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Datasheet for the decision of 17 April 2019

Case Number: T 0773/15 - 3.3.08

Application Number: 10152432.0

Publication Number: 2186902

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Language of the proceedings: EN

Title of invention:
Medical preparations for the treatment of alpha-galactosidase A deficiency

Patent Proprietor:
Shire Human Genetic Therapies, Inc.

Opponents:
Protalix Ltd
GLAXO GROUP LIMITED

Headword:
Alpha-galactosidase complex-type glycans/SHIRE HUMAN GENETIC THERAPIES

Relevant legal provisions:
EPC Art. 76(1), 113(1), 123(2)
RPBA Art. 12(4), 15(3)

Keyword:
Main request and auxiliary request 2 - added subject-matter (yes);
Auxiliary request 1 - admission (no);

Decisions cited:
T 0674/96, T 0667/08, T 0312/12

Catchword:

Europäisches Patentamt
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Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

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

Case Number: T 0773/15 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 17 April 2019

Appellant: (Patent Proprietor)	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington MA 02421 (US)
Representative:	Goodfellow, Hugh Robin Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent I: (Opponent 1)	Protalix Ltd 2 Snunit Street Science Park 201000 Carmiel (IL)
Representative:	Stolzenburg, Friederike Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Respondent II: (Opponent 2)	GLAXO GROUP LIMITED Berkeley Avenue Greenford, Middlesex UB6 0NN (GB)
Representative:	Chiappinelli, Susan Ann GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 6 February 2015 revoking European patent No. 2186902 pursuant to Articles 101(2) and 101(3)(b) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	P. Julià
	D. Rogers

Summary of Facts and Submissions

I. European patent no. 2 186 902 is based on European patent application no. 10 152 432.0 (hereinafter "the patent application"), a divisional application of the earlier European patent applications nos. 06 025 159.2 and 00 913 825.6, the latter published under the PCT as International patent application WO 00/53730 (hereinafter "the earlier patent application"). The patent was granted with 16 claims.

II. Two oppositions were filed on the grounds set out in Articles 100(a), 100(b) and 100(c) EPC. At the oral proceedings held on 14 January 2015, the opposition division considered the main request (claims as granted) and the auxiliary request (filed with letter dated 17 December 2013) to contravene Articles 76(1) and 123(2) EPC. Accordingly, the patent was revoked.

III. An appeal was lodged by the patent proprietor (appellant). With the statement setting out the grounds of appeal, the appellant maintained its main request (claims as granted) and filed auxiliary requests 1 and and 2. Oral proceedings were requested as an auxiliary measure.

IV. Opponent 01 (respondent I) replied to the appellant's statement of grounds of appeal, but not opponent 02 (respondent II). As an auxiliary measure, oral proceedings were also requested by respondent I.

V. The board summoned the parties to oral proceedings scheduled for 17 April 2019. In reply thereto, respondent II announced its intention not to attend these proceedings.

VI. On 17 January 2019, the board issued a communication pursuant to Article 17(2) of the Rules of Procedure of the Boards of Appeal (RPBA) informing the parties of its provisional, non-binding opinion on some issues of the case. In particular, the board stated that the main request and auxiliary request 2 appeared to contravene Articles 76(1) and 123(2) EPC and that the board was not minded to admit auxiliary request 1 into the appeal proceedings (Article 12(4) RPBA).

VII. Under cover of a letter dated 26 February 2019, the appellant, without making any substantive submissions, withdrew its request for oral proceedings and informed the board of its intention not to attend the scheduled oral proceedings.

VIII. Under cover of a letter dated 5 March 2019, respondent I, without making any substantive submissions, informed the board that, if the board intended to maintain its provisional opinion, its request for oral proceedings was withdrawn and cancellation of the oral proceedings was requested.

IX. In a communication dated 15 March 2019, the board informed the parties that oral proceedings were to take place for procedural reasons to allow for a decision to be taken on the date of these proceedings.

X. Under cover of a letter dated 9 April 2019, the respondent I informed the board of its intention not to attend the oral proceedings.

XI. Oral proceedings took place on 17 April 2019 in the absence of all parties.

XII. Claim 1 as granted (main request) reads as follows:

"1. A pharmaceutical composition of α-Gal A wherein at least 50% of the total glycans of said α-Gal A preparation are complex-type glycans for use in the treatment of an α-Gal A deficiency at a weekly or biweekly dose of between 0.05 mg to 5.0 mg of an α-Gal A preparation per kg of body weight of a subject."

XIII. Claim 1 of auxiliary request 1 is identical to claim 1 of the main request except for the introduction of the following features at the end of the claim:

"1. [as claim 1 of the main request] ..., wherein the complex-type glycans have (i) one to four sialic acid residues; or (ii) no terminal sialic acid and galactoside residues."

XIV. Claim 1 of auxiliary request 2 is identical to claim 1 of auxiliary request 1 except for the pharmaceutical composition being defined as:

"1. A pharmaceutical composition of a human glycosylated α-Gal A preparation, wherein ... [as claim 1 of auxiliary request 1]" (underlined by the board).

XV. The submissions made by the appellant, insofar as relevant to the present decision, may be summarised as follows:

Main request
Articles 76(1) and 123(2) EPC

Although the patent application did not provide explicit support for the subject-matter of the granted

claims, the opposition division should have followed the established case law - as summarised in decision T 667/08 of 20 April 2012, point 4.1.4 of the Reasons - and should have taken into account what the patent application disclosed implicitly to a skilled person.

The passages on page 2, line 10 and lines 21 to 24; page 5, lines 21 to 28; page 6, lines 7 and 8; page 8, lines 8 to 12, and page 24, lines 10 to 13 of the earlier patent application (page 2, line 35 and lines 46 to 48; page 4, lines 13 to 19 and line 25; page 5, lines 16 to 19 of the patent application), indicated the problem faced by the skilled person (extending the circulating half-life of an α-Gal A preparation) and how this problem could be solved. Since all complex-glycans were sialylated, when the patent application stated that at least 50% of the oligosaccharides (glycans) were charged, the skilled reader was given a clear guidance that at least 50% of the glycans were complex-glycans (which were inherently charged because of the presence of sialic acid residues).

From the disclosures on page 24, lines 10 to 13 and Example 4 of the earlier patent application (page 12, lines 31 to 34 and Example 4 of the patent application), it could be concluded that pharmaceutical compositions of α-Gal A in which at least 50% of the total glycans were complex-type were implicitly but directly and unambiguously derivable from the patent application. The fact that preferred embodiments in the patent application related to 50% complex-glycans with e.g. 2-4 sialic acid residues did not take away from the general technical teaching of the patent application as understood by the skilled person.

Admission of auxiliary request 1 into the appeal proceedings

No submissions were made in this respect.

Auxiliary request 2
Articles 76(1) and 123(2) EPC

Basis for the claimed subject-matter was provided on page 20, lines 18 to 21 and lines 24 to 28 of the earlier patent application (page 10, paragraphs [0065] and [0066] of the patent application); page 8, lines 8 to 12 of the earlier patent application (page 5, paragraph [0025] of the patent application); page 9, lines 5 to 9 of the earlier patent application (page 5, paragraph [0029] of the patent application); and page 11, lines 3 to 7 of the earlier patent application (page 6, paragraph [0034] of the patent application).

The passage on page 20 of the earlier patent application (page 10, paragraphs [0065] and [0066] of the patent application) provided a basis for the feature "50% complex-type glycans" without restriction to 2-4 sialic acid residues and provided the skilled person with different means for obtaining a charge on the oligosaccharides of the α-Gal A preparation. Three options were offered to the skilled person, namely the addition of: i) 1-4 sialic acid residues on complex glycans, ii) 1-2 phosphate moieties on high-mannose glycans, and iii) a single phosphate and a single sialic acid on hybrid glycans. The skilled person was able to choose one of these three options to obtain α-Gal A in which at least 50% of the oligosaccharides were charged. The cited passage was thus a direct and unambiguous disclosure of an α-Gal A composition in wich at least 50% of the total glycans of the α-Gal A

preparation were complex-type glycans with 1-4 sialic acid residues.

On page 8, lines 7 to 12 of the earlier patent application (page 5, paragraph [0025] of the patent application), four distinct solutions were offered for extending the circulating half-life of the α-Gal A preparation. The use of the definitive article ("the sialic acid content") in this passage made clear that the very same sialic acid residues that had been added to increase the sialic acid content of the α-Gal A could also be removed to enhance the circulating half-life. Since in a preferred embodiment, the increased sialic acid content was the result of providing α-Gal A with at least 50% complex-type sialylated glycans, it was implicit in this disclosure that α-Gal A modified by sequential removal of sialic acid and galactose residues preferably comprised at least 50% complex-type glycans. Moreover, the skilled person reading the patent application would have understood that a preferred embodiment in which at least 50% of the oligosaccharides were charged was not desirable because of the charge itself, but because an increased charge meant an increased amount of complex-type glycans on the α-Gal A enzyme which, due to their sialylation, shielded the enzyme and thus prevented its removal from circulation.

Although the passage on page 9, lines 5 to 9 of the earlier patent application (page 5, paragraph [0029] of the patent application) was slightly different, it was also implicit in that disclosure that the sialic acid and galactose residues could only be removed from oligosaccharides that contained these modifications, i.e. primarily for sialylated complex-type glycans. Example 4 demonstrated that glycosylated human α-Gal A

with complex-glycans, from which sialic acid residues and any exposed galactose residues had been removed, had a therapeutic efficacy comparable to that of a control preparation of glycosylated human α-Gal A that was negatively charged due to the presence of 1-4 sialic acid residues on its complex-glycans. Therefore, as far as a threshold level of 50% was considered preferable in the provision of a highly sialylated α-Gal A with extended circulating half-life, it was necessarily also considered preferable for α-Gal A molecules that did not contain exposed galactose residues (i.e. because they had been removed).

XVI. The submissions made by the respondent I, insofar as relevant to the present decision, may be summarised as follows:

Main request
Articles 76(1) and 123(2) EPC

The only passage disclosing the feature "at least 50%" associated with the feature "complex-glycans" was found in the third paragraph of page 6 of the earlier patent application (page 4, paragraph [0019] of the patent application). However, this passage referred to complex-glycans "with 2 to 4 sialic acid residues" and, when read in the context of the whole paragraph, it was clearly understood that the feature "with 2 to 4 sialic acid residues" could not be suppressed. This deficiency was not compensated by the disclosure on page 20, lines 16 to 19 of the earlier patent application (page 10, lines 25 to 34 of the patent application) where it was stated that "preferably at least 50% of the oligosaccharides" be charged. From all the possible definitions of the term "complex-glycans" given by the appellant during the opposition and appeal proceedings,

it was understood that the term "oligosaccharide" was not necessarily identical to the term "complex-glycan", at least a certain degree of uncertainty remained. Nor was the term "charged oligosaccharides" interchangeable with the term "complex-glycans" because charged preparations could include complex-glycans having one to four sialic acid residues, hybrid glycans having a single sialic acid residue and a single phosphate, and high-mannose glycans having one to two phosphate moieties. In a preparation, these groups of charged compounds could fully overlap, only partially overlap or there could be no overlap at all. In Example 4, the protein lacked sialic acids and galactose and thus it was not charged. The reference to this Example only created further contradictions.

Admission of auxiliary request 1 into the appeal proceedings

The subject-matter of auxiliary request 1 was never on file before and comprised a new combination of features. The appellant did not provide any explanation as to why this request could not have been filed during the proceedings before the opposition division. Nor did auxiliary request 1 address any issue that had been discussed for the first time at the oral proceedings before the opposition division. Accordingly, for this reason alone, the filing of this auxiliary request 1 constituted a serious procedural abuse.

Auxiliary request 2
Articles 76(1) and 123(2) EPC

The feature "one to four sialic acid residues" was not supported by the patent application. The disclosure on page 6, third paragraph of the earlier patent

application (page 4, paragraph [0019] of the patent application) required at least 50% of complex-glycans with "two to four sialic acid residues". The passage on page 20, lines 19 to 21 and lines 24 to 27 of the earlier patent application (page 10, paragraphs [0065] and [0066] of the patent application) did not refer to the percentage of complex-type glycans in the preparation but to the percentage of charged oligosaccharides. The charged oligosaccharides in α-Gal A preparations did not only comprise complex-glycans but also high-mannose glycans and hybrid glycans. Therefore, the term "at least 50% of the oligosaccharides being charged" in this passage could not be equated with "50% complex-glycans with one to four sialic acid residues".

The feature "no terminal sialic acid and galactoside residues" was not supported by the patent application. As stated for the main request, the only passage that provided support for the feature "wherein at least 50% of the total glycans of said α-Gal A preparation were complex-glycans" was found on page 6, third paragraph of the earlier patent application (page 4, paragraph [0019] of the patent application). However, there was definitely no disclosure that in such a preparation the specified percentage of complex-glycans were complex-glycans which did not have sialic acid residues attached to them. The disclosure on page 9, lines 5 to 9 of the earlier patent application (page 5, paragraph [0029] of the patent application) did not at all refer to a percentage of "at least 50% complex-type glycans". Moreover, this disclosure could not be combined with the passage on page 6, third paragraph of the earlier patent application (page 4, paragraph [0019] of the patent application) because they described different embodiments - removal of

sialic acid residues on page 9 *vs*. increase of sialic acid content so as to increase the charge on page 6 of the earlier patent application. Likewise, the disclosure on page 24 of the earlier patent application (page 12, paragraph [0070] of the patent application), where emphasis was put on the importance of the presence of sialic acid residues, could not possibly be combined with the completely opposite teaching on page 9 of the earlier patent application (page 5, paragraph [0029] of the patent application).

XVII. There are no submissions on file from respondent II.

XVIII. The appellant (patent proprietor) requested that the decision under appeal be set aside and that the case be remitted to the opposition division for further prosecution on the basis of the main request (claims as granted) or, in the alternative, any one of auxiliary requests 1 or 2 filed with the statement of grounds of appeal.

XIX. Respondent I (opponent 01) requested that the appeal be dismissed. There are no requests on file from respondent II (opponent 02).

Reasons for the Decision

Article 113(1) EPC

1. By their decision not to attend the oral proceedings and not to file substantive arguments in reply to the issues raised in the board's communication pursuant to Article 17(2) RPBA, the parties have chosen not to make use of the opportunity to comment on the board's provisional, non-binding opinion which was unfavourable to the appellant, either in writing or at the oral

proceedings. According to Article 15(3) RPBA, the board is not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who may then be treated as relying on its written case.

2. In the light thereof, the present decision is based on the same grounds, arguments and evidence on which the provisional opinion of the board was based.

Main request

3. The main request (claims as granted) is identical to the main request underlying the decision under appeal.

Articles 76(1) and 123(2) EPC

4. The description and Figures of the patent application and those of the earlier patent application are identical, only the claims of these applications are different.

5. The objection under Articles 76(1) and 123(2) EPC concerns the feature in claim 1 "wherein at least 50% of the total glycans of said α-Gal A preparation are complex-type glycans", without any reference to the number of sialic acid residues.

6. The opposition division considered that the sole passage that specifically referred to this feature was on page 6, lines 9 to 11 of the earlier patent application (page 4, paragraph [0019] of the patent application). Claim 11 of the earlier patent application and claim 6(b) of the patent application referred to a percentage (at least 20%) of complex-glycans of the α-Gal A preparation. In all these

passages, the contested feature was directly associated with the feature "with 2-4 sialic acid residues". The opposition division did not find any other passage in the earlier patent application or in the patent application, in particular in the passages on page 20, lines 20 to 29; page 24, line 14; and page 59, Table 6 of the earlier patent application (page 10, lines 25 to 34; page 12, lines 33 and 34; and page 28, Table 6 of the patent application), that could serve as a basis for the contested feature alone, i.e. unlinked from the number of sialic acid residues (cf. page 4, last paragraph to page 5, third paragraph of the decision under appeal).

7. In view of the decision taken by the opposition division and the arguments submitted by the parties in appeal proceedings, the board, in its communication pursuant to Article 17(2) RPBA, considered it necessary to analyse the technical information provided by both the earlier patent application and the patent application to the skilled person. As a result of this analysis, the board concluded that the skilled person was informed that:

7.1 Alpha-galactosidase (α-Gal A) is a homodimeric glycoprotein used in the (enzyme replacement) treatment of Fabry disease (cf. page 11, lines 1 and 2 and line 26 *et seq.* of the earlier patent application; page 6, paragraph [0034] and paragraph [0039] *et seq.* of the patent application). There are various α-Gal A glycoforms which are classified according to their glycan structure, namely i) high-mannose glycans, ii) hybrid glycans, and iii) complex-glycans; wherein i) and ii) are also referred to as neutral glycans (cf. *inter alia*, paragraph bridging pages 20 and 21 of the earlier patent application; page 10, paragraph [0066]

of the patent application). Complex-glycans may be divided into several subgroups depending on the number of "antennae" attached to their core, namely mono-, bi-, tri-, and tetra-antennary. Complex-glycans may also be sialylated and thus, depending *inter alia* on the method of production/preparation, they may be non-sialylated/asialylated, mono-, bi-, tri-, or tetra-sialylated (cf. *inter alia*, page 22, Table 1 of the earlier patent application; page 11, Table 1 of the patent application).

7.2 The board agrees with the appellant that the technical problem addressed by the (earlier) patent application is the extension of the circulating half-life of α-Gal A preparations and that one of several methods disclosed in the (earlier) patent application for solving this problem is to alter the charge of the α-Gal A preparations, by increasing either the sialic acid content and/or the phosphorylation of these preparations (cf. *inter alia*, page 5, last two paragraphs of the earlier patent application; page 4, paragraphs [0015] and [0016] of the patent application).

7.3 The disclosure on page 6, lines 9 to 11 of the earlier patent application (page 4, lines 24 to 26 of the patent application) refers to "... preferred human glycosylated α-Gal A preparations have multiple α-Gal A glycoforms with preferably ... at least 50% ... complex glycans with 2-4 sialic acid residues". This disclosure defines only the percentage of complex-glycans sialylated with 2-4 sialic acid residues but not the percentage of all complex-glycans in these preparations since they may also comprise mono- and/or non-sialylated complex-glycans. On page 20, lines 17 to 21 of the earlier patent application (cf. page 10,

paragraph [0065] of the patent application), it is stated that the methods of the invention provide human glycosylated α-Gal A preparations with "preferably at least 50% of the oligosaccharides being charged" (emphasis added). However, three possible alterations for obtaining these negatively charged oligosaccharides are listed immediately thereafter: "the addition of one to four sialic acid residues on complex glycans, or of one to two phosphate moieties on high-mannose glycans, or of a single phosphate and a single sialic acid on hybrid glycans" (cf. page 20, lines 24 to 28 of the earlier patent application; page 10, lines 30 to 33 of the patent application). Thus, the antecedent reference to "at least 50% of oligosaccharides being charged" cannot be understood as referring directly and unambiguously to α-Gal A preparations containing at least 50% of complex-glycans because the 50% negatively charged oligosaccharides may consist of different types of glycans, namely high-mannose, hybrid and complex-glycans. In the board's view, this is in line with the whole teaching of the (earlier) patent application that the technical problem is not solved by the presence of a certain (total) percentage of complex glycans but by altering (increasing) the negative charge of the glycans, regardless of their type (hybrid, complex or high-mannose).

7.4 Indeed, on page 24 of the earlier patent application (page 12, paragraph [0070] of the patent application), comparison is made between human α-Gal A preparations produced in CHO cells and human α-Gal A preparations expressed in HT-1080 cells. Whilst most of the oligosaccharides are (41%) high-mannose and the level of sialylated complex-glycans is very low in preparations from CHO cells (11%; 2/3 of the complex chains are not sialylated), the preparations from

HT-1080 cells contain "approximately 67% complex glycans with 2 to 4 sialic acid residues" ("essentially all of the complex chains are sialylated"). The proportions of phosphorylated glycans are 24% and 16% in CHO and HT-1080 cells, respectively. In the board's view, the relevance of this disclosure lies not in the presence of a high percentage of complex-glycans, since not all of them may necessarily be negatively charged (as is the case in CHO cells), but in the total percentage of negatively charged oligosaccharides (11% and 24% = 35% in CHO cells *vs*. 16% and 67% = 83% in HT-1080 cells) (see also page 59, lines 10 to 15, and Table 6 of the earlier patent application; page 28, lines 16 to 19, and Table 6 of the patent application). This is in line with the whole teaching of the (earlier) patent application. Contrary thereto, the contested feature in claim 1 defines the total content of complex-glycans but without reference to the sialic acid residues.

7.5 Since claim 1 does not define the percentage of negatively charged complex-glycans and since the board finds neither explicit nor implicit basis for the subject-matter of claim 1 in the (earlier) patent application, the main request contravenes Articles 76(1) and 123(2) EPC.

Admission of auxiliary request 1 into the appeal proceedings

8. According to the established case law, the function of an appeal is to give a judicial decision upon the correctness of a separate earlier decision taken by an examining/opposition division. Appeal proceedings are not an opportunity to re-run/re-open the proceedings before any of these divisions, nor do they provide an opportunity to improve the drafting of the claims by

including or deleting subject-matter such that the claims contain subject-matter that was not present in the previous requests. Appeal proceedings are not an opportunity for continuing the drafting of the claims at the patent proprietor's convenience. The admission of new requests into the appeal proceedings is always at the board's discretion (Articles 12(4) and 13(1) RPBA; "Case Law of the Boards of Appeal of the EPO", 8th edition 2016, IV.E.1, 1065 and IV.E.4, 1127; T 674/96 of 29 April 1999, point 3.10 of the Reasons).

9. Claim 1 of auxiliary request 1 reads as granted claim 1 except for the additional feature at the end of the claim: "wherein the complex-type glycans have (i) one to four sialic acid residues; or (ii) no terminal sialic acid and galactoside residues". This feature was also introduced into the auxiliary request before the opposition division, wherein the claimed pharmaceutical composition was however further limited to "... a human glycosylated α-Gal A preparation, ...". The subject-matter of auxiliary request 1 in appeal proceedings falls thus in-between that of the main request and of the auxiliary request underlying the decision under appeal.

10. In the statement of grounds of appeal, the appellant did not provide any reasons why auxiliary request 1 could not have been filed at an earlier stage of the proceedings before the opposition division. The board observes that in the Notices of opposition one of the objections raised under Article 100(c) EPC concerned the feature "wherein at least 50% of the total glycans of said α-Gal A preparation are complex-type glycans" (cf. page 8, point D.1 of the Notice of opposition of opponent 01/respondent I; and page 10, point 52 *et seq*. of the Notice of opposition of

opponent 02/respondent II). This issue was also addressed by the opposition division in its communication attached to the "Summons to attend the oral proceedings" (issued on 10 June 2014), wherein the parties were informed that it considered the claimed subject-matter to contravene Article 123(2) EPC (cf. page 3, point 10.1 *et seq.* of the "Summons to attend the oral proceedings").

11. Under these circumstances, the board considers that auxiliary request 1 could, and should, have been filed at an earlier stage of the proceedings (cf. T 312/12 of 31 August 2018, points 25 and 26 of the Reasons). Therefore, the board, in the exercise of its discretion (Article 12(4) RPBA), does not admit auxiliary request 1 into the appeal proceedings.

Auxiliary request 2

12. Auxiliary request 2 is identical to the auxiliary request underlying the decision under appeal and thus, it already forms part of the appeal proceedings.

Articles 76(1) and 123(2) EPC

13. Claim 1 of this auxiliary request defines "A pharmaceutical composition of a human glycosylated α-Gal A preparation, wherein at least 50% of the total glycans ... are complex-type glycans" and "wherein the complex-type glycans have (i) one to four sialic acid residues; or (ii) no terminal sialic acid and galactoside residues". The opposition division considered this auxiliary request to violate Articles 76(1) and 123(2) EPC "for at least the same reasons as the" main request, without further

elaboration (cf. page 10, point 14 of the decision under appeal).

14. The appellant has referred to several passages in the (earlier) patent application as providing a basis for the subject-matter of auxiliary request 2. In particular, the appellant has cited pages 8, 9, and 20 of the earlier patent application (page 5, paragraphs [0025] and [0029]; page 10, paragraphs [0065] and [0066] of the patent application) as well as Example 4 of the (earlier) patent application (*supra*).

15. As stated above, the reference to "at least 50% of the oligosaccharides being charged" on page 20, lines 18 to 21 of the earlier patent application (page 10, paragraph [0065] of the patent application) would be understood by the skilled person as referring to the total sum of all negatively charged oligosaccharides of the isolated human glycosylated α-Gal A preparation, i.e. the combination of the negatively charged glycans of all possible types, such as the complex, high-mannose and hybrid glycans mentioned in the same paragraph on page 20, lines 24 to 28 of the earlier patent application (page 10, paragraph [0066] of the patent application). Indeed, such a combination of negatively charged glycans is disclosed on page 24 of the earlier application (page 12, paragraph [0070] of the patent application) for α-Gal A expressed in CHO cells and in HT-1080 cells (cf. Example 2.3, Table 6, over 67% sialylated complex-glycans, 16% phosphorylated glycans and less than 16% neutral glycans). Contrary to the appellant, the board does not see in these passages an implicit, direct and unambiguous, disclosure of a human glycosylated α-Gal A preparation having at least 50% complex-glycans with 1-4 sialic acid residues.

16. On page 8 of the earlier patent application (page 5, paragraph [0025] of the patent application) four methods for extending the circulating half-life of α-Gal A preparations are described. Contrary to the appellant, the board considers that these methods are clearly independent and the fourth method, describing the "sequential removal of the sialic acid and terminal galactose residues", is not inevitably linked to the first method describing the preparation of α-Gal A with increased amounts of sialic acid. Moreover, there is no reference to any percentage of complex-glycans in this paragraph, let alone to complex-glycans with 1-4 sialic acid residues. Nor does the passage on page 9 of the earlier patent application (page 5, paragraph [0029] of the patent application) provide an implicit, direct and unambiguous, disclosure of a particular percentage of complex-glycans having no terminal sialic acid and galactose residues.

17. In Example 4 of the (earlier) patent application, there is no information on the source of the purified α-Gal A preparation. Since this example compares a sequentially deglycosylated (sialidase/galactosidase/ acetylglucosaminidase) α-Gal A preparation with an untreated preparation, there is no reason to assume that the α-Gal A was expressed in HT-1080 cells (with composition reported in Example 2.3, Table 6) and not in CHO cells (cf. page 24, lines 10 to 15 of the earlier patent application; page 12, paragraph [0070], lines 31 to 24 of the patent application). In any case, even if the α-Gal A was expressed in HT-1080 cells, there is no information in Example 4 regarding the extent/degree of sialic acid removal, nor on the sialidase-treated portion reacted with ß-galactosidase. In the board's view, it is thus not possible to deduce

from Example 4, in a direct and unambiguous manner, the actual percentage of complex glycans having no terminal sialic acid and galactoside residues.

18. Therefore, auxiliary request 2 contravenes Articles 76(1) and 123(2) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated