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Datasheet for the decision of 31 January 2024

Case Number: T 2395/22 - 3.3.02

Application Number: 16157001.5

Publication Number: 3078667

IPC: C07F5/02, C07F5/04, C07K5/078, A61K38/05, A61K31/69, A61P35/00, A61P29/00

Language of the proceedings: EN

Title of invention:
FORMULATION OF BORONIC ACID COMPOUNDS

Patent Proprietor:
The United States of America, represented by the Secretary, Department of Health and Human Services

Opponents:
Teva Pharmaceutical Industries Ltd
Fresenius Kabi Deutschland GmbH
Pfizer Inc.
LEK Pharmaceuticals d.d.
Synthon BV
PENTAFARMA, Sociedade Técnico-Medicinal, SA
KRKA, d.d., Novo mesto
Zentiva k.s.
Accord Healthcare
Dr. Reddy's Laboratories Ltd./ Betapharm Arzneimittel GmbH
Generics [UK] Ltd

Headword:

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2)
RPBA 2020 Art. 12(3), 11, 12(5), 13(1), 13(2)
RPBA Art. 12(4) (2007)

Keyword:
Novelty with regard to an alleged public prior use - obligation to confidentiality
Added subject-matter
Sufficiency of disclosure
Inventive step

Decisions cited:
G 0003/14, T 0906/01, T 0152/03, T 0007/07, T 1348/14, T 1800/20

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 2395/22 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 31 January 2024

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Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 5 September 2022 rejecting the oppositions filed against European patent No. 3078667 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	P. O'Sullivan
	M. Blasi

Summary of Facts and Submissions

I. The appeals of opponents 1, 8, 10 and 11 (hereinafter appellant-opponents 1, 8, 10 and 11) lie from the decision of the opposition division to reject the oppositions against European patent 3 078 667.

II. The following documents were among those cited by the parties in opposition proceedings:

D1: WO 96/13266
D2: US 5,780,454
D5: US 6,083,903
D7: Pikal, M., Freeze Drying, Encyclopedia of Pharmaceutical Technology 1992, pages 275-303,
D8: "Parenteral Preparations", Chapter 84, Remington's Pharmaceutical Sciences; 18th Ed., 1990, 1565-1567
D9: Bauer, K.H., *et al.*, Pharmazeutische Technologie, 1991, pages 126-129
D10: Voigt, R., Pharmazeutische Technologie, 2000, pages 23-24
D13: WO 00/57887
D14: Mori, Y., *et al.*, Pigment Cell Research, 1989, pages 273-277
D15: Kuivila, H. G., *et al.*, J. Org. Chem., 1954, pages 780-783
D16: Yoshino K. *et al.*, Strahlenther Onkol., 1989, pages 127-129
D17: R. J. Ferrier, "Carbohydrate Boronates" in Advances in Carbohydrate Chemistry and Biochemistry, 1978, volume 35, pages 31-80
D19: WO 02/059130
D21: US 60/264,160
D23: Jennings, T.A., Lyophilization: Introduction and

Basic Principles, 1999, pages 29-33

D32: Cappola, Freeze Drying, 2000

D36: Experimental report: "Report on Stability Studies" dated 23 December 2016

D38: Nuijen, B., *et al.*, PDA Journal of Pharmaceutical Science and Technology, 2000

D51: Declaration of Dr Roel Fokkens dated 7 July 2016

D52: Walker, S. *et al.*, Can. J. Hosp. Pharm., 2008, pages 14-20

D53: Declaration of Dr Roel Fokkens dated 11 December 2017

D93: PowerPoint presentation, "The Story of Velcade - A Biotech Love Story"

D96: Scientific discussion of the European Medicines Agency (EMA) on Velcade

D97: US 5,780,454

D98: Kelly *et al.*, "lmmunosuppressive Boronic Acid Dipeptides: Correlation between Conformation and Activity", J. Am. Chem. Soc., 1993, pages 12637-12638

D99: Shenvi, "Alpha-Aminoboronic Acid Derivatives: Effective Inhibitors of Aminopeptidases" Biochemistry, 1986, pages 1286-1291

D100: Andre *et al.*, "Stability of Bortezomib 1-mg/ml Solution in Plastic Syringe and Glass Vial" The Annals of Pharmacotherapy, September 2005, pages 1462-1466

D101: Summary of Product Characteristics of Velcade, dated 28 March 2019

D105: Declaration of Dr Roel Fokkens dated 9 December 2011

D106: Declaration of Dr Roel Fokkens dated 19 February 2014

D125: Declaration of Alice Choi dated 24 March 2020

D125b: Informed Consent Form

D125c: Pharmacy manual for Protocol M34100-025
D126: A. Eitel *et al.*, "Handling Cytostatic Drugs - A practical guide",
D134: Bachovchin declaration dated 6 January 2022
D142: Richardson declaration dated 3 February 2022

III. With its statement of grounds of appeal and subsequent letter dated 4 January 2023, appellant-opponent 8 submitted documents BB26-BB32. In the following, these documents are renumbered respectively as documents A145 to A151 as follows:

A145: Excerpt from infringement proceedings (case no 4c O 41/22) at the Regional Court of Düsseldorf, Germany
A146: Communication from the Regional Court of Düsseldorf on 4c O 41/22
A147: Decision of the Opposition Division in relation to the contested patent
A148: Minutes of the oral proceeding leading to the contested decision
A149: Adams *et al.* in Bioorg. & Med. Chem. Lett. 8, 1998, pages 333-338
A150: US 4,499,082
A151: World Medical Association Declaration of Helsinki.

IV. With their statement of grounds of appeal, appellant-opponents 10 submitted document D152, hereinafter referred to as

A152: Encyclopedia of Bioethics, 2004, "Informed Consent", 1995, pages 1271-1280.

V. With the reply to the statements of grounds of appeal, the patent proprietor (hereinafter respondent) submitted the following document:

A153: Declaration of Paul Richardson dated 9 May 2023

VI. With the letter dated 10 July 2023, appellant-opponents 10 submitted the following documents:

A154: Zhaoxin Gu *et al.*, Acta Biomaterialia Volume 80, 15 October 2018, pages 288-295
A155: Email from Jin-Wang Lai dated 18 January 2001 regarding LPD-341 (bortezomib)
A156: "Preparation of kits for $^{99}Tc^{m}$ radiopharmaceuticals", IAEA-TECDOC-649 (excerpt), May 1992
A157: The first two pages of the website: https://www.drugs.com/velcade.html#
A158: Civil Action No. 05-cv-2308 (PGS) - extract
A159: Decision T 7/07 - extract
A160: "Anhang I - Zusammenfassung der Merkmale des Arzneimittels" for Velcade
A161: Declaration of Christopher Hunter dated 15 May 2023
A162: Memorandum opinion submitted to United States District Court for The District of Delaware in lawsuit between Millennium Pharmaceuticals and Sandoz Inc.

VII. The parties were summoned to oral proceedings in line with their corresponding requests. With a communication pursuant to Article 15(1) RPBA, the board set out its preliminary opinion. The board *inter alia* provided the view that claim 1 of the main request, i.e. of the patent as granted, comprised added subject-matter. The

subject-matter of the claims of the main request was considered sufficiently disclosed, and was novel over a public prior use allegedly disclosed in document D93.

VIII. Oral proceedings before the board were held in person on 30 and 31 January 2024 in the presence of appellant-opponents 1, 8, 10 and 11 and the respondent.

IX. Requests relevant to the present decision

All appellants requested that the decision under appeal be set aside and the patent be revoked in its entirety.

Appellant-opponents 1, 8 and 10 also requested that auxiliary requests 1 to 15 not be admitted into the appeal proceedings.

Appellant-opponent 8 also requested that documents A145 to A151 be admitted into the appeal proceedings.

Appellant-opponents 10 also requested that documents A154 to A162 be admitted into the appeal proceedings and that A153 not be admitted.

The respondent requested that the appealed decision be upheld, i.e. dismissal of the appeals and maintenance of the patent as granted, or alternatively, that the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 1 to 5, 5a, or 6 to 15, auxiliary requests 1 to 15 being submitted with the reply to the statements of grounds of appeal and being identical to auxiliary requests 1 to 15 submitted before the opposition division, and auxiliary request 5a being submitted during oral proceedings before the board.

The respondent also requested that the following not be admitted into appeal proceedings:

- documents A149 to A152 submitted by appellant-opponents 8 and 10;
- documents A154 to A158 and A160 to A162 submitted by appellant-opponents 10;
- appellant-opponent 1's objection of lack of inventive step starting from D1 or D2 as closest prior art;
- the assertion of appellant-opponent 8 in relation to sufficiency of disclosure that the molecular species at m/z = 531 (in example 1, paragraph [0071] of the patent; paragraph [0141] of D19) could have been formed during the process of FAB-MS analysis, rather than during the production method of example 1 (point 67 of the reply) (hereinafter referred to in short as "objection linked to the nature of the obtained product, in particular whether it was a monomer or a dimer"), and
- the objection of insufficient disclosure by appellant-opponents 10 with reference to a macrocyclic compound and the associated discussion.

The respondent also requested that A153, submitted with its reply to the statements of grounds of appeal, be admitted into the appeal proceedings.

Opponents 2, 3, 4, 5, 6 and 9 were parties as of right and neither filed any requests in appeal nor attended oral proceedings before the board. Opponent 7, having withdrawn the opposition prior to the appeal proceedings, never became a party to the appeal proceedings.

X. For the text of the independent claims of the main request and the relevant auxiliary requests, reference is made to the reasons for the decision, below.

XI. For the relevant party submissions, reference is made to the reasons for the decision, below.

Reasons for the Decision

Auxiliary request 5

The subject-matter of the main request and auxiliary requests 1 to 4 is addressed below, subsequent to auxiliary request 5.

1. Admittance

1.1 All appellants requested that *inter alia* auxiliary request 5 not be admitted into the appeal proceedings.

1.2 Auxiliary request 5 was among auxiliary requests 1 to 15 submitted by the respondent with the reply to the grounds of appeal, but first submitted during opposition proceedings with the letter dated 7 January 2022, after expiry of the time limit set under Rule 79(1) EPC and on the final date for making written submissions under Rule 116 EPC.

1.3 The appellants essentially argued that auxiliary request 5 should not be admitted as it had not been admissibly raised during opposition proceedings. In particular, the requirements for convergence were not met. Moreover, if admitted, the board would not be

reviewing the opposition division's decision but would rather perform a first-time examination of a new set of claims, contrary to Article 12(2) RPBA.

1.3.1 Article 12(2) RPBA stipulates that in view of the primary object of the appeal proceedings to review the decision under appeal in a judicial manner, a party's appeal case shall be directed *inter alia* to the requests on which the decision was based. In the present case, the contested decision was not based on auxiliary request 5, as the oppositions were rejected. The requirements of Article 12(2) RPBA are thus not met.

1.3.2 According to Article 12(4) RPBA, any part of a party's appeal case which does not meet the requirements of Article 12(2) RPBA is to be regarded as an amendment, unless the party demonstrates that this part was admissibly raised and maintained in the proceedings leading to the decision under appeal.

1.3.3 To judge whether a claim request was admissibly raised in opposition proceedings, the board considered whether the opposition division would have admitted the claim request, had a decision on admittance been required. If so, the claim request was admissibly raised.

1.3.4 The appellants objected to the admittance of auxiliary request 5 on the basis that the auxiliary requests 1 to 15 to which it belonged were not convergent.

1.3.5 In the present case, with the letter dated 7 January 2022 filed before the opposition division, the respondent set out the reasons behind the amendments to the respective auxiliary requests. In particular, it was explained that the amendments to

auxiliary request 1 were intended to deal with the opposition division's preliminary view that the subject-matter of certain dependent claims did not meet the requirements of Article 123(2) EPC (letter, point 22). For auxiliary requests 2 and 3, the respective claim 1 was amended by limitations to D-mannitol and *tert*-butanol, respectively. The claims of auxiliary requests 4 and 5 were directed to a combination of the amendments to auxiliary requests 1 and 2, and 2 and 3, respectively, and it was explained that the amendments were in response to objections under Article 123(2) EPC raised by the appellants (respondent's letter of 7 January 2022, points 24 to 31).

1.3.6 In the circumstances of the present case, the amendments to auxiliary requests 1 to 5 progressively limit the claims in view of the individual objections of the opposition division or the appellants under Article 123(2) EPC, with later requests combining amendments in a single claim to cover the situation in which more than one objection would be found convincing. Moreover, the patent proprietor faced eleven opponents, each having raised various objections under all grounds for opposition. Hence, in the board's view, these claim requests are sufficiently convergent.

1.3.7 Appellant-opponent 8 also submitted that auxiliary request 5 had not been substantiated in opposition proceedings in relation to novelty and inventive step, as no arguments had been submitted by the respondent in this regard. However, the board considers that an explicit substantiation for novelty or inventive step was not necessary, since as set out above, it was clear from the respondent's explanations submitted with the letter dated 7 January 2022 that the request was submitted to overcome added subject-matter objections.

1.4 Consequently, even if, to the appellants advantage, it were to be assumed that the opposition division would have had discretion not to admit these requests into opposition proceedings on the basis that they were not convergent, this is not the case for the requests in question. At least auxiliary request 5 was therefore admissibly raised in opposition proceedings. It was not disputed that this request had been maintained before the opposition division. Hence, auxiliary request 5 was not to be regarded as an amendment and the board thus had no discretion pursuant to Article 12(4) RPBA.

1.5 Appellant-opponent 8 referred to decision T 1800/20 to further support the argument that auxiliary request 5 was not admissibly raised in opposition proceedings. However, as set out by the respondent, the factual situation in that case was different to the present. Specifically, the request which was not admitted by the deciding board in that case had been submitted for the first time during oral proceedings before the opposition division (reasons, 3.1). Hence, T 1800/20 is not relevant in the present context.

1.6 In view of the above, auxiliary request 5 is part of the appeal proceedings.

2. Added subject-matter - Article 123(2) EPC

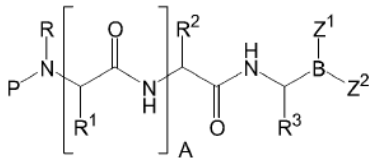
2.1 The appellants submitted that *inter alia* independent claim 1 of auxiliary request 5 comprised added subject-matter.

2.1.1 In their arguments, the parties for the most part referred to the grandparent application as filed, D19. It was undisputed in appeal that the content of D19 was

identical to that of the application as filed, insofar as the assessment of compliance of the claimed subject-matter with Article 123(2) EPC was concerned.

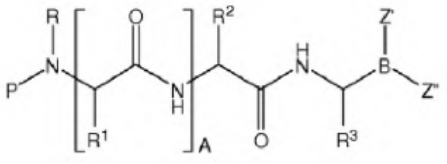
2.2 Claim 1 of auxiliary request 5 reads as follows:

"1. A method of preparing a lyophilized compound of the formula (1):



(1)

wherein
P is hydrogen or an amino-group protecting moiety;
R is hydrogen or alkyl;
A is 0, 1, or 2;
R^1, R^2, and R^3 are each independently hydrogen, alkyl, cycloalkyl, aryl, or $-CH_2-R^5$
R^5 in each instance is aryl, aralkyl, alkaryl, cycloalkyl, heterocyclyl, heteroaryl, or $-W-R^6$, where W is a chalcogen and R^6 is alkyl;
wherein the ring portion of any said aryl, aralkyl, alkyaryl, cycloalkyl, heterocyclyl, or heteroaryl in R^1, R^2, R^3, or R^5 can be optionally substituted; and
Z^1 and Z^2 together form a moiety derived from D-mannitol;
the method comprising:
(a) preparing a mixture comprising
(i) water,
(ii) a compound of formula (3)



(3)

wherein P, R, A, R^1, R^2, and R^3 are as described above; and Z' and Z" are OH;
(iii) ~~*a moiety derived from sugar*~~ ***D-mannitol; and***
(iv) tert-butanol;

wherein the D-mannitol and the compound of formula (3) are present in a w/w ratio of 10:1;
and

(b) lyophilizing the mixture;

wherein:
the compound of formula (1) is D-mannitol N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate; and
the compound of formula (3) is N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid." (text in strike through and bold representing deletion and addition compared to independent claim 35 of D19)

2.2.1 In the following, the compound of formula (3), namely N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid is abbreviated to "bortezomib", and the compound of formula (1), namely D-mannitol N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate is abbreviated to "bortezomib D-mannitol ester".

2.2.2 Although a general formula is defined in claim 1 of auxiliary request 5, it was undisputed that the subject-matter of the claim concerns a single compound

(1) and a single compound (3). Hence for the sake of simplicity, claim 1 of auxiliary request 5 can be condensed without changing its meaning, as follows:

1. A method of preparing lyophilised bortezomib D-mannitol ester, comprising:

(a) preparing a mixture comprising

(i) water,

(ii) bortezomib,

(iii) D-mannitol; and

(iv) *tert*-butanol;

wherein the D-mannitol and the bortezomib are present in a w/w ratio of 10:1;

and

(b) lyophilising the mixture.

Similarly, independent claim 3 of auxiliary request 5 can be condensed for the same reason and in the same way without changing its meaning to read as follows:

3. A lyophilised composition comprising bortezomib D-mannitol ester, wherein the lyophilised composition is prepared by the method comprising:

(a) preparing a mixture comprising

(i) water,

(ii) bortezomib,

(iii) D-mannitol; and

(iv) *tert*-butanol;

wherein the D-mannitol and the bortezomib are present in a w/w ratio of 10:1;

and

(b) lyophilising the mixture.

The board notes that in the composition specified in both claim 1 and 3, by the virtue of the ratio feature, free D-mannitol is present in excess.

2.3 As basis for claim 1, the opposition division and the appellants started from claim 35 of D19. The respondent did not dispute this approach. Hence, starting from claim 35 of D19, in claim 1 of auxiliary request 5:

- the compound of formula (1) was specified to be the D-mannitol ester of bortezomib,
- the compound of formula (3) was specified to be bortezomib,
- the moiety derived from sugar was specified to be D-mannitol,
- *tert*-butanol was added to the mixture to be lyophilised, and
- the w/w ratio of D-mannitol to the compound of formula (3) was specified to be 10:1.

2.4 As a first general observation, the board notes that D19 discloses four separate "aspects" of the invention. It is undisputed that the subject-matter of claim 35 and dependent claims 36 to 54 of D19, and thus of claim 1 of auxiliary request 5, is directed to the "third aspect" of the invention, which concerns a method of formulating a boronic acid compound (paragraphs [0026] - [0031] and [0102] - [0133] of D19), while the subject-matter of independent claim 3 of auxiliary request 5 corresponds to the fourth aspect of the invention directed to compositions prepared according

to the methods of the invention (paragraphs [0032] and [0134] - [0137] of D19).

2.4.1 The appellants in their arguments characterised the four separate aspects of the invention as distinct and separate embodiments which, for the purpose of determining the disclosure of D19, could not be combined (e.g. appellant-opponent 11, statement of grounds of appeal, point (11)).

2.4.2 The board does not agree. As argued by the respondent, the four aspects of the invention are interconnected and would be understood as such by the skilled person (see e.g. page 7 of the respondent's reply, footnote 23). Hence, a suitable basis for the subject-matter of contested claim 1 is not necessarily limited to the parts of D19 dealing exclusively with the third aspect of the invention.

2.5 The appellants also argued that the combination of features in claim 1 of auxiliary request 5 could not be derived by the skilled person from dependent claims 36 to 53 of D19. Specifically, although all of those claims ultimately depended on claim 35, they did not depend on each other. For example, although claim 49 referring to bortezomib, claim 39 referring to mannitol forming the ester and claim 50 referring to a water-miscible solvent all individually referred back to claim 35, they were not linked to each other in terms of dependency.

2.5.1 The board agrees with the respondent that it is not the format or the order of the claims which is decisive in determining whether the subject-matter of claim 1 of auxiliary request 5 is disclosed in D19. Strict literal support is not required by Articles 123(2) EPC.

Nevertheless, the subject-matter of claims 1 and 3 of auxiliary request 5 should be directly and unambiguously derivable from D19 as a whole, as understood by the skilled person. When a claim concerns a combination of features, as is the case for present claim 1, direct and unambiguous disclosure in the earlier application is required. Not only the individual features themselves, but also the combination of those features must be directly and unambiguously disclosed therein.

2.6 The specific objections of the appellants in relation to claim 1 of auxiliary request 5 concern the allegation that the subject-matter of claim 1 results from cherry-picking from within the disclosure of D19, without any disclosure of the selections in combination, i.e. without any pointer to the combination of selections resulting in claim 1. In particular claim 1 was arrived at by selecting:

(i) bortezomib, which was not disclosed in D19 as being preferred,
(ii) bortezomib D-mannitol ester, which was not disclosed in D19 as being preferred,
(iii) D-mannitol,
(iv) the specific w/w ratio of D-mannitol to bortezomib of 1:10 from a list of equally ranked alternatives, and
(v) the addition of *tert*-butanol to the mixture, which was not preferred.

Each of these amendments are addressed in the following.

2.6.1 Amendments (i) and (ii) - bortezomib and bortezomib D-mannitol ester

Method claim 35 of D19 discloses an ester of a moiety derived from sugar (component (ii) in step (a)) and a boronic acid compound of formula (1). To arrive at bortezomib and bortezomib D-mannitol ester starting from claim 35 of D19, two selections are needed, namely of bortezomib for the compound of formula (1) and of D-mannitol for the moiety derived from sugar.

As stated by the respondent, D19 discloses bortezomib as the preferred boronic acid compound and its mannitol ester as the preferred ester. Thus claim 49 singles out bortezomib from the boronic acids listed in claim 47, and claim 48 concerns solely bortezomib as an ester with D-mannitol. Furthermore, bortezomib is the only boronic acid featured in the examples, thus confirming that it represents the boronic acid of choice to the skilled person reading D19. Similarly, bortezomib D-mannitol ester is the preferred bortezomib ester in view of claim 48 of D19, as well as the examples in which it is prepared.

2.6.2 Amendment (iii) - the choice of D-mannitol

Appellant-opponent 1 submitted that there was no basis in D19 for the replacement of "the moiety derived from sugar" in claim 35 with "D-mannitol" in present claim 1. In particular, "the moiety derived from sugar" was defined in D19 in paragraph [0063] as "a moiety formed by removing the hydrogen atoms from two hydroxyl groups of any sugar moiety". According to paragraph [0064], the sugar was *inter alia* mannitol. Hence, paragraph [0063] did not refer to mannitol, but rather to a mannitol derivative lacking two hydrogen atoms.

The board disagrees. As stated by the respondent, this argument amounts to a purely literal reading of claim 35 of D19, without taking into account the understanding of the skilled person. Said claim concerns the preparation of a mixture, one of the constituents of which is "a moiety derived from sugar". The skilled person would understand that claim 35 is to be interpreted as using, in the claimed process, a sugar molecule, rather than a fragment of a sugar molecule absent two hydrogen atoms, which would not make technical sense. Hence, the appellant's arguments in this regard fail.

For the sake of completeness, the board also notes that D-mannitol is the preferred sugar moiety according to D19 (see for example D19, claim 48; paragraph [0098], and the examples of D19 in which only D-mannitol is employed), and indeed the argument that D-mannitol was preferred was invoked by the appellants to argue a lack of compliance with Article 123(2) EPC in relation to higher ranking requests in which "mannitol", and not "D-mannitol" was specified.

2.6.3 Amendment (iv)- ratio mannitol:bortezomib of 10:1 w/w

In relation to this amendment the appellants argued that D19 did not comprise a pointer to the claimed ratio, neither alone nor in combination with the further features of claim 1. In particular, dependent claims 53 and 54 provided a ratio of 1:1 and 5:1, but were silent as to the claimed ratio. Paragraph [0110] of D19 was also not an appropriate basis.

The board disagrees. As set out above, it is the totality of the disclosure of D19 which counts for

assessment of compliance with Article 123(2) EPC, and hence there is no reason to conclude that a pointer to the claimed ratio feature is lacking solely on the basis that dependent claims 53 and 54 fail to disclose said ratio. Rather, as stated by the respondent, these claims express a general preference for the specifically claimed ratios in the general context of independent claim 35, which itself is not limited to bortezomib and D-mannitol, or bortezomib D-mannitol ester.

As argued by the respondent, the claimed ratio of 10:1 w/w is disclosed in paragraph [0110] of D19. It is true however, as stated by the appellants, that this paragraph discloses the claimed ratio as one possibility among 11 ratios mentioned, ranging from 1:1 to 100:1, with no preference expressed for any specific ratio. Hence paragraph [0110] alone does not provide a pointer to the claimed ratio.

However, in example 1 of D19, bortezomib and D-mannitol were employed in a process to prepare bortezomib mannitol ester in a ratio of 0.4 g of mannitol (i.e. D-mannitol, see title of example 1 and paragraph [0140]) to 40 mg of bortezomib, and hence a ratio of 10:1. Having made the specific choice to use the preferred bortezomib and the preferred D-mannitol, the skilled person would have looked to the examples of D19 for guidance on the manner in which to carry out the invention for that specific preferred combination, including the ratio of these compounds to be employed. Hence, example 1 serves as a pointer, in the specific context of bortezomib and D-mannitol, to the 10:1 ratio specified in paragraph [0110]. Both disclosures therefore serve as the basis for the 10:1 ratio in

combination with the choice of bortezomib and D-mannitol.

In relation to the same amendment, it was argued by appellant-opponents 10 that the choice of the ratio of 10:1 over the ratios of 1:1 and 5:1 disclosed in claims 53 and 54 of D19 amounted to cherry picking of a single choice from several non-converging alternatives.

The board disagrees. The employment of weight amounts in example 1 in a ratio of 10:1 serves as a specific pointer to this ratio in paragraph [0110] as the sole preferred embodiment in the specific context of bortezomib and D-mannitol. Hence, in this specific context, the ratios stipulated in claims 53 and 54 of D19 do not represent the same level of preference.

Also in relation to the same amendment, appellant-opponent 11 submitted that although example 1 referred to specific amounts of bortezomib and D-mannitol from which a ratio could be calculated, it did not disclose the ratio itself, which had a different level of precision. Hence, example 1 could not serve as basis for the ratio feature of 1:10.

The board disagrees. As stated by the respondent, example 1 is not the sole basis for the ratio, but rather serves as a specific pointer to the ratio of 10:1 in paragraph [0110] of D19 as being preferred in the context of bortezomib and D-mannitol.

2.6.4 Amendment (v) - the addition of *tert*-butanol to the mixture

D19 discloses the use of *tert*-butanol as a water-miscible solvent in the mixture at the end of a chain

of preference in dependent claims 50 to 52 (which ultimately depend on claim 35). Similarly, paragraph [0108] discloses that the water-miscible co-solvent is an alcohol, including ethanol and *tert*-butanol. It is stated that in certain preferred embodiments, the aqueous solvent mixture comprises about 40% *tert*-butanol. However, paragraph [0109] of D19 describes another embodiment in which "in certain preferred embodiments", the aqueous solvent mixture comprises from about 5% to 10% ethanol.

As argued by the appellants, it cannot be concluded from these paragraphs that the choice of *tert*-butanol is preferred. Rather, it is on an equal standing with ethanol. On the other hand, even if a preference for *tert*-butanol were to be derivable from claim 52 of D19, the preference is only expressed in the general context of claim 35, and lacks any limitation to the specifically preferred bortezomib, D-mannitol, and in particular, the specific claimed ratio of 10:1 which as set out above, finds basis in paragraph [0110] in combination with example 1. As stated by appellant-opponents 1 and 10 in particular, since at least the ratio feature addressed above requires a pointer in example 1 of D19 which also specifies bortezomib and D-mannitol, an appropriate basis for *tert*-butanol must also be disclosed in D19 in association with these further features of claim 1. The only possible disclosure of such an association is necessarily in example 1, since this example is required as partial basis for the ratio feature as set out above. However, as stated by the appellants, example 1 does not disclose generally that *tert*-butanol is the water-miscible solvent, but rather more specifically that 16 ml of *tert*-butanol were employed along with 24 ml of

water, i.e. an aqueous solvent mixture comprising 40% v/v *tert*-butanol.

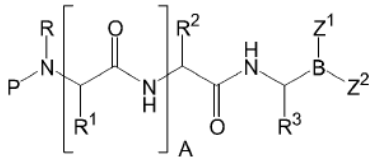
Since there is no basis in example 1 of D19 for the generalisation of this disclosure to the use of *tert*-butanol as a solvent, it follows that the subject-matter of claim 1 of auxiliary request 5 extents beyond the content of the application as filed.

2.7 Consequently, the requirements of Article 123(2) EPC are not fulfilled, and the set of claims of auxiliary request 5 is not allowable.

Main request - Article 100(c) EPC - and auxiliary requests 1 to 4 - Article 123(2) EPC

3. Claim 1 of the main request (patent as granted) reads as follows:

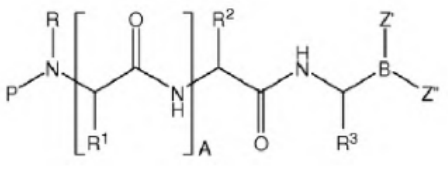
"1. A method of preparing a lyophilized compound of the formula (1):



(1)

wherein
P is hydrogen or an amino-group protecting moiety;
R is hydrogen or alkyl;
A is 0, 1, or 2;
R^1, R^2, and R^3 are each independently hydrogen, alkyl, cycloalkyl, aryl, or $-CH_2-R^5$;
R^5 in each instance is aryl, aralkyl, alkaryl, cycloalkyl, heterocyclyl, heteroaryl, or $-W-R^6$, where W is a chalcogen and R^6 is alkyl;
wherein the ring portion of any said aryl, aralkyl, alkyaryl, cycloalkyl, heterocyclyl, or

heteroaryl in R^1, R^2, R^3, or R^5 can be optionally substituted; and
Z^1 and Z^2 together form a moiety derived from mannitol;
the method comprising:
(a) preparing a mixture comprising
(i) water,
(ii) a compound of formula (3)



(3)

wherein P, R, A, R^1, R^2, and R^3 are as described above; and Z' and Z" are OH;
(iii) mannitol; and
(iv) a water-miscible solvent;

wherein the mannitol and the compound of formula (3) are present in a w/w ratio of 10:1;
and

(b) lyophilizing the mixture;

wherein:
the compound of formula (1) is a mannitol ester of N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucineboronic acid; and
the compound of formula (3) is N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid."

3.1 Claim 1 of auxiliary request 1 is identical to claim 1 of the main request.

Claim 1 of auxiliary request 2 differs from claim 1 of the main request in that it specifies that the mannitol component (iii) is D-mannitol, and that the compound of formula (1) is D-mannitol N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate.

Claim 1 of auxiliary request 3 differs from claim 1 of the main request in that component (iv) of the mixture prepared in step (a) is specified as being *tert*-butanol.

Claim 1 of auxiliary request 4 is identical to claim 1 of auxiliary request 2.

3.2 As concluded in relation to claim 1 of auxiliary request 5, above, amendment (iv), namely the w/w ratio of D-mannitol to bortezomib of 10:1 stipulated in claim 1 of all requests requires example 1 as a specific pointer to the ratio of 10:1 specified in the description in paragraph [0110]. Claim 1 of auxiliary request 5 did not meet the requirements of Article 123(2) EPC because the example did not disclose the use of *tert*-butanol in general as a water-miscible solvent.

3.3 Similarly, the respective claim 1 of the main request and auxiliary requests 1, 2 and 4 require that the mixture (a) comprises "(iv) a water-miscible solvent". Similarly to the issue with *tert*-butanol in claim 1 of auxiliary request 5, example 1 does not disclose the use of a water-miscible solvent in general, and hence cannot provide a basis for these claims in combination with the further features of claim, in particular the 10:1 ratio feature.

3.4 In claim 1 of auxiliary request 3, the mixture (a) comprises "(iv) *tert*-butanol".

3.5 Hence, the same issues arise for claim 1 of all of these requests under Article 123(2) EPC as for claim 1 of auxiliary request 5. This was also conceded by the respondent at oral proceedings.

3.6 Furthermore, since none of auxiliary requests 1 to 4 were allowable, there was no need for the board to address, at oral proceedings, their admittance into the proceedings, contested by appellant-opponents 1, 8 and 10. Having decided on auxiliary requests 1 to 4 on their merits, these requests were in the proceedings. As these requests are not allowable, the appellants were not adversely affected.

3.7 Consequently, the ground for opposition under Article 100(c) EPC prejudices the maintenance of the patent as granted (main request). Additionally, the requirements of Article 123(2) EPC are not met in relation to auxiliary requests 1 to 4.

Auxiliary request 5a

4. Admittance - Article 13(2) RPBA

The set of claims of auxiliary request 5a was submitted by the respondent during oral proceedings before the board. It differs from auxiliary request 5 in independent claims 1 and 3 (claims 1 and 2 of auxiliary request 5a respectively), by the addition at the end of method step (a) of the following text from claims 6 and 12 as granted:

"wherein the aqueous solvent mixture comprises 40% v/v tert-butanol; and"

4.1 Admittance of this request into the proceedings was to be assessed pursuant to Article 13(2) RPBA. According to this provision, any amendment to a party's appeal case made after notification of a communication under Article 15(1) RPBA shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

4.2 The respondent submitted that the amendment was intended to overcome the appellants' objection under Article 123(2) EPC set out for claim 1 of auxiliary request 5 according to which example 1 did not provide a pointer to the use of *tert*-butanol in general as the preferred water-miscible solvent. This objection had been submitted by the appellants for the first time at oral proceedings. Hence, the filing of auxiliary request 5a during oral proceedings represented the first opportunity to address the new objection.

4.3 The board agrees. As stated by the respondent, the subject-matter of auxiliary request 3, in which the limitation of component (iv) to "*tert*-butanol" was first applied to the mixture prepared in step (a) of claim 1, was addressed in its reply to the statements of grounds of appeal, paragraphs 438 to 440. In paragraph 438, it was stated that the amendment to *tert*-butanol closely followed the preferred species for the water-miscible solvent as used in the mixture, and that *tert*-butanol was used in the experimental examples of the application as filed. In paragraph 440, it was stated that basis for the limitation can be found in item 52 and paragraph [0108] of the application as

filed (corresponding to claim 52 and paragraph [0108] of D19).

4.4 The board understands from the separate statements in paragraphs 438 and 440 of the respondent's reply that basis for "*tert*-butanol" was found in claim 52 and paragraph [0108] of D19, and, in terms of meaning, that the experimental examples served as a pointer to this feature being preferred.

4.5 The appellants argued that an objection had been raised against the *tert*-butanol feature in written proceedings, and pointed in this regard to various submissions (e.g. letter of appellant-opponent 8 dated 30 June 2023, point 36; letter of appellant-opponents 10 dated 20 August 2019, section 17.7; statement of grounds of appeal of appellant-opponents 10, point 33; statement of grounds of appeal of appellant-opponent 1, point 4 in relation to sufficiency of disclosure). However, although the appellants indeed argued that basis for this feature was not provided in paragraph [0108] or claim 52 of D19 due to the lack of any explicit preference expressed therein for *tert*-butanol, no arguments were submitted according to which the examples of D19 could not serve as a pointer (i.e. not an explicit basis *per se*) to a preference for *tert*-butanol, expressed explicitly elsewhere in the description, but without an indication of a specific preference.

4.6 For the sake of completeness, although appellant-opponent 1 in the statement of grounds of appeal (point 4, first paragraph) stated that "[t]he only water-miscible solvent that is used in the example section of the opposed patent is *tert*-butanol in an amount of 40% v/v", this statement was submitted in the

context of sufficiency of disclosure, and not as part of an argument that the use of *tert*-butanol in the example could not serve as a pointer to a preference for this solvent.

4.7 The appellants' further arguments in relation to the admittance of auxiliary request 5a into the proceedings concerned the question of whether the amendments *prima facie* overcame the issues and did not give rise to new issues, as set out Article 13(1) RPBA.

4.8 The board acknowledges that these criteria may also be considered in the context of deciding, under Article 13(1) RPBA, on the admittance of auxiliary request 5a, in addition to the criteria of Article 13(2) RPBA.

4.9 In this context, some appellants argued that the amendments in auxiliary request 5a *prima facie* gave rise to new issues under Articles 123(2) and 84 EPC. At oral proceedings, the board heard the parties in relation to the appellants' objections under Article 123(2) and Article 84 EPC also on the merits, but did not find the appellants' arguments convincing (see below). Based on essentially the same considerations, the amendments to auxiliary request 5a were also considered *prima facie* not to give rise to new issues.

4.10 Hence, there is no reason on the basis of the appellants' arguments to doubt that the criteria set out in Article 13(1) RPBA are met.

4.11 Consequently, the submission of auxiliary request 5a during oral proceedings was justified by the exceptional circumstances set out above. Hence, the

board decided to admit auxiliary request 5a into the proceedings pursuant to Article 13(2) RPBA.

5. Article 123(2) EPC

5.1 Claim 1 of auxiliary request 5 was found to contravene the requirements of Article 123(2) EPC because example 1 did not disclose generally that *tert*-butanol is the water-miscible solvent, but rather more specifically that 16 ml of *tert*-butanol were employed along with 24 ml of water, i.e. an aqueous solvent mixture comprising 40% v/v *tert*-butanol.

5.2 Claim 1 of auxiliary request 5a is limited to a mixture comprising 40% v/v *tert*-butanol. As set out above, this is the concentration of *tert*-butanol used in example 1. Hence, in a similar manner as for the 10:1 ratio feature of claim 1 of auxiliary request 5 addressed above, the stipulation in paragraph [0108] of D19 that the aqueous solvent mixture comprises about 40% *tert*-butanol, in combination with the fact that this concentration is used in example 1, serves as a pointer to this feature as the preferred feature in relation to the water-miscible solvent in D19. This applies in particular in the context of the further preferred features set out in claim 1 such as the 10:1 ratio, and the selection of D-mannitol and bortezomib to prepare bortezomib D-mannitol ester.

5.3 In relation to claim 2, appellant-opponent 8 submitted (in relation to then claim 7 of the main request, corresponding to claim 2 of auxiliary request 5a) that in contrast to the basis provided for claim 1, method claim 35 of D19 did not provide a basis for composition claim 2. Basis was also not provided by paragraph [0032] and [0134] of D19, which stated that in a fourth

aspect, the invention provides compositions prepared according to the methods of the third aspect of the invention, i.e the aspect covered by claim 35 of D19.

5.4 The board disagrees. As stated above, the four aspects of the invention are interconnected and would be understood as such by the skilled person. Hence, basis for contested claim 2 of auxiliary request 5a is provided by the above references in D19 to the methods of the third aspect of the invention.

5.5 Further objections under Article 123(2) EPC were submitted by the appellants against auxiliary request 5a both in the context of admittance (addressed above) and in substance.

5.6 Appellant-opponent 8 in particular argued that the amendments in auxiliary request 5a gave rise to new issues under Article 123(2) EPC. First, paragraph [0108] of D19 did not specify that the unit for the amount of *tert*-butanol was "v/v" as specified in the claims.

5.7 The board disagrees. As stated by the respondent, paragraph [0108] stipulates that "[t]he composition of the solvent mixture may range from about 5% to about 95% v/v alcohol". In the following text, some embodiments are listed, culminating in "[i]n certain preferred embodiments, the aqueous solvent mixture comprises about 40% *tert*-butanol". It is thus clear that the v/v unit indicated for the percentage range provided for the broadest embodiment in paragraph [0108] applies also to subsequent embodiments. In particular, in the absence of an explicit indication, the skilled person would not suspect that any other unit were intended.

5.8 Second, appellant-opponent 8 also argued that further important features of example 1 were not incorporated into claim 1, such as reaction times, temperatures, and the specifics of the lyophilisation process. Hence, claim 1 represented an intermediate generalisation of example 1, and the requirements of Article 123(2) EPC were not met.

5.9 The board disagrees. As set out above, example 1 of D19 does not represent the sole basis for the subject-matter of claim 1, but rather the use therein of an aqueous solvent mixture comprising 40% v/v *tert*-butanol serves as a pointer to a preference for this feature as expressed in the description in paragraph [0108]. Since claim 1 is not based solely on example 1, it cannot be argued that it represents a unallowable generalisation of the conditions specified therein.

6. Article 84 EPC

6.1 In a further objection submitted in the context of admittance of auxiliary request 5a (addressed above) as well as in substance, the appellants argued that the amendment to claims 1 and 2 led to a lack of clarity pursuant to Article 84 EPC. Specifically, the expression "the aqueous solvent mixture" in the amendment did not have an antecedent in the claim, since step (a) only concerned "preparing a mixture". Hence, it was unclear whether this expression referred to the mixture prepared in step (a) as a whole, or only to the liquid components (i) and (iv).

6.2 The board disagrees. While it is true that a lack of an antecedent exists as argued, there is an antecedent for the term "mixture". More importantly however, as argued

by the respondent, the alleged lack of clarity was already present in the granted claims (claim 1 in combination with claim 6, and claim 7 in combination with claim 12), and hence cannot be raised post-grant in accordance with Enlarged Board of Appeal decision G 3/14.

7. Remittal - Article 111(1) EPC, Article 11 RPBA

7.1 During oral proceedings, subsequent to the board's announcement of its conclusion in relation to Article 123(2) EPC for auxiliary request 5a, appellant-opponent 8 requested that the case be remitted to the opposition division for further prosecution on the basis of auxiliary request 5a, so as to allow an additional prior art search, as it was not foreseeable whether or how the respondent would rely on the amendment in the context of the issues to be discussed.

7.2 Pursuant to Article 111(1) EPC, following the examination as to the allowability of the appeal, the board shall decide on the appeal. Under this provision, the board has discretion over whether or not to remit the case to the department whose decision was appealed. According to Article 11 RPBA, the board shall however not remit a case for further prosecution, unless special reasons present themselves for doing so.

7.3 As stated by the respondent, in the present case, no special reasons justifying a remittal were apparent. The board did not see any specific reasons, and none were set out by the appellants explaining why the inclusion of the solvent feature necessitated an additional prior art search. Furthermore, the feature added to claim 1 of auxiliary request 5a originates from a dependent granted claim, and as set out above,

the application as filed specifically pointed to this feature. Hence incorporating this feature into claim 1 of auxiliary request 5a cannot have come as a surprise to the appellants.

7.4 The board therefore decided not to remit the case to the opposition division at the stage of the proceedings at which the request was made (see in this regard the minutes of the oral proceedings before the board, paragraph bridging pages 7 and 8).

7.5 The board at the same time also noted that this conclusion did not prevent the parties from requesting remittal later in the proceeding if a party, based on later submissions, saw a specific reason for remittal.

7.6 Ultimately, no subsequent request for remittal was submitted during the course of the oral proceedings.

8. Sufficiency of disclosure - Article 83 EPC

8.1 Claim 1 of auxiliary request 5a concerns a method of preparing lyophilised bortezomib D-mannitol ester, comprising:

(a) preparing a mixture comprising
(i) water,
(ii) bortezomib,
(iii) D-mannitol; and
(iv) *tert*-butanol

wherein the D-mannitol and the bortezomib are present in a w/w ratio of 10:1; and
wherein the aqueous solvent mixture comprises 40% v/v *tert*-butanol; and

(b) lyophilising the mixture.

8.2 It is established jurisprudence of the boards of appeal that a successful objection of lack of sufficiency of disclosure presupposes that there are serious doubts, substantiated by verifiable facts. In order to establish insufficiency of disclosure, the burden of proof is upon the opponents (here: appellants) to establish, on the balance of probabilities, that a skilled person in the light of the information in the application as filed (in this case represented by D19), using common general knowledge, would be unable to carry out the claimed invention.

8.3 The appellants argued that the invention defined in independent claims 1 and 2 was not sufficiently disclosed. In the following only claim 1 is addressed. However, the considerations set out below apply equally to claim 2, since the same objections, set out below, apply to both claims in the same way. In agreement with all parties, grandparent application D19 was taken to represent the application as filed.

8.4 A first objection was submitted by appellant-opponent 1 in relation to claim 1 of the main request. Specifically, that claim referred to the use in the claimed method of a "water-miscible solvent", while example 1 of the patent and D19 only described the use of *tert*-butanol in an amount of 40% v/v. Since known water-miscible solvents differed greatly in properties such as boiling point, melting point, etc., it was not expected that all such solvents could be successfully employed in a mixture comprising bortezomib and mannitol to be lyophilised according to claim 1.

8.5 Claims 1 and 2 of auxiliary request 5a do not define the presence of a "water-miscible solvent", but are limited to a mixture comprising *tert*-butanol, wherein the aqueous solvent mixture comprises 40% v/v *tert*-butanol. This corresponds to the solvent mixture employed in example 1, to which the appellant's objection did not apply (see preceding paragraph). Hence, this objection is rendered moot in view of the amendments in auxiliary request 5a compared to the main request.

8.6 A second objection was submitted by the appellants during oral proceedings before the board and related to the fact, addressed above in relation to Article 84 EPC, that the term "the aqueous solvent mixture" in claim 1 of auxiliary request 5a did not have an antecedent. It was argued that as a result of this lack of clarity, the skilled person would not know whether the 40% v/v *tert*-butanol in claim 1 was to be calculated solely on the basis of the liquid components of the mixture in step (a), namely (i) water and (iv) *tert*-butanol, or on the basis of all four component (i) to (iv). This lack of clarity in the claim led to a lack of sufficiency to carry out the claimed invention, as the skilled person was unable to prepare the required mixture.

8.7 The board disagrees. As stated by the respondent, although there is no antecedent for the entire term "the aqueous solvent mixture", an antecedent does exist for the term "mixture". Since the only other incidence of this term in the claim occurs in relation to the mixture (a), it would be clear to the skilled person that the "mixture" referred to all four components listed. Hence, the achievement of 40% v/v *tert*-butanol

was to be calculated based on all four components. Irrespective of this, as stated by the respondent, even if the skilled person were to perceive a lack of clarity in this regard, adequate guidance is provided by the examples, in particular example 1, in which the amounts of each component added into mixture (a) are provided.

Consequently, this objection failed to convince the board.

8.8 In a third objection, appellant-opponent 8 submitted that the application as filed did not demonstrate that the ester prepared in example 1 was a mannitol ester of bortezomib as specified in claim 1, i.e. a monoester of one molecule of bortezomib and one molecule of mannitol. The FAB-MS method used in the application as filed (paragraph [0141] of D19) to identify the product of the method of claim 1 was not suitable to prove that the product of the example in the patent was this compound. In a related objection, appellant-opponents 10 argued that the product of example 1 was a diester, i.e. a dimer compound comprising two bortezomib moieties and two mannitol moieties, and not a monomer comprising one moiety of each as set out in claim 1. In this regard, appellant-opponents 10 in their statement of grounds of appeal referred only in passing, without providing any details, to four separate declarations (D51, D53, D105 and D106) which allegedly provided evidence that the product of example 1 of D19 was in fact a dimer.

In essence, the appellants' argument was therefore that the application as filed provides a teaching for obtaining a diester only, while a teaching to obtain the claimed monoester was missing. The skilled person

was therefore unable, given the information in D19 and the common general knowledge, to prepare the product as defined in the claims of auxiliary request 5a.

8.9 The respondent requested that these objections, linked to the nature of the obtained product, in particular whether it was a monomer (i.e. the claimed monoester) or a dimer (i.e. a diester), and the objection of insufficient disclosure by appellant-opponents 10 with reference to a macrocyclic compound (i.e. the dimer) and the associated submissions, not be admitted into the proceedings. The respondent submitted in this regard that the appellants had failed to mention the relevant parts of the decision of the opposition division, and explain why the opposition division's finding was in any way incorrect.

8.10 According to Article 12(2) RPBA, in view of the primary object of the appeal proceedings to review the decision under appeal in a judicial manner, a party's appeal case shall be directed to *inter alia* the facts, objections, arguments and evidence on which the decision under appeal was based. Article 12(3) RPBA stipulates that the statement of grounds of appeal shall contain a party's complete case, and shall set out clearly and concisely the reasons why it is requested that the decision under appeal be reversed, amended or upheld, and should specify expressly all the facts, objections, arguments and evidence relied on.

According to Article 12(5) RPBA, the board has discretion not to admit any part of a submission by a party which does not meet the requirements in Article 12(3) RPBA.

8.11 As noted by the respondent (reply to the statements of grounds of appeal, point 74), the opposition division considered in detail the arguments of the parties in relation to the appellants' allegation that the product of example 1 of D19 was a dimer, including the four Fokkens declarations mentioned in the statement of grounds of appeal of appellant-opponents 10 (D51, D53, D105 and D106), and provided detailed reasons in the contested decision as to why, in its opinion, the appellants' objections were not convincing (see decision of the opposition division, point 37.1 on page 23 to point 37.3.2 on page 27). In particular, after a detailed examination, the opposition division concluded that it had not been demonstrated that the FAB-MS spectral analysis used in the patent (paragraph [0071]) to analyse the product of example 1 was unsuitable. Consequently, the appellants' allegation that a (mono)ester had not been formed in example 1 was not found to be convincing (decision, point 37.2.3, final paragraph). It was thus concluded that the peak at m/z = 531 in the FAB-MS set out in paragraph [0071] of the patent was indicative of the mannitol boronate monoester (point 37.3.2, second paragraph).

8.12 In their respective statements of grounds of appeal however, the appellants failed to explain why the opposition division's finding in relation to this issue was incorrect. In this regard, it is not the task of the board to reopen issues already decided in opposition proceedings when the appellants have not

explained why the conclusions reached by the opposition division were flawed, or incorrect.

8.13 As stated in the board's communication pursuant to Article 15(1) RPBA, due to the lack of substantiation, the board is in fact unable to assess the correctness of the decision of the opposition division without examining *ex officio* the reasons for the conclusion provided by the opposition division in their entirety. As stated above, this is not the task of the board, but rather of the appellants.

8.14 Consequently, in accordance with Article 12(5) RPBA, the board decided not to admit the objections linked to the nature of the obtained product, in particular whether it was a monomer or a dimer.

8.15 Since there were no further objections related to sufficiency of disclosure (minutes of the oral proceedings, page 8, final paragraph), the invention defined in claims 1 and 2 of auxiliary request 5a is sufficiently disclosed.

9. Priority

9.1 The application on which the patent in suit was granted, was filed on 25 January 2002 and claims priority from previous US application 60/264,160 (D21) filed on 25 January 2001. The appellants submitted that the priority date of the opposed patent was not validly claimed from the priority application D21 at least for the reason that the combination of features in claim 1 did not find basis in D21 in the same way as set out above in relation to added subject-matter, and that the 10:1 w/w ratio feature in claim 1 was not disclosed

therein by virtue of the absence of any reference to the kind of ratio (i.e. w/w or molar ratio).

9.2 The appellants also argued that the priority was invalid on the grounds that the respondent was not the successor in title of the priority application as required under Article 87(1) EPC.

9.3 As stated by the respondent however, and as set out in the communication of the board pursuant to Article 15(1) RPBA, the issue of novelty in the present case does not turn on the validity of the claimed priority, since the alleged public prior use on which a novelty objection was based (see below) is alleged to have occurred before the claimed priority date.

9.4 Hence, the validity of the priority is not relevant to the present decision.

10. Novelty - Article 54 EPC - public prior use

10.1 Novelty over an alleged public prior use - the vials disclosed in D93

Lack of novelty based on an alleged public prior use is the sole novelty objection raised in appeal proceedings.

The appellants argued that the subject-matter of claims 1 and 2 of auxiliary request 5a lacked novelty in view of the administration of Velcade® in clinical studies that had started before the priority and filing date of the contested patent. Velcade® was the authorised and marketed medicinal product of bortezomib. Specifically, the basis for the allegation, document D93, a PowerPoint presentation entitled "The Story of Velcade™

- A Biotech Love Story", disclosed on page 16 a photo of a vial and an indication of "4000 vials (February 1999)". These vials comprised a lyophilised powder comprising bortezomib and a 10-fold weight excess of D-mannitol, i.e. 2.5 mg PS-341 and 25 mg Mannitol USP, i.e. D-mannitol, and are hereinafter referred to as "the vials".

10.2 In the following, the question of whether the information depicted on the vials had been made available to the public in the sense of Article 54(2) EPC is addressed.

10.3 As stated by the respondent, it is not up to the respondent to establish that an alleged public prior use did not take place, in particular because of the difficulty in proving a negative fact. Instead, the burden of proof lies with the appellants.

10.4 The appellants' objections in relation to how the subject-matter of claims 1 and/or 2 became accessible to the public followed three main lines of argumentation:

- the staff involved in the clinical trials as well as the broader staff cohort and further personnel coming into contact with the vials were not bound by an obligation to confidentiality, and hence could have disseminated the information depicted on the vials,
- the patients (and associated others by extension) would have had physical access to the vials such that the information depicted thereon would have become available to members of the public, or
- the clinical staff would have been obliged to share information on the medicament with the

patients (and associated others by extension) to the extent that the information depicted on the vials would have been revealed.

Each of these lines of argumentation are addressed in turn in the following.

10.5 Public availability - Obligation to confidentiality

10.5.1 In the first line of argumentation, several appellants submitted that the vials would have been accessible and available for inspection to a large number of clinical staff, including doctors and nurses. Access to the vials would not have been limited to those directly involved in the clinical trial, but would have extended to other staff working at the institute in which the trials were carried out. Furthermore, access to the vials would have occurred through various processes, such as the planning of the trials, the manufacturing process, the logistics and storage of the vials, quality control, administrative record keeping, monitoring of patient medication, and the final disposal of the vials. Since there was no evidence of a confidentiality agreement preventing the staff directly involved in the clinical trial, other staff in the same institution or others involved in the above processes from sharing the information available on the vials with the public, it was likely that the information on the vials had been disseminated in one way or another.

10.5.2 The board does not consider the alleged prior use proven based on this line of argumentation. First, as stated by the respondent, there is an assumption that all personnel present at a medical institution and tasked with carrying out clinical trials in the medical field are considered bound at least implicitly by an

obligation of confidentiality. This is in line with decisions T 152/03 (reasons, 3.4) and T 906/01 (reasons 3.5). Although both of these decisions concerned medical devices, the underlying principle is the same in the present case. Specifically, in decision T 906/01 for example, the deciding board stated that the development and testing phases of such products or devices are necessarily surrounded by secrecy as long as said products or devices have not been approved and commercialised. Hence, the deciding board concluded that the clinical tests in question conferred to the overall operation an implicit obligation of confidentiality which had to be extended to the whole team involved in said operation (reasons 3.5).

10.5.3 Hence, in the present case, the presence of an implicit obligation to confidentiality is to be assumed. Consequently, in order to conclude that the information on the vials was made available to the public via the personnel, evidence is required, and none has been submitted by the appellants in this regard.

10.5.4 The presence of an implicit confidentiality agreement is also supported in the present case by declaration D125, signed by Ms Choi, a Senior director of clinical operations at Takeda Pharmaceuticals which, in 2008, acquired Millennium Pharmaceuticals, the company that developed Velcade®. In this declaration, Ms Choi stated that all members of staff involved in the trials would have known that any and all information relating to the trials had to be kept confidential, and that this was the usual practice when clinical trials were conducted within a participating medical institution (D125, point 14).

10.5.5 In response to criticism that Ms Choi was not personally involved specifically in the clinical trials of bortezomib which occurred before the effective date of the patent, the respondent submitted *inter alia* a declaration from Mr Richardson (D142), who was directly involved in said clinical trials. In D142 Mr Richardson expressed his full support and agreement with the opinion set out in declaration D125, and confirmed that the comments of Ms Choi were consistent with his personal experience. Mr Richardson also confirmed his recollection that all staff were under an obligation of confidentiality to the trial sponsor and that they understood this obligation.

The board sees no reason to doubt the accuracy of Ms Choi and Mr Richardson's statements in this regard, and no such reasons were provided by the appellants.

10.5.6 As stated by the respondent, the appellants have not provided any evidence on the basis of which it could be concluded that contrary to normal practice, the personnel involved would not have been subject to an obligation to confidentiality with respect to the nature of the medicaments being administered.

10.5.7 The board also agrees with the respondent that the obligation to confidentiality would logically extend not only to the staff directly involved in the clinical trials, but also to the staff in general at the institution having a contractual relationship with the trial sponsor. Indeed it would not be logical that an implicit obligation to confidentiality would apply only to those staff directly involved in clinical trials, and not extend to staff who, despite not being involved in the trials, would have had physical access to the vials. Such a conclusion would undermine the obligation

of confidentiality of staff members participating in the clinical trial, because the information could become publicly available via other staff members.

10.5.8 The same applies to other individuals who may have had access to the vials via one of the processes mentioned in particular by appellant-opponents 10 (statement of grounds of appeal, page 17, point 70). In particular, if a person involved in such processes were to have access to the vials, it can only be assumed in the absence of evidence to the contrary that an implicit obligation of confidentiality would also have applied. The argument that the vials were "likely" to have been made public through a variety of processes is not supported by any evidence whatsoever. It is hence purely speculative. The starting assumption, as stated by the respondent, is that all parties involved in such processes are at least implicitly bound by confidentiality.

10.5.9 In relation to the final disposal of the vials, appellant-opponent 1 stated that it was highly unlikely that all unused product was returned at the end of the clinical trial. However, in the view of the board, there is no reason to doubt declaration D125 (points 11 and 12) in which Ms Choi explained that all used and unused vials were collected and saved for reconciliation by a study monitor. This is supported by evidence from D125c, a pharmacy manual from one of the clinical trials in which clear instructions for the disposal of study medicine are provided (page 6, point 1.7). Hence, the argument that some vials may have been unaccounted for and may have found their way into the public domain amounts to unsubstantiated speculation. These arguments must therefore fail.

10.6 Public availability - physical access of patients to the vials

10.6.1 In a second line of argumentation, the appellants alleged that members of the public, in particular patients, would have had physical access to the vials. However, despite the extensive argumentation on file, there is no evidence for this allegation.

10.6.2 In more detail, in declaration D125, Ms Choi *inter alia* explained that bortezomib is a highly cytotoxic drug and as such must be handled carefully (D125, points 9 and 10) - such handling would have involved storage and reconstitution of the drug in a dedicated area of the hospital pharmacy - and hence not in the presence of the patient. Such careful handling is addressed in document D126 entitled "Handling Cytotoxic Drugs". This document explains *inter alia* that the reconstitution of cytotoxic drugs should be centralised, e.g. reconstituted and delivered to the wards by the internal pharmacy (D126, page 10, left hand column, first paragraph). The document further states that reconstitution should be performed in an area clearly separate from areas of other activities, and that access to the work area should be restricted to authorised and trained personnel only (page 10, right hand column). There is no reason to believe that the handling of the vials in the clinical trials of bortezomib, a cytotoxic drug substance, would have been any different. Hence there is also no reason to conclude that the patients to the clinical trials, or any other unauthorised members of the public for that matter, would have had physical access to the vials such that it would have been possible to read the information depicted thereon.

10.6.3 In this regard appellant-opponents 10 submitted document A160 to challenge the contention that the patients would not physically have been able to observe the vials. A160 is the summary of product characteristics for the authorised medicament Velcade®. This document taught that aseptic conditions must be observed (section 6.6, pages 35 to 36) and the formulation must be used immediately after preparation (page 35, point 6.3). The appellant concluded that it was therefore unrealistic that the reconstitution would have taken place in another room, requiring transport to the location of the patient. Hence, the patient was able to see the vials.

10.6.4 The board does not find this argument convincing. Firstly, as stated by the respondent, the handling instructions for Velcade® set out in A160 were not in existence at the time of the clinical trials and therefore cannot provide evidence of what took place during said trials. Secondly, the instruction in A160 relied upon by the appellant that the reconstituted solution was to be used immediately is contradicted by the instruction elsewhere in the same document that said solution could be used within a time frame of 8 hours (A160, page 35, point 6.3, second paragraph).

Hence there is no evidence on file that the vials could have been physically observed by the patients, or if present, other members of the public in their company during administration of the medicament.

10.7 Public availability - access of patients to information on the nature and composition of the medicament

10.7.1 In a third line of argumentation, the appellants submitted that patients participating in the clinical

trials (and by extension, their families, close acquaintances, etc.) would have been provided with detailed information, not only on the nature of the medicament to be administered, in this case bortezomib, but also on the composition of the pharmaceutical form to be administered. For example, if patients to a clinical trial were to ask such questions, the staff in question would have been obliged to share detailed information on the exact nature of the formulation, which thereby would be made available to members of the public.

10.7.2 However, there is no evidence on file demonstrating that the patients would have been able to obtain detailed information corresponding to the subject-matter of claims 1 and/or 2 of auxiliary request 5a. As stated in declaration D125 (point 7), the patients in the clinical trial were informed via a consent form D125b, and were required to read and sign the form prior to participation. The consent form indicates that the trial involved the administration of a substance "PS-341" by means of an intravenous infusion (D125b, page 2, first paragraph), but there was no indication that the solution to be administered was to be obtained by reconstitution of a lyophilised composition comprising bortezomib D-mannitol ester and D-mannitol, or that others features of claims 1 and 2 such as the ratio of bortezomib to D-mannitol, would have been revealed. This was confirmed in the declaration of Mr Richardson (D142, point 7) in which it was stated that a clinician would have reviewed the information in the consent form with a view to facilitating the patient's decision of whether to participate in the clinical trial. Discussions could have covered for example, potential benefits and risks associated with participation in a trial of the investigational drug,

alternatives, and practical matters such as the dosage regimen, tests required, etc. However, there is no evidence that it would have been required to share the exact composition or method of preparation of the medicament to be administered with the patient. In declaration D142 it was also stated that although patients in the clinical trials were aware that they were being administered an investigational drug identified to them as "PS-341", they did not know that they were receiving bortezomib and did not know that bortezomib had been presented prior to reconstitution as a lyophilised composition containing the D-mannitol ester of bortezomib and D-mannitol (D142, point 10).

10.7.3 To further support their arguments the appellants also submitted A151 and A152 in appeal. A151 is a document entitled "World medical association declaration of Helsinki" and concerns ethical principles for medical research involving human subjects. In paragraph 22 it is stated that in any research on human beings, each potential subject must be adequately informed *inter alia* of the aims, methods, benefits and risks, discomfort it may entail, and the right to abstain from participation or withdraw consent at any time. A152 is an excerpt from a book entitled "Encyclopedia of bioethics" and states that informed consent must be obtained (page 1278).

10.7.4 As set out by the respondent however, while the cited portions of A151 and A152 concern ethical principles and informed consent, neither discloses that patients to a clinical trial must be provided with all information in relation to the medicament to be administered, i.e. not only the nature of the active substance, but also in particular, the exact nature of the administered composition in which the active

compound is comprised, including the presence of D-mannitol and the specific claimed ratio of D-mannitol to bortezomib of 10:1, and/or the method by which it is prepared.

10.7.5 Appellant-opponents 10 also submitted on the basis of A157 that clinical staff would have been obliged to inform patients about the presence of further ingredients, in particular D-mannitol, present in the medicament to be administered. In A157, a printout of a page from the website "Drugs.com", it is stated in relation to Velcade® that "you should not be treated with Velcade if you are allergic to bortezomib, mannitol, or boron".

10.7.6 As stated by the respondent however, A157 was last updated on 27 March 2023, and hence cannot support the appellant's contention that at the time of the clinical trials, mannitol was considered sufficiently allergenic to necessitate the disclosure of its presence to participating patients. This is supported by the informed consent form D125b (section 4) in which mannitol is not listed among the foreseeable risks associated with the administration of the contents of the vials. Finally, the board notes that even if it were assumed that clinical staff were obliged to inform patients of the presence of D-mannitol in the medicament to be administered, this would still not amount to a direct and unambiguous disclosure of the subject-matter of claims 1 and 2, at least in relation to the claimed ratio feature of 10:1.

10.7.7 It was also argued that the fact that the clinical trials in question were "open label" (see D125c, page 3) meant that all information regarding the administered medicament was shared with patients.

However, as stated by the respondent, the term "open label" merely indicates that both patients and staff knew that the patients were receiving the investigational drug, and not a different therapy or a placebo (such as in a double-blinded clinical trial). The term "open label" does not mean that the patients had access to the specifics of the formulation employed in the tests, in particular the specific composition thereof (see D142, point 8). Hence, the appellants' allegation that patients (and associated others) could theoretically have been provided with such complete information amounts to unsupported speculation.

10.7.8 Appellant-opponent 10 referred *inter alia* to decision T 7/07 to argue that the composition of the vials was made available to the public, since the patients to the clinical trials were not bound by secrecy. However, the respondent did not assert that patients to the clinical trial were bound by secrecy, but rather that the patients would not have had physical access to the vials, nor access to the information depicted on the vials relevant for present claims 1 and 2.

10.7.9 Nevertheless, as stated by the respondent, decision T 7/07 concerned medicaments taken home by the trial participants. Control of the medicament was thereby lost, leading to it being made available to the public. In decision T 7/07, the conclusion that the medicament in question had been made publicly available was contrasted with the situation underlying other decisions in which patients would not have been in a situation to inspect the - in those cases - devices themselves (see decision T 7/07, reasons 3.3 fourth to sixth paragraphs). It is the latter situation which appears more closely related to the present situation in relation to the vials. In the present case, there is

no evidence of loss of control of the vials, no evidence that patients to the trials would have had any access to the vials such that they would have been able to read the labels on the vials, and no evidence that there would have been any obligation for information to be shared with patients to the extent that it would constitute public availability of the subject-matter of claims 1 and 2. Hence, the situation underlying decision T 7/07 is different to the present situation.

10.7.10 Hence there is no evidence on file that patients involved in the clinical trials (and by extension associated others) would have been able to access information on the nature and composition of the medicament to the extent that this information would reveal the features of contested claims 1 and/or 2.

10.8 The alleged public prior use thus does not form state of the art within the meaning of Article 54(2) EPC.

10.9 Hence, novelty is acknowledged for the subject-matter of claims 1 and 2 of auxiliary request 5a pursuant to Article 54 EPC.

10.10 This conclusion was reached taking into account all documents submitted in relation to the public prior use by the appellants, the admittance of which was contested by the respondent, and not taking into account document A153 submitted by the respondent, the admittance of which was contested by the appellants. As the appellants' documents were considered in substance, they were in the proceedings.

11. Admittance - documents submitted in the context of inventive step

11.1 Documents A149 and A150

11.1.1 Documents A149 and A150 were submitted by appellant-opponent 8 with the statement of grounds of appeal and further submission dated 4 January 2023 to show that lyophilised bortezomib was known before priority date.

11.1.2 The respondent requested that these documents not be admitted into the proceedings.

According to Article 12(4) RPBA, any amendment to a party's appeal case may be admitted only at the board's discretion. Pursuant to Article 12(6) RPBA, the board shall not admit *inter alia* evidence which should have been submitted in the proceedings leading to the decision under appeal, unless the circumstances of the appeal case justify their admittance.

11.1.3 Appellant-opponent 8 justified the admittance of A149 and A150 on the basis that the opposition division "had not appropriately considered that lyophilized bortezomib was known". However, as stated by the respondent, this does not constitute an explanation as to why the documents should not have been filed earlier during the course of opposition proceedings. It is the opponents' rather than the opposition division's task to set out which features of a relevant claim are anticipated by the prior art. Not having provided any evidence during opposition proceedings supporting the contention that lyophilised bortezomib was known, there was no reason why the opposition division should have considered such a question. The absence of this consideration in the opposition division's decision is

therefore not sufficient justification for the filing of A149 and A150 only in appeal.

11.1.4 There is therefore no reason apparent why A149 and A150 were only filed on appeal.

11.1.5 Consequently, the board decided not to admit these documents into the proceedings pursuant to Article 12(6) RPBA.

11.2 Documents A154, A155, A156, A161 and A162

11.2.1 These documents were submitted by appellant-opponents 10 with the letter dated 10 July 2023, i.e. after appellant-opponents 10 had filed their reply to the patent proprietor's grounds of appeal, and before the notification of the board's communication pursuant to Article 15(1) RPBA.

The respondent requested that they not be admitted into appeal proceedings.

11.2.2 A154 is a journal article submitted to show that pinanediol in D97 was not toxic as alleged by the respondent. A155 and A162 relate to an Email and an opinion of a related US district court in which the respondent allegedly stated that lyophilisation and the use of mannitol were obvious. A156 was submitted to show that freeze dried formulations were more stable than liquid or frozen solutions, and A161 is an expert declaration stating *inter alia* that boronate esters were known as prodrugs, and therefore would completely and rapidly hydrolyse in aqueous media.

11.2.3 Since these documents were submitted after appellant-opponents 10 had replied to the patent proprietor's

grounds of appeal and before the notification of the communication under Article 15(1) RPBA dated 20 December 2023, the admittance thereof into the proceedings was governed by Article 13(1) RPBA.

11.2.4 Amended Article 13(2) RPBA, which entered into force on 1 January 2024, does not apply to admittance under the present circumstances. With this amendment, the legislator decided to postpone, for cases such as the current one in which a summons to oral proceedings was issued, to be followed by a communication under Article 15(1) RPBA, the application of stricter criteria from the notification of the summons (previous Article 13(2) RPBA) to the notification of the communication under Article 15(1) RPBA (amended Article 13(2) RPBA). Amended Article 13(2) RPBA applies to all appeal proceedings pending on or after 1 January 2024 (see Article 2 of the Decision of the Administrative Council of 13 December 2023 approving amendments to the Rules of Procedure of the Boards of Appeal (CA/D 24/23), OJ EPO 2023, A103), and, hence, applied to the current case which was decided at the oral proceedings on 31 January 2024. With the entry into force of amended Article 13(2) RPBA on 1 January 2024, the version of Article 13(2) RPBA as in force until 31 December 2023 ceased to apply.

11.2.5 Under Article 13(1) RPBA, any amendment to a party's appeal case after it has filed its grounds of appeal or reply is subject to the party's justification for its amendment and may be admitted only at the discretion of the board. The board shall exercise its discretion in view of, inter alia, the current state of the proceedings, the suitability of the amendment to resolve the issues which were admissibly raised by

another party in the appeal proceedings or which were raised by the board and whether the amendment is detrimental to procedural economy.

11.2.6 According to appellant-opponents 10, the submission of these documents represented a response to the opposition division's decision unexpectedly selecting a different closest prior art compared to that communicated with its preliminary opinion, and was also in response to new arguments filed by the respondent with its reply to the statements of grounds of appeal, including the auxiliary requests.

11.2.7 However, as submitted by the respondent, the allegation that the opposition division unexpectedly selected a different closest prior art compared to that communicated with its preliminary opinion is factually incorrect. Specifically, during oral proceedings before the opposition division, there was agreement on the choice of D5 as closest prior art (see decision of the opposition division, page 36, point 39.2.1). The same document was chosen as the closest prior art according to the preliminary opinion of the opposition division dated 8 December 2020 (point 18.3). This argument therefore failed to convince the board.

11.2.8 In relation to A154, appellant-opponents 10 referred to point 276 of the respondent's reply to the grounds of appeal where it was allegedly stated that pinanediol used in document D97 is toxic. However, as stated by the respondent, no such assertion is made in said point. Hence, appellant-opponents 10's justification for the late filing of document A154 is without merit.

11.2.9 A155 and A162, according to appellant-opponents 10, were submitted to demonstrate that, in a case related

to the same invention as the present patent, the respondent had argued that "when you have a less than satisfactory liquid product, the obvious option is a lyophilized formulation", that "one of the most commonly used excipients for a lyophilized formula is mannitol", and that there "was nothing inventive about thinking to lyophilize bortezomib". Hence, both documents were *prima facie* relevant to the issue of inventive step.

11.2.10 The *prima facie* relevance of evidence is however not listed as a criterion relevant to admittance under Article 13(1) RPBA. The board has doubts whether this criterion should be taken into account. Even if it were, to the benefit of the party concerned, the board considered that neither A155 nor A162 were *prima facie* relevant. Specifically, as argued by the respondent, A155 is a non-public E-mail from an expert from within the company that developed Velcade®, who already had knowledge of the invention. Hence, it cannot provide evidence of what the skilled person would have understood at the filing date of the patent. A162 is a first instance decision of a US court relating to the US patent, which, according to the respondent, and not challenged by the appellants, was overturned on appeal. It relates to a different jurisdiction applying different legal standards, and is hence also irrelevant to the question of what the skilled person would have done before the filing date following the problem-solution approach applied at the EPO. Hence, neither document is *prima facie* relevant to the present proceedings. Appellant-opponents 10's justification for the late filing of A155 and A162 is therefore without merit.

11.2.11 As justification for the submission of document A156, appellant-opponents 10 referred to the statements in point 266 of the respondent's reply to the statements of grounds of appeal. However, as stated by the respondent, an identical statement was made by the respondent in its reply to the notices of opposition dated 26 March 2020 (point 174). There is therefore no convincing justification for the late filing of this document in appeal.

11.2.12 A161 is a declaration by an expert who was asked by appellant-opponents 10 to answer questions concerning lyophilisation, hydrolysis and administration to patients of mannitol bortezomib ester. Appellant-opponents 10 justified the admittance of A161 by stating that it addresses several points made by the respondent in the reply to the statements of grounds of appeal, with specific reference to point 323 thereof and in particular:

- confirms that boronic acid esters were known from the prior art as prodrugs,
- that lyophilisation is routine and applicable to said esters,
- that the formation of the bortezomib mannitol ester would be reversible, and
- there would have been no concern regarding the administration of said drugs.

11.2.13 However, as stated by the respondent, this justification is not convincing. Specifically, the issues of hydrolysis of the ester addressed by the respondent in point 323 of the reply to the statements of grounds of appeal was dealt with extensively in the decision of the opposition division (point 39.6.3.4.1 on page 53), and was addressed by the respondent already with the reply to the notices of opposition

with reference to paragraph [0075] of the patent (points 148 and 149). Similarly, lyophilisation, the administration, and the general discussion concerning the esterification and hydrolysis of the bortezomib mannitol ester and its use in the clinic were all extensively addressed during opposition proceedings (see points 32 to 34 of the respondent's letter dated 21 August 2023). The respondent also stated at oral proceedings before the board that all of these points had been discussed during oral proceedings before the opposition division. This allegation was not contested by appellant-opponents 10.

11.2.14 Considering the above aspects, the board decided pursuant to Article 13(1) RPBA not to admit documents A154, A155, A156, A161 and A162 into the appeal proceedings.

12. Inventive step - Article 56 EPC

12.1 Background and introduction

12.1.1 According to the patent, the invention relates to stable, pharmaceutically acceptable compositions prepared from boronic acid compounds (paragraph [0001]). According to paragraph [0006], such formulations would be conveniently prepared, would exhibit enhanced stability and longer shelf life as compared to the free boronic acid compound, and would readily liberate the bioactive boronic acid compound when administered.

12.1.2 As set out above, claim 1 of auxiliary request 5a is directed to a method of preparing a lyophilised compound, while claim 2 concerns a lyophilised

composition prepared by a method corresponding to the method of claim 1.

12.1.3 The appellants raised inventive step objections against claims 1 and 2 of auxiliary request 5a starting from D5 as closest prior art, or starting from D1 or D2 as closest prior art. In the following the board will first address objections starting from D5 as closest prior art.

13. D5 as closest prior art - the contested decision and the parties' positions in appeal

13.1 D5 is a journal article entitled "Degradation pathways of a peptide boronic acid derivative, 2-Pyz-(CO)-Phe-Leu-$B(OH)_2$". The derivative recited in the title corresponds to bortezomib, the free boronic acid moiety of the D-mannitol ester recited in claim 1 at issue. The study underlying D5 arose from the observation that "*during an effort to formulate [bortezomib] for parenteral administration, the compound showed erratic stability behaviour and was quite unstable in certain solvents*" (D5, page 758, right hand column, final paragraph). The stability of bortezomib in several solvents was then investigated, and the isolation of degradants A, B, C and D is described (page 758, final line - page 759, first partial paragraph).

13.2 According to the contested decision, D5 was the closest prior art. The closest prior art embodiment within document D5 was the solid bortezomib drug substance (decision, 39.2.1 and 39.2.2). The objective technical problem was the provision of a form of bortezomib which had improved long-term stability and enhanced dissolution properties as compared to the bortezomib drug substance (decision, point 39.5). The solution to

this problem set out in the claims as granted involved an inventive step.

14. The choice of starting point within document D5

14.1 All parties agreed that D5 could be taken as the closest prior art disclosure. The starting point within the disclosure of D5 was however a matter of dispute.

14.2 As stated above, the starting point in D5 according to the contested decision was represented by the solid bortezomib drug substance ("2-Pyz-(CO)-Phe-Leu-$B(OH)_2$") mentioned on page 759, right hand column, last two lines - left hand column, line 3 (decision, 39.2.1 and 39.2.2). In appeal proceedings, the respondent agreed with this choice.

14.3 All appellants argued that the correct starting point in D5 was represented by the liquid formulation represented by the solution comprising 2% EtOH in normal saline at pH 6.9, without the addition of EDTA (D5, page 762, right hand column, under heading "Effects of ascorbic acid ..."; figure 5), hereinafter referred to as "the liquid formulation of D5". The appellants either disagreed with the starting point chosen in the contested decision (e.g. appellant-opponents 1 and 10), or argued at least that the assessment of inventive step starting from the liquid formulation of D5 could not be excluded (e.g. appellants 8 and 11), i.e. that inventive step was to be assessed from both potential starting points.

14.4 The board assessed inventive step from both of the above-mentioned starting points. Hence, there was no need to consider whether one starting point was closer to the claimed invention than the other, or whether an

assessment of inventive step starting from the liquid formulation of D5 can be excluded.

15. D5 as closest prior art - starting from the solid bortezomib drug substance

15.1 Distinguishing features

Although expressed in different ways by the parties, the distinguishing features of contested claim 1 in relation to the solid bortezomib drug substance of D5 were not a matter of dispute. In relation to the common subject-matter of both independent claims of auxiliary request 5a, these were at least:

- the use of a 10:1 ratio of D-mannitol to bortezomib,
- the presence of the D-mannitol ester of bortezomib,
- in the form of a lyophilised powder

15.2 Technical effect/s of the distinguishing features

According to the respondent, the technical effects of the distinguishing features compared to the solid bortezomib drug substance in D5 were

(a) improved long-term stability (hereinafter: "solid stability")
(b) improved dissolution behaviour, and
(c) the provision of a stable solution on dissolution in water or normal saline, whilst allowing the free boronic acid of bortezomib to be readily liberated at the time of use in the clinic

In the following, only effects (a) and (c) are addressed.

15.2.1 Effect (a): improved solid stability

The respondent argued that the lyophilised composition according to the claims had a greater long term stability than the solid bortezomib drug substance.

The board agrees. As stated by the respondent, evidence for the effect is demonstrated in the patent itself. More specifically, example 5 (paragraph [0079]) discloses that the solid bortezomib drug substance, when stored at a temperature of 2 to 8°C, was not stable for longer than 3 to 6 months. In contrast, according to paragraph [0081], the stability of the claimed lyophilised composition was tested by storage at 5°C, ambient temperature, 37°C, and 50°C. Stability was monitored for approximately 18 months by periodically reconstituting a sample and analysing by HPLC. Over this time period, there was reportedly "no loss of drug" in the lyophilised product stored at any of the tested temperatures and "no evidence of degradation product peaks in the HPLC chromatograms". Since these tests were carried out over a much longer time period and under harsher conditions than for the tests in paragraph [0079] for the solid bortezomib drug substance, they credibly demonstrate an improvement in long term stability for the claimed lyophilisate compared to the solid bortezomib drug substance. The same data is provided in the application as filed (example 5, paragraphs [0147] and [0149]).

Appellant-opponent 8 submitted that the data provided in paragraphs [0079] and [0081] of the patent did not represent a true comparison because it was unclear whether comparable lyophilisation conditions were

present, and in view of the fact that the stability studies were performed at different temperatures.

The board disagrees. As stated by the respondent, the solid bortezomib drug substance was not lyophilised, and therefore comparable lyophilisation conditions were not possible. Furthermore, despite the difference in the temperature of the respective stability studies, the claimed composition was tested at 5°C, which falls within the range of 2 to 8°C stipulated in paragraph [0079], and demonstrated superior stability for 18 months. Furthermore the stability demonstrated at higher temperatures (37 and 50°C), i.e. harsher conditions than those under which the solid bortezomib drug substance was tested, leave no doubt that the claimed compositions displays improved stability compared to the solid bortezomib drug substance.

As stated by the respondent, the results reported in the patent are supported by the data in D36, a test report submitted by appellant-opponent 4 during opposition proceedings. Specifically, D36 describes studies in which the stability of the claimed lyophilised composition prepared according to example 1 of the patent (samples "5A" and "5N") and stored under the same conditions displayed superior long term stability when compared with the solid bortezomib drug substance, when stored under air or nitrogen (samples "1A" and "1N", respectively). Specifically, at 50°C in air (i.e. under exposure to oxygen), sample 1A comprised 9.43% degradation products (D36, table 2, final column, first entry). This represented 8.96% more than the sample initially (0.47%; second column, "initial"). On the other hand, under the same conditions, the claimed lyophilised composition sample 5A comprised 0.85% degradation products, which

represented 0.68% more than the sample initially; (0.17%). Hence, an improvement in storage stability for the claimed lyophilised composition compared to the bortezomib drug substance is demonstrated. This result was also acknowledged in D36 in which it was stated in relation to the solid bortezomib substance that "extensive degradation was seen in samples under air at 50°C after 3 months" (D36, page 4, fifth line from the bottom).

As stated by the respondent, further support for the improvement in long term stability is provided by D101, a summary of product characteristics for Velcade®, i.e. the claimed composition, in which it is reported that Velcade® has a shelf life of at least 3 years in an unopened vial, without any particular storage conditions being specified (D101, page 30, section 6.3). Further supporting evidence is provided by European Medicines Agency (EMA) document D96, in which it is reported that the bortezomib drug substance "appears to be intrinsically unstable", and required storage under refrigeration and protection from light (D96, page 3/42, under "Stability"), which lies in contrast with the teaching concerning the long term stability of Velcade® provided in D101, above.

Hence the effect of improved solid stability of the claimed lyophilised composition compared to the solid bortezomib drug substance of D5 is credible.

15.2.2 Effect (c): the provision of a stable solution on dissolution in water or normal saline, whilst allowing the free boronic acid of bortezomib to be readily liberated at the time of use in the clinic

The aspect of this effect which related to the free boronic acid of bortezomib being readily liberated at the time of use in the clinic was not called into question by the appellants. Indeed, the claimed lyophilised composition corresponds to the composition of the marketed product Velcade®, the therapeutic effectiveness of which has not been called into question. Therefore, this aspect of the effect is credible to the board. The following therefore addresses only the further aspect of providing a stable solution.

The respondent argued that the lyophilised composition according to the claims provided a stable solution on reconstitution. This effect was not to be dismissed, since, as reported in D5, during an effort to formulate bortezomib for parenteral administration, the compound showed erratic stability behaviour and was quite unstable in certain solvents (D5, page 758, right hand column, final paragraph).

The board agrees. As stated in the patent (paragraph [0082]), the reconstituted lyophilised composition of the claims showed no sign of degradation when stored at ambient temperature (23°C) for 43 hours, despite the fact that no special care was taken to protect the solution from light. As stated by the respondent, additional support is provided by D52, a report on the stability of the claimed lyophilised composition (i.e. Velcade®; see page 16, left hand column, lines 7; reference 1, page 20). Specifically, six vials of the claimed lyophilised composition were reconstituted with 3.5 ml normal saline (0.9% w/v) to prepare solutions with a concentration of 1 mg/ml. Three of the vials were stored in a refrigerator, and three were stored at room temperature, unprotected from fluorescent room

light (D52, page 16, "Stability Study"). Over a period of 42 study days, samples were withdrawn for analysis of concentration and were inspected visually for changes in colour and the presence of particulate matter (page 16, "Physical Stability"). All solutions were reported as initially clear and colourless and remained so for the duration of the study - no visible particles were observed in any solution throughout the study period (D52, page 18, "Bortezomib Stability Study"). Furthermore, for samples stored at ambient temperature, the concentration of bortezomib was maintained above 99% during the study period (D52, page 18, table 1).

The appellants' arguments against this effect failed to convince the board.

Appellant-opponent 1 argued that the solution stability shown in D52 did not exceed the stability of the liquid composition in D5 (figure 5, upper curve). In a similar argument, appellant-opponents 10 referred to D100. In D100 it was reported that solutions of the reconstituted claimed lyophilisate (i.e. Velcade®) were stable for 5 days (D100, abstract). The appellants argued that neither document contained any comparison with the solutions in D5, and hence no improvement had been shown.

However, as stated by the respondent, the effect relied on is not an improvement of stability over D5. Hence, an improvement over the prior art solutions in D5 is not required for the above effect to be acknowledged. Rather, even if even there are certain solutions disclosed in D5 the stability of which is comparable to that of the reconstituted claimed lyophilisate, that does not translate to a conclusion that the effect of

providing a stable solution should not be taken into account. On the contrary, D5 teaches that solutions of the solid bortezomib drug substance have erratic stability.

Appellant-opponents 10 also argued that the stability of the reconstituted claimed composition reported in paragraph [0082] of the patent was less than that of the liquid solutions in D5 on the basis that stability was reported in the patent for only 43 hours at 23°C, whereas the solutions in figure 5 of D5 were stable for more than 50 days. However, as stated by the respondent, the fact that the patent reports stability for 43 hours at 23°C does not exclude the possibility that stability is maintained over a longer time frame, as indeed demonstrated in D52. Hence, the appellant's conclusion is without merit.

Hence, the board accepts that the claimed lyophilised solution when reconstituted results in a solution that is stable.

16. Objective technical problem

In view of the board's acknowledgement of effects a) and c) above, the objective technical problem underlying the claimed subject-matter starting from the solid bortezomib drug substance of D5 may be formulated similarly to the formulation provided by the respondent (reply to the statements of grounds of appeal, point 239), namely as the provision of a form of bortezomib which, as compared to the solid bortezomib drug substance of D5, at least displays an improved long term stability, whilst providing for a stable solution on dissolution and whilst allowing the free boronic

acid of bortezomib to be readily liberated at the time of use in the clinic.

17. Obviousness

17.1 The appellants' main line of argumentation was that the liquid solution of D5 should be taken as the starting point for the assessment of inventive step, and that the claimed solution was obvious from that starting point. It was however also submitted that the claimed subject-matter would have been obvious starting from the solid bortezomib drug substance of D5. In this regard, the board notes that the appellants did not accept that the technical effect of improved stability relative to the solid bortezomib drug substance in D5 had been credibly demonstrated. Hence, the appellants' arguments did not specifically address obviousness of the claimed solution starting from the solid bortezomib drug substance in D5 specifically in the context of above-mentioned objective technical problem. For this reason alone, the board sees no reason why, starting from the solid bortezomib drug substance and taking the above-mentioned objective technical problem into account, the claimed solution would have been obvious to the skilled person. In addition, the board notes the following in relation to obviousness.

17.2 Lyophilisation

In relation to lyophilisation, the board notes the respondent's acknowledgement that lyophilisation is well known in the preparation of compositions for parenteral administration. However, as stated by the respondent, while some of the prior art documents cited by the appellants teach that lyophilisation can result in a solid composition of a pharmaceutical having an

improved long term stability relative to an aqueous solution of said medicament, none of the cited documents either teaches or suggests that specifically lyophilisation would result in a pharmaceutical product having an improved long term stability relative to the solid pharmaceutical agent *per se*.

17.2.1 In relation to lyophilisation, the appellants cited D7, an extract from the Encyclopedia of Pharmaceutical Technology. It is stated therein that "a product is freeze dried if the aqueous solution does not have sufficient stability for marketing, and if the product cannot be crystallized in bulk" (page 275, second paragraph). As stated by the respondent, this indicates to the skilled person that the pure solid bortezomib drug substance should be used crystallised in bulk when the aqueous solution of the pharmaceutical agent is found to exhibit an insufficient stability for commercialisation, and lyophilisation only when both the aqueous solution is unstable, and bulk crystallisation impossible. As stated by the respondent, bortezomib can be crystallised in bulk (D96, page 2/42, final paragraph). D7 is therefore absent any suggestion that a lyophilised composition would demonstrate improved stability compared to the solid bortezomib drug substance, the reference point therein being the aqueous solution of the product.

17.2.2 D8, cited by several appellants, is a book extract concerning freeze-drying (i.e. lyophilisation), and states *inter alia*:

"*The particular advantages of [lyophilization] are that biologicals and pharmaceuticals which are relatively unstable in aqueous solution can be processed and filled into dosage containers in the liquid state,*

taking advantage of the relative ease of processing a liquid. They can be dried without elevated temperatures, thereby eliminating adverse thermal effects, and stored in the dry state in which there are relatively few stability problems" (D8, page 1585, sentence bridging right and left columns).

17.2.3 This passage teaches that as a result of the elimination of water and the conversion of the pharmaceutical agent into a "dry state", lyophilisation can produce a solid composition in which the stability of the pharmaceutical agent is improved relative to its formulation within an aqueous solution. D8 however does not suggest that lyophilisation would have resulted in a product having an increased long term stability relative to the solid bortezomib drug substance *per se*.

17.2.4 The board acknowledges that D8 also refers to the "enhanced stability" of lyophilised products subject to degradation by oxidation due to the fact that the process is carried out in a vacuum (D8, page 1585, right hand column, first full paragraph). However, as noted by the respondent, the stability gain described in this passage of D8 arises from the absence of oxygen, but there is no teaching that under an atmosphere including oxygen, a stability gain could be achieved by a lyophilised formulation compared to a solid drug substance.

17.2.5 Similarly, appellant-opponents 1 and 8 cited D10, an excerpt from a book concerning pharmaceutical technology. This document refers to freeze drying (i.e. lyophilisation) as a gentle process for drying thermolabile and hydrolytically sensitive substances (D10, page 23, point 1.5.3.1, first sentence), but it is silent on any suggestion that the lyophilisation

could lead to improved stability compared to the corresponding solid drug substance. A similar teaching to that in D10 is provided in D9 (page 127, right hand column, final paragraph).

17.2.6 Hence, based on the documents cited in relation to lyophilisation, the skilled person would not have been taught to lyophilise specifically to provide a solution to the above-mentioned objective technical problem.

17.3 The further distinguishing features: *inter alia* D-mannitol and the presence of D-mannitol bortezomib ester

17.3.1 The skilled person, in order to solve the above-mentioned problem, would also not have implemented the remaining common distinguishing features of independent claims 1 and 2, namely the inclusion of D-mannitol in the lyophilised powder in the claimed ratio of mannitol:bortezomib of 10:1, leading to the presence of bortezomib D-mannitol ester.

The appellants relied on several documents and declarations in this regard.

17.3.2 With regard to the formation of a D-mannitol ester of bortezomib, patent document D13 and journal articles D14, D16 and D33 were cited. Since essentially the same argument applies to all four documents, only D13 is addressed. The appellant argued that D13 taught the preparation of cyclic boronophenylalanine adducts with improved storage properties (D13, page 4, lines 15 to 17). Example 7 on page 26 of D13 disclosed a boronophenylalanine-D-mannitol complex obtained from the boronophenylalanine and D-mannitol in a freeze-drying process.

17.3.3 However, as stated by the respondent, even if the skilled person starting at D5 and given the above objective technical problem were to consider D13, based on the stability data provided in table 1 to 3 (pages 13 and 14 of D13), the stability referred to therein appears to concern the association between the compound in question and the complexing carbohydrate or polyol such as mannitol. This does not provide any indication that said complex would have improved stability relative to the uncomplexed compound itself. Hence, there is no teaching in D13 which would have motivated the skilled person to lyophilise bortezomib in the presence of D-mannitol with a view to providing improved long term stability relative to the solid bortezomib drug substance.

17.3.4 In particular but not exclusively, appellant-opponent 1 also relied on *inter alia* D1, D2 and D99, with reference to the interpretation of these documents set out in declaration D134, to argue that the skilled person would have known that the esterification of bortezomib with D-mannitol would lead to an improvement in stability. In relation to patent documents D1 and D2, it was argued that both documents disclosed bortezomib and its esters with dihydroxy compounds (e.g. D2, column 10, lines 11 to 13; column 15, lines 54 to 55 disclosing bortezomib; example 4B, column 33). In declaration D134 it is stated that the skilled person would clearly understand from D2 that bortezomib and its esters could be lyophilised (D134, page 17, first paragraph). It is further stated that "many boronate esters can be reverted to free boronic acids by adding water" (D134, page 12, first paragraph), and that D-mannitol was a dihydroxy compound which was

known to form reversible boronate esters with boronic acid compounds.

17.3.5 The board disagrees with these assertions. As set out by the respondent, none of these documents would have incited the skilled person to prepare an ester of bortezomib in the expectation of improving the long term stability of the bortezomib drug substance. In particular, mannitol, let alone D-mannitol, is not mentioned in D1 or D2, nor is any carbohydrate polyol (e.g. D2, column 12, lines 47 to 53), and the appellants' arguments are based on a diol different from mannitol, namely pinanediol. Furthermore, this diol is used in D2 as a protecting group, and requires more than mere aqueous hydrolysis for its removal (e.g. D2, column 34, lines 52 to 60). Additionally, as set out by the respondent, in the tests of example 18 of D2, the biological activities of various boronic acids and boronic acid esters were measured. It was observed that certain boronic acid esters had much lower activity than the corresponding acid, thus indicating that the boronate esters in question did not readily hydrolyse (e.g. D2, columns 47 and 48, compare the third row of data with the ninth row for boronic acid ester MG-264 and its corresponding boronic acid MG-274). Hence D2 (and D1) rather provide evidence that boronate esters do not necessarily completely and rapidly hydrolyse to the boronic acid in aqueous media. This is also conceded in D134 in which the declarant stated that many (i.e. not all) boronate esters can be reverted to free boronic acids by adding water (D134, page 12, D.5, (c)). Similarly, D98, while recognising the potential for some boronate esters to hydrolyse, also provides an example where harsher conditions are required to effect hydrolysis (D98, page 12638, scheme 1, step b).

17.3.6 Journal article D38 was cited by appellant-opponents 10 in a similar context, although as a secondary document to be combined with D5 as closest prior art. D38 discloses the lyophilisation of aplidine, a pharmaceutical compound, with mannitol. Appellant-opponents 10, although not referring to obviousness specifically in the context of the above objective technical problem, argued that the skilled person would have turned to D38, since both bortezomib and aplidine belonged to the same class of peptide drugs for cancer. However, as noted by the respondent, aplidine is a macrocyclic compound without a boronic acid group, and is therefore at least structurally unrelated to bortezomib. Furthermore, even if the skilled person starting at the solid bortezomib drug substance of D5 were to have turned to D38, no motivation is provided therein to lyophilise bortezomib in the presence of D-mannitol specifically to solve the above objective technical problem. Rather, D38 indicates that the purpose of D-mannitol was solely to act as a bulking agent (page 196, right hand column line 3).

17.3.7 It follows that none of these documents provide any information which would have motivated the skilled person to choose D-mannitol specifically to improve stability compared to the solid bortezomib drug substance, nor as to whether a bortezomib D-mannitol ester would hydrolyse in solution, thus allowing the free boronic acid of bortezomib to be readily liberated at the time of use in the clinic.

17.3.8 In a related line of argumentation, the appellants argued that in order to arrive at the claimed features of a D-mannitol ester of bortezomib and free D-mannitol, it would have been an obvious measure to

add a bulking agent for bortezomib, more specifically to add D-mannitol, since it was common general knowledge that D-mannitol was the most commonly used bulking agent for lyophilisation (e.g. from D23).

17.3.9 The respondent argued that the skilled person, even having contemplated the dissolution and lyophilisation of bortezomib, would not necessarily have decided to incorporate a bulking agent, let alone mannitol in particular.

17.3.10 The board agrees with the respondent. Specifically, even if the skilled person were to have contemplated incorporating a bulking agent, even acknowledging that mannitol was a well-known, or indeed the most common bulking agent in the art as argued by the appellants, there were many others to choose from. For example, D7 refers to glycine as an alternative to mannitol (D7, page 296, line 3), D8 refers to a long list of possible bulking agents (D8, page 1566, right hand column, second paragraph) and D32 refers in addition to mannitol to glycine, lactose, sucrose and dextran (page 182, first paragraph).

17.3.11 Furthermore, and crucially in the board's view, as argued by the respondent, the skilled person searching for a bulking agent/excipient, would not in the first place have selected such an agent if it were known (as the appellants have argued) to react with bortezomib to provide a composition of a drug in which the drug substance is modified. Rather, the skilled person would have recognised that the process of formulating a drug substance into a pharmaceutical composition is not meant to alter the chemical structure of said substance. Rather, the very notion of a "bulking agent" is limited to an inert material with certain functions,

none of those functions being a chemical reaction with the active substance intended for administration. Therefore, the skilled person would have been dissuaded from employing D-mannitol as the bulking agent of choice.

17.3.12 Furthermore, of at least equal importance is the fact that, as stated by the respondent, if the skilled person in searching for a bulking agent would have anticipated the reaction of D-mannitol with bortezomib to form a bortezomib D-mannitol ester, there is no information in any of the cited prior art according to which the skilled person could have predicted that after reconstitution of the claimed lyophilisate, the specific D-mannitol bortezomib ester would hydrolyse to the free boronic acid, thereby allowing it to be readily liberated at the time of use in the clinic. The fact as argued by the appellants that many boronic acid esters, or certain specific boronic acid esters were known to hydrolyse rapidly is insufficient to extrapolate the same conclusion to the specific bortezomib D-mannitol ester of the contested claims.

17.4 In conclusion, the subject-matter of claims 1 and 2 of auxiliary request 5a involves an inventive step starting from the solid bortezomib drug substance.

18. D5 as closest prior art - starting from the liquid formulation of D5

18.1 As set out above, all appellants argued that the correct starting point in D5 was represented by the liquid formulation of D5, i.e. the formulation represented by the solution comprising 2% EtOH in normal saline at pH 6.9, without the addition of EDTA (D5, page 762, right hand column, under heading

"Effects of ascorbic acid ..."; figure 5). Starting from this disclosure in D5, it would have been obvious to the skilled person to lyophilise bortezomib in the presence of D-mannitol according to the contested claims.

18.2 The board disagrees. As argued by the respondent in particular during oral proceedings, if the skilled person were to have started from the liquid formulation of D5, and in view of the inherent instability thereof as addressed in D5, were to have contemplated the preparation of a solid formulation of bortezomib, then both conceptually as well as practically, the skilled person would effectively have moved from the liquid formulation to the solid bortezomib drug substance disclosed in D5. Thus, although the skilled person may have started conceptually with the liquid formulation of D5, the contemplation of providing a solid form of bortezomib as a solution to stability issues would necessarily entail a shift in focus from the liquid formulation to the solid bortezomib drug substance.

18.3 However, since the claimed invention involves an inventive step starting from the solid bortezomib drug substance of D5 as set out above, it also follows that inventive step is acknowledged where the skilled person starts from a different point, but conceptually, practically, and necessarily passes through the starting point from which inventive step was already acknowledged.

18.4 Some appellants argued that the skilled person starting from the liquid formulation of D5 would not have returned to the solid bortezomib drug substance.

18.5 Appellant-opponents 10 for example argued that the skilled person would rather have lyophilised the liquid formulation of D5 in the presence of mannitol, however by omitting the salt present therein by virtue of the normal saline content. The board notes however that practically, the skilled person would not simply omit salt, but would prepare a solution without using normal saline. However, doing so would again necessitate a return to the solid bortezomib drug substance as the starting point for the preparation of said solution.

18.6 It was also argued by appellant-opponents 1 and 11 that the skilled person would not have returned to the solid bortezomib drug substance on the basis that it did not represent "a formulation" suitable for administration. This contention is however inconsistent with the appellants' argument that the skilled person starting from the liquid would have arrived at the claimed solid and the claimed solution would therefore be obvious. Furthermore, the solid bortezomib drug substance in D5 is equally close to a formulation for administration as the claimed lyophilised composition: both require the addition of a solvent to provide a solution suitable for parenteral administration (for D5: as alleged by the appellants). Therefore, while it is true that the solid bortezomib drug substance in D5 is a compound, while the contested claims concern a composition, both are to the same extent "formulations" in the sense referred to by appellant-opponent 1, namely as substances from which parenteral solutions can be prepared.

Consequently, at least for these reasons, the subject-matter of contested claims 1 and 2 involves an inventive step starting from the liquid formulation of D5.

18.7 Decision T 1348/14 in relation to the grandparent patent

18.7.1 The patent in suit had been granted on a second generation divisional application. Some appellants argued that the conclusion of the deciding board of appeal in relation to inventive step for the patent which had been granted on the earliest application ("grandparent patent") should also apply to the facts of the present case.

18.7.2 As stated by the respondent however, the facts and evidence presented in that case are different from the present case. Specifically, in that case, the relevant claim was directed to the lyophilised mannitol ester of bortezomib *per se*. This factual situation differentiates appeal case T 1348/14 from the present case. In particular, the distinguishing features over the closest prior art are different. For example, the present claims concern a lyophilised composition which, by virtue of the 10:1 ratio feature, comprises a large excess of D-mannitol. In view of these distinguishing features, the objective technical problem set out above is different to that in the grandparent case. Hence, the outcome in that case is irrelevant to the present case. The question of whether the decision taken in relation to the grandparent patent can have any binding or *res iudicata* effect on the current divisional patent at all therefore did not need to be addressed by the board.

18.8 Since the subject-matter of claims 1 and 2 involves an inventive step starting from either of the two potential starting points in D5 proposed by the parties, the board concludes that the subject-matter of

claims 1 and 2 involves an inventive step over D5 pursuant to Article 56 EPC.

19. D1 or D2 as closest prior art - admittance

19.1 With the statement of grounds of appeal, appellant-opponent 1 submitted that
"*if the provision of a form of bortezomib is maintained to be the objective technical problem, the closest prior art document would be either D1 or D2 as they were concerned with boronic acids esters itself, which are useful in pharmaceutical compositions. Any surprising technical effect would need to be established between the purified and isolated mannitol ester of bortezomib (to remove any effect by remaining mannitol and tert-butanol) and the bortezomib esters disclosed and suggested in D1/D2. We are not aware of any experimental data establishing or supporting any effect from the mannitol ester of bortezomib per se.*"

19.2 The respondent requested that the objection of lack of inventive step starting from D1 or D2 as closest prior art not be admitted into the proceedings *inter alia* pursuant to Article 12(3) and (5) RPBA.

19.3 According to Article 12(3) RPBA, the statement of grounds of appeal shall contain a party's complete appeal case and shall set out clearly and concisely the reasons why it is requested that the decision under appeal be reversed, amended or upheld, and should specify expressly all the requests, facts, objections, arguments and evidence relied on. According to Article 12(5) RPBA, the board has discretion not to admit any part of a submission by a party which does not meet the requirements in paragraph 3.

19.4 The board has some difficulty understanding the very brief reasoning provided by appellant-opponent 1. As set out by the respondent, the basis for the choice of closest prior art cannot be the objective technical problem as stated by the appellant, because the objective technical problem is based on a comparison of the closest prior art with the claimed inventions and the effects linked to the distinguishing features. Hence, the choice of closest prior art precedes the formulation of the objective technical problem. Furthermore, the appellant's arguments are not substantiated, because they amount to a mere allegation that the appellant is not aware of any technical effect that is associated with the claimed invention, but without identifying the distinguishing features and the potential technical effects which may arise and if any such potential technical effects should be present, why, in the appellant's view, they are not associated with the claimed invention.

19.5 Hence, in the board's view, the attacks based on D1 and D2 are not understandable and do not provide enough detail for the board or the respondent to form an opinion thereon. Hence, the objections are not substantiated as required by Article 12(3) RPBA, and the board decided not to admit them into appeal proceedings pursuant to Article 12(5) RPBA.

20. Consequently, the subject-matter of the sole claims 1 and 2 of auxiliary request 5a involves an inventive step pursuant to Article 56 EPC.

21. Since there were no further objections, the set of claims of auxiliary request 5a is allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form with the claims according to auxiliary request 5a filed on 30 January 2024 at the oral proceedings before the board, and a description to be adapted thereto if appropriate.

The Registrar: The Chairman:

L. Stridde M. O. Müller

Decision electronically authenticated