectants such as glycerin inhibit drying of the mucous membranes and prevent irritation.

Difference iii) does not produce any technical effect. The application states in paragraph [0014], last sentence, that there is a need to produce a pharmaceutically stable aqueous composition of cyanocobalamin that has low viscosity, is optionally free of mercury compounds, and has sufficient

bioavailability. However, it fails to explain which effect would be obtained by the exclusion of mercury-containing compounds. In this respect, the appellant argued in the statement of grounds of appeal (see page 5, last paragraph) that mercury-free compositions are stable and better tolerated by patients. This argument is an assertion that, in the absence of supporting evidence, has to be rejected.

5.5 Thus, taking into consideration that differences i) and iii) do not produce any technical effect and that difference ii) results in compositions that are less irritating to the nasal mucosa, the objective technical problem to be solved by the subject-matter of claim 1 of auxiliary request 5 may be formulated as the provision of a less irritating cyanocobalamin nasal spray.

5.6 The solution proposed in claim 1 is obvious.

Citric acid/sodium citrate and acetic acid/sodium acetate buffers have long been two of the most popular and well-known buffers in pharmaceutical compositions. The skilled person was aware that they could be exchanged to obtain a solution with a pH equivalent to that of the closest prior art. Hence, difference i) is merely one of the obvious modifications the skilled person would have made.

Concerning the addition of glycerin, D1 states on page 4, lines 17-20, that the solution may contain a humectant such as glycerin to inhibit drying of the mucous membrane and prevent irritation. Hence, it was obvious to the skilled person that the addition of glycerin to the nasal spray would reduce mucosa irritation.

Lastly, the aqueous solutions of D1 comprise a mercury-containing compound as one among other preservatives. However, D1 does not teach that mercury-containing preservatives are essential, or even that they are preferred. The document merely states on page 5, paragraph 1, that:

"A preservative may be employed to increase the shelf life of the compositions. Benzyl alcohol is suitable, although a variety of preservatives including, for example, Parabens, thimerosal, chlorobutanol, or benzalkonium chloride may also be employed."

Thus, although the examples of D1 contain the mercury-containing compounds thimerosal or phenylmercuric acetate as preservatives, these compounds were not disclosed as being compulsory. The examples also include other preservatives such as benzalkonium chloride and boric acid. In fact, D1 never refers to mercury-containing preservatives in general, and its claims do not disclose any specific composition comprising mercury-containing compounds. Hence, the replacement of the mercury-containing preservatives in the nasal sprays of the examples in D1 with alternative preservatives was also an obvious modification.

For the sake of completeness, the board notes that citric acid, sodium citrate, glycerin and benzalkonium chloride have all been customary ingredients in pharmaceutical compositions for decades, and that the specific amounts disclosed in claim 1 of auxiliary request 5 fall within the customary ranges used in pharmaceutical formulations. Those amounts cannot therefore constitute a basis for inventive step either.

6. Inventive step (Article 56 EPC) - claim 1 of auxiliary request 6

Claim 1 of auxiliary request 6 results from deleting, from claim 1 of auxiliary request 5, the condition that the aqueous solution contains no mercury or mercury-containing compounds.

That condition did not constitute a real restriction on claim 1 of auxiliary request 5, because the claim defined a nasal spray consisting of an aqueous solution containing ingredients which add up to 100 wt.%. Hence, the subject-matter of claim 1 of auxiliary request 6 is identical to that of auxiliary request 5, and for the reasons put forward in point 5 above lacks inventive step (Article 56 EPC) over the content of document D1.

7. Reimbursement of the appeal fee (Rule 103(4)(c) EPC)

7.1 The appellant had initially requested oral proceedings. The request was subsequently withdrawn, enabling the board to decide on the case without holding oral proceedings.

7.2 Pursuant to Rule 103(4)(c) EPC, as in force since 1 April 2020, the appeal fee shall be reimbursed at 25% if any request for oral proceedings is withdrawn within one month of notification of the communication issued by the board in preparation for the oral proceedings, and no oral proceedings take place. The amended provision applies to any pending appeal pursuant to Article 2(2) of the Decision of the Administrative Council of 12 December 2019 amending Rule 103 EPC (CA/D 14/19, see OJ EPO 2020, A5), and thus to the present appeal case.

A request by the party concerned for a reimbursement is not a prerequisite of Rule 103(4)(c) EPC. Accordingly, any reimbursement has to be ordered *ex officio* by the board if the requirements of the provision are met.

Rule 103(4)(c) EPC refers to "*the communication issued by the Board of Appeal in preparation for the oral proceedings*". The provision therefore presupposes that the board has indeed issued a communication. However, in particular the provision (i) is silent on the possible content or nature of the communication except that it is "*issued ... in preparation for the oral proceedings*", and (ii) leaves it open whether, once a first communication has been issued in preparation for the oral proceedings, any second or further such communication re-opens the period for requesting reimbursement. However, these points, and their application in respect of the date of the entry into force of the provision, do not need to be considered further in the present case, since there are other reasons why no reimbursement of the appeal fee is to be ordered.

7.3 For a reimbursement of the appeal fee pursuant to Rule 103(4)(c) EPC the request for oral proceedings must have been withdrawn within one month of notification of the communication issued by the board.

The withdrawal of the request for oral proceedings by the appellant's letter received on 24 June 2020 was made too late. Calculated from notification of the communication dated 13 May 2020, receipt of the letter was outside the one-month period under Rule 103(4)(c) EPC, which had expired on 23 June 2020 pursuant to Rule 126(2) and Rule 131(2), (4) EPC.

The fact that the board was informed on 22 June 2020 - and therefore still in good time - that no one would attend the oral proceedings for the appellant did not have any legal consequences. The question which arises in this context, namely whether or not the statement of non-attendance at oral proceedings qualifies as a withdrawal of the request for oral proceedings - within the meaning of Rule 103(4)(c) EPC or in general - does not need to be addressed further.

Proceedings before the boards of appeal are primarily in writing (cf. Article 12 RPBA and Rule 100(2) EPC), and any submitted document must in particular have been transmitted to the EPO in a permitted manner and validly signed (cf. Rule 2(1) and Rule 50(3) EPC). Where oral proceedings pursuant to Article 116 EPC are arranged in accordance with Rule 115(1) EPC, they take place before the board, during which a party may make procedurally relevant oral submissions.

In the present case, the appellant's statement on the telephone relating to non-attendance at oral proceedings was made outside the framework of oral proceedings, and so cannot have any legal effect, irrespective of whether the fact that the registrar had received it could in any case be considered equivalent to receipt by the board. Nor does the fact that the registrar minuted the statement and passed it on to the board mean that it subsequently became a written submission by the appellant.

Only upon receipt of the appellant's letter on 24 June 2020 was there a procedurally relevant submission on the part of the appellant, but this fell outside the one-month period under Rule 103(4)(c) EPC.

7.4 Before arriving at the present negative findings, there was no need for the board to provide the appellant with the opportunity to comment on the question of reimbursement of the appeal fee. No request for reimbursement of the appeal fee had been submitted by the appellant, the board's conclusion instead being in conformity with such a request not having been made, so there was no request to reject. Furthermore, the question of reimbursement of the appeal fee does not entail any legal or further financial disadvantage for the appellant.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated