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Datasheet for the decision of 2 December 2021

Case Number: T 2466/19 - 3.3.07

Application Number: 06827036.2

Publication Number: 1942868

IPC: A61K9/08, A61K47/02, A61K9/19, A61K38/48, A61K47/26

Language of the proceedings: EN

Title of invention:
SODIUM CHLORIDE SOLUTION FOR DRUG RECONSTITUTION OR DILUTION

Patent Proprietor:
Wyeth LLC

Opponent:
Brady, Paul Andrew

Headword:
Sodium chloride solution for reconstitution / WYETH

Relevant legal provisions:
RPBA Art. 12(4)
RPBA 2020 Art. 11, 13(1), 13(2), 25(2)
EPC Art. 100(b), 83, 100(a), 54, 56

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Keyword:
Late-filed evidence - admittance of documents filed in appeal proceedings
Remittal - (no)
(Late-filed) requests - admittance in appeal proceedings
Sufficiency of disclosure - main request, auxiliary request 9 - (yes)
Novelty - main request, auxiliary request 9 - (yes)
Inventive step - main request (no), auxiliary requests 1-8 (no), auxiliary request 9 (yes)

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Case Number: T 2466/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 2 December 2021

Appellant: (Opponent)	Brady, Paul Andrew Abel & Imray 20 St. Andrew Street London Greater London EC4A 3AG (GB)
Representative:	Zwicker, Jörk ZSP Patentanwälte PartG mbB Hansastraße 32 80686 München (DE)
Respondent: (Patent Proprietor)	Wyeth LLC 235 East 42nd Street New York, NY 10017-5755 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 5 July 2019 rejecting the opposition filed against European patent No. 1942868 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	Y. Podbielski

Summary of Facts and Submissions

I. European patent 1 942 868 (hereinafter "the patent") was granted on the basis of 17 claims. The independent claims of the patent as granted read as follows:

"1. A method for preparing a Factor IX formulation for intravenous injection, the method comprising adding a 25 mM to 150 mM sodium chloride solution to a lyophilized Factor IX formulation thereby resulting in a formulation prepared for intravenous injection, wherein the lyophilized formulation, if reconstituted in water, does not contain more than 5 mM of an ionizing salt, and, wherein the prepared formulation is about isotonic with respect to plasma and has an osmolarity that is from 270 mOsm/L to 330 mOsm/L, or, is slightly hypotonic with respect to plasma and has an osmolarity that is from 220 mOsm/L to 270 mOsm/L, or, is slightly hypertonic with respect to plasma, and has an osmolarity that is from 330 mOsm/L to 600 mOsm/L and, wherein the prepared formulation has a sufficient ionic strength to prevent erythrocyte agglutination upon intravenous injection."

"16. A pharmaceutical kit comprising:

(a) a vial containing a lyophilized cake, wherein if the lyophilized cake is reconstituted in 5 mL of water the solution would comprise:

(i) from 5 mM to 30 mM histidine;
(ii) from 0.1 M to 0.3 M glycine;
(iii) from 0.5 to 2 percent sucrose;
(iv) from 0.001 to 0.05 percent polysorbate;
(v) from 50 IU/mL to 2000 IU/mL of Factor IX; and

(vi) not more than 5 mM of an ionizing salt;

(b) a 25 mM to 150 mM sodium chloride solution; and
(c) instructions for reconstituting the lyophilized cake with the sodium chloride solution, such that after reconstitution the resultant solution is isotonic with respect to plasma and has an osmolarity that is from 270 mOsm/L to 330 mOsm/L and has a sufficient ionic strength to prevent erythrocyte aggregation upon intravenous injection."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as originally filed.

III. The opposition division took the decision to reject the opposition.

IV. The decision of the opposition division, posted on 5 July 2019, cited inter alia the following documents:

D1: WO 2005/058283
D2: Summary of Product Characteristics - EMA Marketing, Authorisation for BeneFIX, 27 August 1997
D3: Van Den Berg, Blood 96(11) Part 1: 641a, 2000
D5: International Blood/Plasma News, 18(9):127, 2001
D6: Chai et al., Acta Radiologica 36:204-209, 1995
D7: Buschle and Saklad, Anesthesiology 14 :53-59, 1953
D8: Constantino and Pikal, Lyophilization of Biopharmaceuticals, pages 197-198, 2004
D12: Avonex label (SUPPL-5008) downloaded from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=103628, 2001

D14: Thyrogen label downloaded at: https:// wwvAaccessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&appfno=2 August 1998, 30 Nov 1998

V. The opposition division decided in particular as follows:

(a) The ground of opposition according to Article 100(c) EPC did not prejudice the maintenance of the patent.

(b) The subject-matter of the granted patent was sufficiently disclosed. In particular, the granted patent rendered the achievement of the claimed effect credible over the entire claimed range of sodium chloride concentration. It also indicated the volume of water to be used for reconstitution.

(c) The granted patent fulfilled the requirements of Article 54 EPC. In particular, multiple selections had to be performed within the disclosure of D1 to arrive at the claimed subject-matter.

(d) D5 was the closest prior art. The distinguishing features lay in the reconstitution medium and the obtained osmolarity. The objective technical problem to be solved was finding an improved method of reconstituting a Factor IX formulation for intravenous injection giving reduced agglutination. The claimed solution was not obvious in light of the prior art. In particular, the skilled person would not have consulted D6.

VI. The opponent (appellant) lodged an appeal against the above decision of the opposition division.

VII. The patent proprietor (respondent) defended its case on the basis of the patent as granted as the main request, and on the basis of 15 auxiliary requests, wherein auxiliary requests 1 to 8 and 10 to 15 were filed with its reply to the appellant's statement setting out the grounds of appeal and auxiliary request 9 was filed during the oral proceedings on 2 December 2021.

The content of the claims upon which the present decision is based can be illustrated as follows:

Claims 1 of auxiliary requests 1-4 are identical to claim 1 of the main request.

Claim 1 of auxiliary request 5 corresponds to claim 1 of the main request wherein the volume of water for reconstitution was defined by introducing the feature "in a volume that is the same as the volume of the formulation prior to lyophilisation" after the terms "if reconstituted in water".

Claim 1 of auxiliary request 6 corresponds to claim 1 of the main request wherein the feature "wherein the prepared formulation has an ionic strength that is at least 30 mEq/L of Na+ and Cl^- ions" was added.

Claim 1 of auxiliary request 7 and claim 1 of auxiliary request 8 correspond to claim 1 of the main request wherein the concentration of the sodium chloride solution was amended to "36 mM to 150 mM" (auxiliary request 7) and "30 mM to 77 mM" (auxiliary request 8), respectively.

Auxiliary request 9 corresponds to the main request, wherein:

- in claim 1, the concentration of the sodium chloride solution was amended to "36 mM to 44 mM", and
- claims 2 to 4, 6, 9, 10, 16 and 17 were deleted.

VIII. The following items of evidence were filed by the parties during the appeal proceedings:

(a) Documents filed by the appellant with its statement setting out the grounds of appeal (D21 to D24, D24a and D24b) and on 4 November 2021 (D29):

D21: WO 2005/089712 Al
D22: Excerpt from text book "Physicochemical Principles of Pharmacy", 2nd ed., 1988
D23: Leaflet on BeneFIX
D24: Declaration by Marc Stranz, PharmD
D24a: Exhibit A, Resume of Marc Stranz
D24b: Exhibit B, Guidelines referred to in D24
D29: Pikal M., Freeze drying in "Encyclopedia of pharmaceutical technology", 1994, Volume 6, pages 275-303

(b) Documents filed by the respondent with its reply to the statement setting out the grounds of appeal:

D25: declaration from Chandra Webb
D26: Wang et al, 1999, Int J Pharmaceutics, 185, pp l29-188
D27: Chi et al, Pharmaceutical Research, vol.20, No.9, Sept 2003
D28: Schellekens, Nature Reviews, vol.l, June 2002, pp 457-462

IX. Oral proceedings were held before the Board on 2 December 2021.

X. The appellant requested that the decision under appeal be set aside and the patent be revoked.

The appellant furthermore requested that auxiliary requests 1-15 (*i.e.* auxiliary requests 1-8 and 10-15 filed with the reply to the statement setting out the grounds of appeal and auxiliary request 9 filed during the oral proceedings) and documents D25-D28 not be admitted into the appeal proceedings.

XI. The respondent requested that the appeal be dismissed, *i.e.* that the patent be maintained as granted, or that the patent be maintained on the basis of one of auxiliary requests 1-15, wherein auxiliary requests 1-8 and 10-15 were filed with the reply to the statement setting out the grounds of appeal and auxiliary request 9 was filed during the oral proceedings.

The respondent furthermore requested that documents D21-D24, D24a and D24b not be admitted into the appeal proceedings, and that the case to be remitted to the first instance, should said documents be admitted. They furthermore requested that document D29 not be admitted into the proceedings.

XII. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) Admittance of items of evidence

The submission of D21, which was *prima facie* highly relevant, was not surprising as it had already been cited in the international search report. D22-D23 were submitted to further substantiate arguments raised in the first instance proceedings. D24 (with D24a and D24b) discussed the teachings of D5 and

D6. D29 was filed in support of common general knowledge, which had been put into question by the respondent. D21-D24, D24a and D24b as well as D29 were thus to be admitted in the appeal proceedings.

D25-D28 supported an entirely fresh and irrelevant argument of the respondent. These documents were thus to be excluded from the appeal proceedings.

(b) The patent in suit was not sufficiently disclosed. The claimed effect could not be achieved with a sodium chloride concentration below 40 mM and the absence of indication of the volume of water used for reconstitution prevented the skilled person from carrying out the claimed method.

(c) Claim 1 of the main request was not novel over D1. No selection in multiple lists was required to arrive at the presently claimed subject-matter, since the sodium chloride concentration in the vehicle required the selection out of a list of merely two embodiments and the further features (factor IX and concentration of ionising salt) were individualised.

(d) D5 represented the closest prior art. The subject-matter of claim 1 of the main request was not inventive over D5 *inter alia* in combination with D6.

(e) Auxiliary requests 1-8 were not to be admitted, as they were not convergent. They further did not involve an inventive step for the same reasons as the main request.

(f) Auxiliary request 9 was not to be admitted. The deletion of the kit claims, which the appellant objected to in the grounds for opposition, changed the factual situation. Such an amendment was not allowable at such a late stage of the appeal proceedings.

(g) Auxiliary request 9 did not meet the requirements of Articles 83, 54 and 56 EPC for the same reasons as the main request. In particular, the modification of the range of sodium chloride concentration did not overcome the objection of lack of inventive step raised for the main request, as no particular effect was linked to the new range. Furthermore lower concentrations falling within the present range were disclosed in D7 and D21.

XIII. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) Admittance of items of evidence

D21-D24, D24a, D24b and D29 were not to be admitted. D21-D24, D24a and D24b were late filed and not *prima facie* relevant. The submission of these documents on appeal was an attempt to obtain a decision based on new facts not discussed in the first instance proceedings. In particular D21 and D24 should have been filed in the first instance proceedings. D29 was filed only a few weeks before the oral proceedings and was not representative of common general knowledge at the priority date.

D25-D28 were filed in response to D24 and were thus to be admitted.

The case was to be remitted to the first instance, should documents D21-D24, D24a and D24b be admitted, to allow the corresponding matter being examined at two instances.

(b) The claimed invention, including the claimed range of sodium chloride concentration and the volume of water for reconstitution, was sufficiently disclosed in the patent.

(c) Claim 1 of the main request was novel over D1, as several selections were needed to arrive at the present subject-matter.

(d) D3 was more suitable as closest prior art than D5. However, when starting from D5, the objective technical problem to be solved (as defined during oral proceedings) resided in the provision of a method to obtain an improved factor IX composition for intravenous administration wherein erythrocyte aggregation is avoided. None of the cited prior art documents suggested to use 25-150 mM sodium chloride as reconstitution solution to solve the problem posed. In particular the skilled person would not have combined the teaching of D6 with the one of D5.

(e) Auxiliary requests 1-8 were to be admitted and, as the main request, involved an inventive step.

(f) Auxiliary request 9 was to be admitted. The claims of this auxiliary request had already been discussed as part of former auxiliary request 9 and the mere deletion of claims did not introduce any new issue.

(g) The amended feature of claim 1 of auxiliary request 9, *i.e.* narrowed sodium chloride concentration range, was disclosed in the granted claims. Furthermore this amendment strengthen the inventive step of the claimed method, as this range was not disclosed in D6. Moreover D21 did not teach the addition of sodium chloride in the diluent and D7 was very old and related to a different use, namely blood transfusion.

Reasons for the Decision

1. Admittance of items of evidence

1.1 Documents D21-D24, D24a, D24b, D25-D28

1.1.1 These documents were submitted with the statement setting out the grounds of appeal filed before 1 January 2020 (D21-D24, D24a, D24b) and the reply thereto (D25-D28). Following the transitional provisions set out in Article 25(2) of the Rules of Procedure of the Boards of Appeal (RPBA) 2020, their admittance must be decided on the basis of Article 12(4) RPBA 2007.

1.1.2 D21 was filed in reply to the first instance decision in relation with the issue of the concentration of sodium chloride to be used in the reconstituted solution and is thus relevant in the context of inventive step. The respondent argued that D21 was already cited in the International preliminary report on patentability established for the granted patent and should thus have been filed earlier. According to the respondent, the purposive choice of the appellant to file this document only on appeal would prevent a

review of the first instance decision on identical facts. According to the appellant, the passage of D21 focused on in the statement setting out the grounds of appeal (namely the penultimate sentence of paragraph [0068] of D21, see point 4.4 of the statement of the grounds) had not been particularly highlighted in the examination proceedings. The Board notes that it cannot always be expected from an opponent to file all possible pieces of evidence for all the arguments made. While D21 could have been filed in the first instance proceedings, the Board sees no compelling reasons why D21, and in particular the reference to the above mentioned specific passage, should have been filed in the first instance proceedings.

1.1.3 D22-D23 were filed to further substantiate the argument brought forward in the first instance by the appellant regarding common general knowledge of the skilled person on Factor IX compositions and intravenous injections. D24 (and the annexes D24a and D24b) relates to an expert's opinion on the teachings of D5 and D6. The filing of these documents constitutes a reaction to the decision of the opposition division to acknowledge inventive step based on the absence of teaching towards the distinguishing features in the prior art. The Board sees no reason for concluding that D22-D24, D24a and D24b should have been filed already in the first instance proceedings (Article 12(4) RPBA 2007). The Board further notes that neither the relevance of said documents to support the objections raised nor potential issues regarding the date of public availability of said documents constitute criteria for admittance mentioned in Article 12(4) RPBA 2007.

1.1.4 Finally D25 and the accompanying documents D26-D28 have been filed in response to the expert's declaration

filed as D24. The Board notes that D25 addresses specifically a number of statements made in D24 and constitutes thus a direct response to D24. The appellant argued that documents D25-D28 would support a fresh argument of the respondent regarding a potential risk of aggregation of Factor IX upon addition of sodium chloride. The Board considers however that the issue of the admittance of this specific argument is independent from the one of the admittance of documents D25-D28 *per se*, in so far as they were filed in response to D24.

1.1.5 Hence, the Board does not exercise its discretion pursuant to Article 12(4) RPBA 2007 to exclude these documents from the appeal proceedings. D21-D24, D24a, D24b and D25-D28 are admitted into the appeal proceedings.

1.2 Document D29

1.2.1 This document was submitted on 4 November 2021 after notification of the summons to oral proceedings. Its admittance must be decided on the basis of Article 13(2) RPBA 2020 (Article 25(1) RPBA 2020). Accordingly, a document submitted at this stage of the appeal proceedings might only be taken into account if there are exceptional circumstances justified with cogent reasons.

1.2.2 The appellant explained that D29 had been provided in reply to the respondent putting the suitability of D8 as evidence of common general knowledge into question. The appellant further argued that it was established practice of the Boards of Appeal, as revealed by the Case Law of the Boards of Appeal, 9th Edition, 2019, V.A.4.13.1, 1st paragraph, that evidence of common

general knowledge could be submitted at any time when said common general knowledge was questioned. According to the appellant, D29 was moreover highly relevant to the question raised in the preliminary opinion of the Board.

1.2.3 The Board notes that the respondent questioned the relevance of D8 already in its reply to the statement setting out the grounds of appeal on 16 April 2020 (see page 19, 8th paragraph to page 20, 6th paragraph). The appellant did not provide any justification for the filing of D29 only on 4 November 2021, *i.e.* more than a year later and a few weeks before the oral proceedings. Moreover, the issue raised in the preliminary opinion of the Board (see page 18 points 5.4.2 and 5.4.3 (a)) did not constitute any new issue, which could have justified the late submission of D29. Finally, as argued by the respondent, D29 is a chapter of a textbook relating to freeze drying technology and published in 1994, *i.e.* more than 10 years before the priority date of the patent in suit. Within these 10 years, further documents (see D12 to D14 and D21) have been published, which describe lyophilisation processes standing against the teaching of D29 mentioned by the appellant. The appellant argued that these individual documents cannot put into question the physical issue regarding crystallisation described in D29, so that the teaching of D29 remains relevant. This argument is not convincing. The technology may have evolved between the publication of D29 and the filing of the patent in suit, thus possibly offering further solutions to said physical issue. It cannot therefore be concluded that D29 unambiguously represents common general knowledge at the priority date of the patent in suit.

1.2.4 Accordingly the Board considers that there are, in the present case, no exceptional circumstances justified with cogent reasons to admit D29 into the appeal proceedings at this late stage (Article 13(2) RPBA 2020).

2. Remittal

2.1.1 Under Article 11 RPBA 2020, which applies in the present case according to Article 25(1) RPBA 2020, the board shall not remit the case to the department whose decision was appealed unless special reasons present themselves for doing so.

2.1.2 The respondent requested that the case be remitted to the first instance, should documents D21-D24, D24a and D24b be admitted into the appeal proceedings. In support of this request, the respondent argued that the absence of a remittal would prevent the corresponding matter from being examined at two instances.

2.1.3 Although it is the primary object of the appeal proceedings to review the decision under appeal in a judicial manner (Article 12(2) RPBA 2020), the parties have no absolute right to have each and every matter examined at two instances (see Case Law of the Boards of Appeal, 9th Edition, 2019, V.A.7.2.1). The Board observes that, in the present case, the legal and factual framework was not significantly altered by the admittance of documents D21-D24, D24a and D24b, which merely served the purpose of further substantiating objections previously raised in the first instance proceedings. Furthermore the respondent had the opportunity to study these documents, as they were filed with the statement setting out the grounds of appeal.

2.1.4 Hence, the Board considers that there are no special reasons justifying a remittal in the present case.

Main request - Patent as granted

3. Sufficiency of disclosure

3.1 The appellant contested that the claimed invention was sufficiently disclosed for the following reasons:

(a) The claimed method performed with a sodium chloride solution having a concentration below 40 mM would not achieve the claimed effect, namely providing a sufficient ionic strength to prevent erythrocyte agglutination upon intravenous injection.

(b) The absence of an indication of the volume of water used for reconstitution would prevent the skilled person from determining the amount of ionizing salt to be used.

3.2 Achievement of the claimed effect with a sodium chloride concentration below 40mM

3.2.1 As the effect of providing a sufficient ionic strength to prevent erythrocyte agglutination upon intravenous injection is part of the claim, its fulfilment over the entire breadth of the claims is indeed an issue of sufficiency of disclosure. The Board observes that the patent provides general indications as well as specific examples rendering credible that Factor IX formulations reconstituted with 25-150 mM sodium chloride achieve the claimed effect. While a concentration of at least 40 mM might be considered as more preferred, there is no unambiguous indication in the patent that the effect

would not be achieved with a sodium chloride solution having a concentration between 25 and 40 mM. Moreover the results reported in examples 2 and 3 (see tables 6-8) do actually substantiate the achievement of the claimed effect with solutions having a concentration of 25, 30, 36 or 40 mM. In the absence of any evidence of the contrary, the Board concludes that the achievement of the claimed effect has been credibly substantiated over the entire claimed range of sodium chloride concentration.

3.2.2 The arguments provided by the appellant in this context are not convincing for the following reasons:

(a) The passages of the patent in suit cited by the appellant do not, contrary to its opinion, support the fact that the effect is not achieved below 40 mM.

Several of these passages (see passages on page 5 line 18, page 14 lines 5-7, page 14 lines 22-23, page 16 lines 4-5, page 17 lines 52-54, paragraphs[0021]-[0022] and [0025]-[0026] and example 4) relate to sodium chloride solutions having a concentration of at least 40 mM. They do not provide any indication regarding the effect on aggregation for solutions having a concentration between 25-40 mM. This absence of information does not mean that the effect cannot still be achieved below 40 mM. The sentence on page 17 lines 52-54 actually goes on by specifying that in the previous example 36 mM was also sufficient to prevent agglutination.

The passage on page 3 lines 13-15 indeed defines the range of 40-150 mM as preferred but the same

paragraph discloses 40 +/-10 mM (*i.e.* a lower value of 30 mM) and the previous paragraph defines the range of 25-150 mM.

Furthermore the passage of paragraph [0103], stating that agglutination was observed with one blood sample "in buffer containing 30 mM or less sodium chloride", does not appear to be clear. The appellant argued that the statement in said paragraph refers to "all concentrations of 30 mM and less" and that "further samples were tested with concentrations below and above the indicated values". However the Board cannot share this conclusion. Said paragraph relates to blood sedimentation testing in "a series of syringes containing BeneFIX® formulation diluted/ reconstituted in decreasing concentrations of NaCl (starting at 40 mM)". No detail as to the exact concentrations tested nor the number of samples used is provided. The passage cited by the appellant furthermore mentions "another" blood sample, *i.e.* using the singular form. It is therefore not possible to conclude whether agglutination was observed in several syringes with concentrations between 25 and 40 mM or whether it is one isolated observation at a specific yet undisclosed concentration. This unclear statement is not sufficient to cast doubt on the results obtained otherwise for concentrations between 25 and 40 mM in the patent in suit (see tables 6-8).

(b) Contrary to the opinion of the appellant, the results of example 2 are relevant. The appellant argued that the Westergren method had been modified in example 2 and no longer corresponded to the commonly used method. A comparison with earlier

assays was thus not possible. The Board observes that the method used is sufficiently described to be repeated and the results reported in Tables 6-7 individually substantiate that agglutination is prevented at sodium chloride concentrations at 25 and 30 mM. Moreover there is no need for a comparison with earlier experiments. Furthermore the allegation that only part of the results would have been presented, is not substantiated and is, in any case, not relevant in the present context. The disclosed results support the fact that the claimed effect can be achieved with sodium chloride solutions at concentrations between 25 and 40 mM.

3.3 Indication of the volume of water used for reconstitution

3.3.1 As argued by the appellant, from the wording of claim 1 alone, it might be difficult to determine whether a given lyophilised composition fulfills the requirement of the maximal ionizing salt concentration of 5 mM, because the concentration will depend on the volume of water added. The Board considers however that the skilled person confronted with this issue would consult the specification of the patent. Paragraph [0016] provides a definition of the reconstitution volume to be used. In particular in view of the use of the brackets after the words "measured as if it was reconstituted in water", the skilled person would have understood said definition as a general one, *i.e.* applying to any described composition and not limited to the specific case subsequently detailed in this paragraph. In this context the Board notes that the paragraphs [0019] and [0020], cited by the appellant and disclosing different volumes, refer to the final reconstitution in the sodium chloride solution and not

in water and are consequently not relevant for the present issue.

3.4 Accordingly, the Board comes to the conclusion that the granted patent is sufficiently disclosed.

4. Novelty

4.1 In the appeal proceedings, the appellant contested the novelty of the subject-matter of the main request over D1.

4.2 The Board notes that D1 generally encompasses the presently claimed subject-matter, however selections out of three lists have to be performed to arrive at the presently claimed subject-matter. The following features have to be selected: (i) presence of sodium chloride at a concentration of 30-60 mM in the vehicle, (ii) Factor IX as specific polypeptide and (iii) amount of ionizing salt in the lyophilized composition being at most 5 mM.

4.2.1 Regarding the presence of sodium chloride (feature (i)), as argued by the appellant, the "further embodiment" disclosed on page 24 lines 10-13 is not a mere specification of preferred concentrations for some elements of the previous list, but an individual embodiment describing components of the vehicle which falls under the previously described broader embodiment. This passage on page 24 lines 10-13 describes the possibility of including in the vehicle a component selected from 5 to 15 mM calcium chloride and 30 to 60 mM sodium chloride. Hence, the feature of the vehicle containing sodium chloride in a concentration of 30 to 60 mM requires a selection out of a list of merely two embodiments.

4.2.2 However, contrary to the appellant's opinion, Factor IX (feature (ii)) is not individualised on page 40 lines 39-41. Said passage discloses a list of two disorders for which two relevant polypeptides are mentioned respectively. Even starting from this reduced list of possible useful active ingredients, a selection out of in total four alternatives is still required.

4.2.3 Finally, regarding feature (iii), the appellant brought forward that D1 disclosed that sodium chloride as tonicity agent was present in an amount of 0-9 mg/ml (see page 16 lines 38-42 and page 17 lines 5-9), *i.e.* D1 disclosed the absence of sodium chloride in the lyophilized composition (0 mg/mL). The Board observes that the passage extending from page 16 line 38 to page 17 line 9 first provides a definition of the term "tonicity modifier" or "tonicity modifying agent" and then lists several embodiments thereof, including from 0 to about 9 mg/ml of sodium chloride. Sodium chloride is merely one of the possible listed tonicity modifiers. Thus, even following the reasoning of the appellant that the disclosed amounts would correspond to the amounts in the lyophilised composition, sodium chloride at 0 mg/ml would have to be singled out of several alternatives.

4.3 As D1 does not disclose these three features in combination nor individually as particularly preferred features, the Board considers that D1 does not directly and unambiguously disclose the subject-matter of the granted claims. The fact that one list is of restricted size (see 4.2.2) is hence not decisive as two additional features still have to be selected from two further longer lists.

4.4 Accordingly, the subject-matter of the main request is novel over D1.

5. Inventive step

5.1 Closest prior art

5.1.1 The patent in suit relates to a method of preparing a Factor IX formulation for intravenous injection wherein erythrocyte agglutination upon injection is prevented. D5 (appellant) or D3 (respondent) were considered by the parties to represent the closest prior art. Both D3 and D5 relate to the preparation of a Factor IX formulation for intravenous injection and the prevention of erythrocyte agglutination upon injection and can thus both constitute a suitable starting point for the assessment of inventive step. In this context, the Board observes that even if D5 does not disclose detailed results, this document is a newsletter of pharmaceutical companies to medical practitioners, *i.e.* it is still a scientific publication even if its content is limited. It therefore qualifies as a suitable starting point for the assessment of inventive step, contrary to the opinion of the respondent.

5.1.2 In such a case of two possible routes starting from two different documents, the inventiveness of the claimed subject-matter needs to be demonstrated relative to both routes for an inventive step to be acknowledged. However, the appellant raised an objection of lack of inventive step only starting from D5 and made no objection starting from D3. Furthermore D5 mentions a possible issue with the low ionic strength of the reconstituted solution and hence addresses the key issue of the patent in suit. The Board considers it

consequently appropriate to limit its assessment of inventive step starting from D5.

5.1.3 D5 (see page 2, second paragraph) discloses BeneFIX recombinant Factor IX concentrate reconstituted in water for injection and the issue of erythrocytes agglutination or aggregation in the tubing and syringe upon intravenous administration thereof. According to D5, it is further suggested that this reaction is due to the low ionic strength of the reconstituted solution. As a solution to this aggregation issue, D5 recommends to avoid *ex vivo* contact of red blood cells with BeneFIX.

5.2 Distinguishing features and effect

5.2.1 The subject-matter of granted claim 1 differs from D5 in the nature of the reconstitution solution (namely 25-150 mM sodium chloride solution in the granted patent and water for injection in D5). The addition of sodium chloride prevents the aggregation of erythrocytes (see examples 1-4 of the patent in suit). In this context the Board notes that the prevention of erythrocyte agglutination upon intravenous injection is part of the claims, so that any formulation which would not achieve the effect, would not fall under the scope of the claims. The argument of the appellant that the effect would not be achieved over the whole scope of the claims is thus, in the present case, not relevant for the discussion on inventive step.

5.2.2 The osmolarity of the solution is not specified in D5. It was discussed whether it is indeed a distinguishing feature or merely an implicit feature being a direct consequence of the composition of BeneFIX and the diluent for reconstitution. The appellant argued that

the osmolarity of the solution of D5 would implicitly fall under the presently claimed range. According to the appellant, the osmolarity can indeed be calculated since the composition of BeneFIX is well-known to the skilled person (see D2, D23, last paragraph under "Description", or paragraph [0068] of the patent in suit) and is around 300 mOsm/l. This value is confirmed in Table 9 of the patent in suit. The appellant further argued that even upon addition of sodium chloride at a concentration within the claimed range (i.e. below 150 mM), the calculated osmolarity of reconstituted BeneFIX will stay within the limits of the range of present claim 1. This was not disputed by the respondent. Moreover, no particular effect directly linked to the claimed osmolarity value was substantiated, apart from providing a solution suitable for intravenous injection (see *e.g.* patent in suit, paragraph [0004] last sentence, paragraph [0007] last sentence, paragraph [0027]). Hence, the presently claimed osmolarity value is not considered to represent a difference *versus* the solution of D5 relevant for the definition of the objective technical problem.

5.3 Objective technical problem

5.3.1 The effect of prevention of erythrocyte agglutination upon intravenous administration is the same as the one achieved in D5, though by different means. However, as argued by respondent, the claimed solution *per se* is improved compared to the one of D5 as its administration does not require the precautions needed with the solution of D5, *i.e.* avoidance of *ex vivo* contact.

5.3.2 The respondent argued that D5 did not disclose a reconstitution method, so that this aspect should not

be part of the objective technical problem. However, while no particular reconstitution step is detailed, D5 still describes a reconstituted solution made from BeneFIX and water for injection.

5.3.3 Accordingly, starting from D5, the objective technical problem resides in the provision of a method to obtain an improved reconstituted factor IX solution for intravenous administration wherein erythrocyte aggregation is avoided.

5.4 Obviousness of the solution

5.4.1 Contrary to the opinion of the respondent, the suggestion of a causal link with the low ionic strength of the reconstituted solution in D5 provides an incentive to increase said ionic strength, even if this solution is not the one that was chosen in D5 (see point 5.1.3 above). However D5 does not mention adding sodium chloride to the reconstitution vehicle. The question to be answered is thus whether any prior art document suggests the present solution of increasing said ionic strength by having a low ionizing salt content in the lyophilized composition and reconstituting the formulation in 25-150 mM sodium chloride.

5.4.2 D6 relates to erythrocyte aggregation upon intravenous injection of a contrast medium used in angiography (see *e.g.* title and abstract). The respondent argued that the skilled person would not have considered D6 because it is not in the same field as the patent in suit. According to the respondent, a protein chemist, who would be the skilled person in the case of the patent in suit, would not have consulted D6 aimed at pharmacists. The Board considers that the skilled

person looking for methods to prevent erythrocyte agglutination upon intravenous injection would have, independently of its field of expertise, consulted documents dealing with the same issue even in neighboring fields, such as D6.

5.4.3 D6 states that the addition of 75 or 150 mM sodium chloride prevents agglutination of red blood cells probably because of its ionic strength (see page 208, left column, first and second full paragraph). The identification of this potential explanation for the beneficial effect of sodium chloride would have prompted the skilled person to try and apply this teaching to the solution of D5, which identified the cause of the aggregation issue as lying in its low ionic strength. It would therefore have appeared obvious to the skilled person to modify the reconstituted solution of D5 by including 75 or 150 mM sodium chloride therein.

5.4.4 In this context, the respondent argued that D6 concerns solutions containing a small molecule (iohexol) which is structurally very different from Factor IX, which is a protein. According to the respondent the teaching of D6 would be limited to iohexol formulations and the induction of aggregation by iohexol. The skilled person would thus not have extrapolated the teaching of D6 to the formulation of Factor IX, even more so as the mechanism of action by which sodium chloride (NaCl) inhibits aggregation in D6 was not known (see page 208, left column, third paragraph, "the site at which NaCl acts is unclear").

This argument is not convincing. The Board agrees with the respondent that in general an effect obtained for the formulation of one particular active ingredient

cannot be extrapolated to another one, especially when it is structurally very different therefrom. However, in the present case, as argued by the appellant, the skilled person would have recognised that the effect of NaCl described in D6 is (at least in part) independent from the active ingredient. Figure 1 of D6 reveals indeed that the addition of NaCl 150 mM to a solution of iohexol prevents aggregation of erythrocytes otherwise observed with the corresponding iohexol solution (compare solution 1 and 3) and furthermore a solution of NaCl in the absence of iohexol does also prevent aggregation of erythrocytes (see solution 6). In this context the respondent underlined that the aggregation in D6 would be induced by iohexol, thus implying that in the absence of iohexol no aggregation would occur. The Board considers however that the skilled person working in the filed of Factor IX formulation would be aware of D3, which states that the vehicle alone induced erythrocyte aggregation. Thus the skilled person would have immediately understood that the result obtained for solution 6 in D6 is indicating that NaCl prevents also erythrocyte agglutination induced by the vehicle. It follows that, even if the exact mechanism of action is not known, the skilled person would have learned from D6 that NaCl prevents erythrocyte agglutination even in absence of iohexol and that this effect is probably due to its ionic strength. In the present case, the skilled person would therefore have concluded that the effect of NaCl, being independent of iohexol, could reasonably be extrapolated to solutions of other active ingredients.

5.4.5 The skilled person willing to modify the reconstituted solution of D5 so that it contains 75 or 150 mM NaCl would have had only two options, namely:
(i) adding NaCl to the lyophilised powder, or

(ii) adding NaCl in the diluent.
No particular effect was substantiated for the addition of NaCl in the diluent for reconstitution. Furthermore, in view of D3 and D21, the skilled person would have been aware that both options had previously been used for the preparation of reconstituted Factor IX solutions. The Board considers therefore that the choice of adding NaCl in the diluent amounts at best to a selection among two equally obvious alternatives, which does not involve any inventive step. Moreover, D8 teaches that it is generally recommended not to add NaCl in the freeze-dried formulation but rather in the diluent (see page 197, penultimate paragraph). This teaching can be considered as common general knowledge because D8 is a textbook on lyophilisation. Such common general knowledge is actually confirmed in the patent in suit itself (see paragraph [101], "although methods for lyophilizing sodium chloride formulations is more difficult as compared to lyophilizing formulations that do not have sodium chloride" (sic)). In view of this common general knowledge, the skilled person would thus even have favoured the presently claimed option, especially as starting from the existing commercial kit as in D5, modifying the reconstitution diluent appears easier than modifying the lyophilised powder.

Hence, the Board considers that the skilled person would have arrive at a method according to present claim 1 without exercising inventive skills by combining the teachings of D5 and D6.

5.4.6 In relation to the remaining arguments brought forward by the respondent, the Board notes the following:

(a) The respondent argued that, as detailed in D25 and with reference to D26-D28, modifying the ionic

strength of a protein formulation by adding salts like NaCl may have unpredictable effects on the stability of the protein, in particular on protein aggregation. According to the respondent, the skilled person would thus have refrained from adding NaCl to a Factor IX formulation. The Board does not put into the question the unpredictability of protein stability in the presence of various salts. Nevertheless, the Board considers that, in the present case, the skilled person would not have had concerns regarding the formulation of Factor IX in the presence of NaCl, as formulations of Factor IX with NaCl were known from the prior art (see for example D3 and paragraph [0068] of D21).

(b) The responded further contended that the skilled person reading D6 would have had concerns in adding NaCl to a Factor IX formulation because of potential interactions with the coagulation. The responded referred to page 208, right column, second paragraph of D6, which mentions an effect of NaCl on coagulation. The Board observes that D6 does not provide details as to the mechanism and the conditions of the effect of NaCl on coagulation. In addition the coagulation experiments in D6 were performed under very different conditions than those of intravenous injection and the conclusions of D6 were reached in relation with the specific use in angiography. The Board considers that these specific results would not have dissuaded the skilled person from adding NaCl to a Factor IX solution, in particular as formulations of Factor IX with NaCl were known from the prior art (see for example D3 and D21).

(c) The respondent considered that the teaching of D8 referred to by the appellant did not constitute common general knowledge because it was too unclear and related to specific examples not covered by the claimed invention. The statement concerning the addition of NaCl in the diluent would indeed refer to its use as tonicifier and in undefined large proportions. Additionally, the specific examples provided in D8, as well as examples in D12 or D14, related to products wherein NaCl had been added in the lyophilisate instead of the diluent. The Board does not share this view. The passage relating to large proportions of NaCl and containing the specific examples mentioned by the respondent is to be found in the paragraph following the one containing the general statement used in the above problem-solution approach (see point 5.4.5). This general statement is therefore not limited by the following paragraph. Furthermore this general statement expresses a mere preference and does not exclude the possibility of including NaCl in the lyophilisate. It is consequently also not in contradiction with the examples cited by the respondent. Finally D8 also states that an excipient may have other functions in addition to tonicifier (see page 198, first paragraph, last sentence). Hence, there is no reason why the general statement concerning the preferred addition of NaCl to the diluent would be limited to NaCl when used as tonicifier.

(d) The respondent argued that using a specific diluent with a specific concentration for the reconstitution would require a kit with two components and would thus be more complicated. The Board is not convinced by this point. The

commercial BeneFIX product is already provided as a kit with two components, namely the lyophilisated BeneFIX composition and water for injection. Providing a ready to use 75 or 150 mM NaCl solution instead of water for injection would thus not complicate the reconstitution method.

(e) The respondent asserted that the presently claimed osmolarity was not suggested in the prior art. Even if osmolarity would constitute a relevant distinguishing feature versus D5 (see point 5.2.2), it would nevertheless be obvious for the skilled person given its common general knowledge that an injectable solution should have a physiologically acceptable osmolarity as claimed in present claim 1.

5.5 As the subject-matter of claim 1 of the main request is obvious to the skilled person starting from D5, the subject-matter of claim 1 of main request lacks an inventive step.

Auxiliary request 1-8

6. Admittance

Auxiliary requests 1-8 were filed by the respondent during the first instance proceedings on 14 June 2018 and resubmitted with the reply to the statement setting out the grounds of appeal. The appellant argued that auxiliary requests 1-8 constituted a procedural abuse, as they would not be convergent. However, the Board does not consider that the filing of these requests constitutes a procedural abuse. As the requests had already been filed during the opposition proceedings, the Board considers them to form part of the appeal

proceedings pursuant to Article 12(4) RPBA 2007 (Article 25(2) RPBA 2020).

7. Inventive step

7.1 The Board considers that the finding of lack of inventive step of claim 1 of the main request (see point 5.) applies *mutatis mutandis* to claims 1 of auxiliary requests 1-8, because:
- claims 1 of auxiliary requests 1-4 are identical to claim 1 of the main request,
- the feature introduced in claim 1 of auxiliary request 5 is meant to addresses an appellant's objection of insufficiency of disclosure and does not change the scope of the claim compared to the main request, and
- the modification suggested by D6 already (inherently) discloses the further features introduced in claims 1 of auxiliary requests 6-8 (ionic strength of the formulation in auxiliary request 6 and NaCl concentration in auxiliary requests 7-8).

7.2 The respondent did furthermore not provide any specific argument why the features of auxiliary requests 1-7 would overcome the lack of inventive step finding for the main request. Regarding claim 1 of auxiliary request 8, the respondent argued in the reply to the statement setting out the grounds of appeal, that the unexpected and narrow sub-range of NaCl concentration claimed (36 mM to 150 mM) would not be suggested by the prior art. The concentration of 75 mM disclosed in D6 does however fall within this narrow range, so that this argument is not convincing.

7.3 As a result, the subject-matter of auxiliary requests 1-8 does not fulfill the requirements of Article 56 EPC.

Auxiliary request 9

8. Admittance

Auxiliary request 9, filed during oral proceedings on 2 December 2021, corresponds to the identically numbered auxiliary request filed during the first instance proceedings and resubmitted with the reply to the statement setting out the grounds of appeal wherein merely the kit claims 10-11 have been deleted. The present claims of auxiliary request 9 were already addressed by both parties during appeal proceedings, as part of this former auxiliary request. In the present case, the mere deletion of the kit claims does thus not alter the legal and factual framework. It does in particular not affect the discussion regarding inventive step of the method claims 1-9. Accordingly the Board considers that the deletion of claims 10-11 in present auxiliary request 9 does not constitute an amendment to the appeal case of the respondent compared to its submissions made with its reply to the statement setting out the grounds of appeal. It follows that, in the present case, Article 13(1) and 13(2) RPBA 2020 do not apply. The same considerations as developed under point 6. applied to former auxiliary request 9. Accordingly present auxiliary request 9, is admitted into the appeal proceedings (Article 12(4) RPBA 2007).

9. Amendments

The subject-matter claimed in auxiliary request 9 is disclosed in the original claims and the original

description. Furthermore the scope of the claims was limited compared to the one of the granted claims. The appellant did not raise any objection under Articles 123(2) and 123(3) EPC for the performed amendments. The Board considers that the requirements of Articles 123(2) and 123(3) EPC are fulfilled.

10. Sufficiency of disclosure and novelty

The reasoning detailed for the main request under points 3. and 4. applies *mutatis mutandis* to the subject-matter of auxiliary request 9, as its scope was merely restricted. Regarding the issue of novelty, the appellant stated that the amended concentration range was not narrow and sufficiently removed from the end-points of the range disclosed in D1. The Board notes that the novelty of the amended range over the broader range of D1 is not relevant in the present case, as the issue of selection of several features in several lists without any disclosure of the combination thereof remains. Hence, auxiliary request 9 fulfills the requirements of Articles 83 and 54 EPC.

11. Inventive step

11.1 Claim 1 of auxiliary request 9 differs from claim 1 of the main request in that the NaCl concentration range was restricted to "36 to 44 mM". Neither the appellant nor the respondent considered any other document than D5 as closest prior art to the subject-matter of claim 1 of the auxiliary request 9. For the reasons detailed for the main request, and as the concentration of the sodium chloride solution of D3 no longer falls within the present amended range, the Board agrees that D5 represents the closest prior art. Starting from D5, the same problem-solution-approach as developed under

points 5.1 to 5.3, including the definition of the objective technical problem to be solved, is followed.

11.2 However the Board considers that none of the prior art documents cited by the appellant suggests to reconstitute a Factor IX formulation in a NaCl solution having a concentration within the claimed range.

11.2.1 D6 discloses only two individual and higher values (75 mM and 150 mM). Contrary to the opinion of the appellant, the Board further considers that D6 does not suggest to try and determine suitable lower concentrations of NaCl. The reference in D6 to finding "the minimum NaCl-addition which minimizes the medium's ability to provoke red cell aggregation" (page 208, right column, fourth paragraph, last sentence) relates to the use in angiogenesis and its associated potential side effects, which differ from the present use. Moreover D6 does not provide any hint to the present specific range.

11.2.2 D21 does indeed teach a concentration of NaCl of 40 mM but D21 unambiguously exclusively refers to lyophilisation processes and the inclusion of the NaCl in the lyophilised composition. The skilled person combining the teachings of D5 and D21 would have had no motivation to add NaCl at a different stage than before lyophilisation. Moreover, no resort to common general knowledge would have been necessary since D21 already provided for all necessary features.

11.2.3 D7, referred to during oral proceedings by the appellant, pertains to a more remote field, namely blood transfusion. The disclosure of D7 differs fundamentally from the patent in suit in that it relates to the administration of blood products instead

of the intravenous injection of an active principle solution without any blood cells. The issue of blood clumping of D7 cannot therefore be compared with the present issue of erythrocytes aggregation in tubing or in the syringe upon intravenous injection. Furthermore D7 was published in 1952 and discloses therefore older technology. The Board considers that the skilled person would thus not have consulted D7, let alone combined its teaching with the one of D5.

11.2.4 In this context the appellant argued that, in the absence of a specific effect, the present range represented an arbitrary selection from the larger range previously claimed in the main request. This argument is not convincing as the teaching of D6 is limited to two single points (*i.e.* D6 does not describe any range).

11.3 Accordingly, auxiliary request 9 fulfills the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The case is remitted to the opposition division with the order to maintain the patent in amended form on the basis of auxiliary request 9 filed during the oral proceedings on 2 December 2021 and a description to be adapted thereto.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated