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Datasheet for the decision of 20 October 2020

Case Number: T 2268/17 - 3.3.04

Application Number: 06848052.4

Publication Number: 1969007

IPC: A61K38/17, C07K14/705, C07K16/28

Language of the proceedings: EN

Title of invention:
Compositions and methods for producing a composition

Patent Proprietor:
Bristol-Myers Squibb Company

Opponents:
D Young & Co
Potter Clarkson LLP
Dr. H. Ulrich Dörries

Headword:
Composition comprising CTLA4-Ig/BRISTOL-MYERS SQUIBB

Relevant legal provisions:
EPC Art. 84, 123(2)
RPBA Art. 13

Keyword:
Main request, auxiliary requests 1a, 1b and 1c: amendments - allowable (no) ;
auxiliary request 1d: clarity (no);
auxiliary request 22: admitted (no)

Decisions cited:
T 0150/82, G 0002/10

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 2268/17 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 20 October 2020

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Appellant III: (Opponent 3)	Dr. H. Ulrich Dörries df-mp Dörries Frank-Molina & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 6 October 2017 concerning maintenance of the European Patent No. 1969007 in amended form.**

Composition of the Board:

Chair G. Alt
Members: R. Morawetz
R. Romandini

Summary of Facts and Submissions

I. The appeals by the patent proprietor (appellant I), by opponent 2 (appellant II) and by opponent 3 (appellant III) lie from the opposition division's interlocutory decision, according to which European patent No. 1 969 007 ("the patent") as amended in the form of auxiliary request 2, and the invention to which it relates, were found to meet the requirements of the EPC.

II. The patent, entitled "*Compositions and methods for producing a composition*", derives from European patent application No. 06 848 052.4 ("the application as filed" or "the application"), which was filed as international application under the PCT with the international application number PCT/US2006/049074, published as WO 2007/076032 ("application as filed" or "application").

III. Three oppositions were filed. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and under Article 100(b) and Article 100(c) EPC.

IV. The opposition division held that the main request, filed by letter of 23 June 2017, and auxiliary request 1, filed as auxiliary request 1a by letter of 23 June 2017, were not admissible under Rule 80 EPC, while auxiliary request 2, filed as auxiliary request 1b by letter of 23 June 2017, was held to meet the requirements of the EPC.

V. In their notice of appeal, appellant III requested that the decision under appeal be set aside "*and the patent be revoked*" (see page 1, last paragraph).

VI. In their statement of grounds of appeal, appellant I stated that they maintained the set of claims in the main request and all the auxiliary requests filed on 23 June 2017 [auxiliary requests 1a, 1b, 1c, 1d, 1e, 2a, 2b, 3a, 3b, 3c, 4, 4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i and 4j]. They provided arguments to the effect that the amendment in claim 2 of the main request and of auxiliary request 1a complied with the requirements of Rule 80 EPC.

Claims 1 and 2 of the main request and of auxiliary request 1a are identical and read as follows:

"1. A composition comprising CTLA4-Ig molecules that is characterized by: (a) an average molar ratio of N-acetyl neuraminic acid (NANA) to CTLA4-Ig molecules of from 8.0 to 11.9, and (b) less than or equal to 2.0 area percent CTLA4-Ig high molecular weight species as determined by size exclusion chromatography and spectrophotometric detection.

2. The composition of claim 1, wherein the CTLA4-Ig molecules are greater than or equal to 97.0 area percent CTLA4-Ig dimers as determined by size exclusion chromatography and spectrophotometric detection and less than or equal to 0.5 area percent low molecular weight species as determined by size exclusion chromatography and spectrophotometric detection."

Claim 1 of auxiliary request 1b and of auxiliary request 1c is identical to claim 1 of the main request and of auxiliary request 1a.

Claim 1 of auxiliary request 1d reads as follows (amendments with respect to claim 1 of the main request are highlighted):

" A composition comprising CTLA4-Ig molecules that is characterized by: (a) an average molar ratio of N-acetyl neuraminic acid (NANA) to CTLA4-Ig molecules of from 8.0 to 11.9, and (b) less than or equal to 2.0 area percent CTLA4-Ig high molecular weight species as determined by size exclusion chromatography and spectrophotometric detection, wherein the composition is obtainable in step (v) of a method comprising: (i) obtaining a soluble fraction of a liquid culture comprising mammalian cells that produce composition comprising CTLA4-Ig molecules; (ii) subjecting the soluble fraction to anion exchange chromatography to obtain an eluted composition comprising CTLA4-Ig molecules; (iii) subjecting the composition of step (ii) to hydrophobic interaction chromatography so as to obtain an enriched composition comprising CTLA4-Ig molecules; (iv) subjecting the composition of (iii) to affinity chromatography to obtain a further enriched composition comprising CTLA4-Ig molecules: and (v) subjecting the composition of (iv) to anion exchange chromatography."

VII. While appellant II filed a statement of grounds of appeal, they subsequently withdrew their appeal by letter dated 29 May 2019. Opponent 2 remained a party as of right in these appeal proceedings.

VIII. In their statement of grounds of appeal, appellant III provided, *inter alia*, arguments as regards added subject-matter (Article 123(2) EPC) with respect to claim 1 of auxiliary request 1b.

IX. In reply to the statements of grounds of appeal by appellant II and by appellant III, appellant I provided their counter-arguments with respect to the basis for the subject-matter of claim 1 of auxiliary request 1b in the application as filed.

X. In reply to appellant I's statement of grounds of appeal, appellant III provided their counter-arguments with respect to the admissibility and allowability of the main request, auxiliary request 1a and auxiliary requests 1c and 1d.

XI. In a communication dated 19 July 2019 the board scheduled oral proceedings.

XII. Appellant III informed the board in writing that they would not attend the oral proceedings.

XIII. The board issued a communication pursuant to Article 15(1) RPBA 2007, in which it indicated, *inter alia*, that it considered that a question to be addressed with respect to claim 1 of the main request was "*whether or not the lack in claim 1 of a reference to the production and purification process results in a product definition that represents an inadmissible intermediate generalisation.*"

XIV. In response, appellant I provided further arguments. They also requested that the hearing be conducted by videoconference (ViCo).

XV. Opponent 1 and opponent 2 informed the board in writing that they would not attend the oral proceedings.

XVI. Oral proceedings were held on 20 October 2020 by ViCo. At the oral proceedings, appellant I filed auxiliary request 22 and withdrew auxiliary requests 1e to 4j.

Claim 1 (sole claim) of auxiliary request 22 reads as follows (amendments with respect to claim 1 of the main request are indicated):

"1. A composition comprising CTLA4-Ig molecules that is characterized by: (a) an average molar ratio of N-acetyl neuraminic acid (NANA) to CTLA4-Ig molecules of from 8.0 to 11.9, and (b) less than or equal to 2.0 area percent CTLA4-Ig high molecular weight species as determined by size exclusion chromatography and spectrophotometric detection, wherein the CTLA4-Ig molecules comprise one or more polypeptides having SEQ ID NO: 2, 5, 6, 7, 8, 9, or 10, wherein in the composition (i) the bioburden is less than 100 cfu/mL; (ii) the amount of residual recombinant protein A is less than or equal to 9.5 ng/mL; (iii) the amount of DNA is less than or equal to 20 pg/mL; (iv) the amount of Triton X-100 is less than or equal to 4 µg/mL; (v) the amount of Chinese hamster ovary host cell proteins (CHOP) is less than or equal to 95 ng/mL; and the amount of monocyte chemotactic protein 1 (MCP-1) is less than or equal to 9.5 ng/mL."

XVII. At the end of the oral proceedings, the Chair announced the board's decision.

XVIII. Appellant I's arguments, submitted in writing and during the oral proceedings, are summarised as follows:

Main request, auxiliary request 1a - claim 2

Rule 80 EPC

Claim 2 had been amended to meet the requirements of Article 123(2) EPC and thus to avoid an objection under Article 100(c) EPC.

Allowability of the main request and auxiliary request 1a

Appellant I's appeal and appellant III's appeal had to be dealt with separately. Appellant I's appeal concerned the admissibility of the main request and auxiliary request 1a under Rule 80 EPC. Once appellant I's appeal was successful, in the absence of an explicit request to dismiss their appeal, the decision under appeal had to be set aside and the patent maintained on the basis of the set of claims in the main request. Allowability of the set of claims in the main request and in auxiliary request 1a was not to be considered by the board.

Main request, auxiliary requests 1a, 1b and 1c - claim 1

Claim construction

The claim covered lots of different compositions with a clear limit with respect to two parameters, the average molar ratio of N-acetyl neuraminic acid (NANA) to CTLA4-Ig molecules of from 8.0 to 11.9, i.e. feature (a), and less than or equal to 2.0 area

percent CTLA4-Ig high molecular weight species (HMW) as determined by size exclusion chromatography and spectrophotometric detection, i.e. feature (b).

Amendments (Article 123(2) EPC)

Features (a) and (b), which characterised the claimed compositions, were disclosed in the application as filed; see paragraphs [00206] and [00208]. The application likewise disclosed compositions as such; see paragraph [0007].

The skilled person read paragraphs [00206] and [00208] of the application with the teaching of the examples in mind.

Paragraph [001073] of Example 28 pointed specifically to the NANA/CTLA4-Ig molar ratio as well as a low CTLA4-Ig HMW species content as the "overriding" common definition for the improved CTLA4-Ig composition of the present invention. Table 15 of Example 29 assigned action limits to these and only to these two key characteristics, and these action limits matched the numbers recited in claim 1. Paragraph [001073] in combination with Table 15 thus pointed to the NANA/ CTLA4-Ig molar ratio and HMW species content, and the two values could therefore be extracted from Table 15. These two parameters were also highlighted in Example 15; see paragraph [00880].

The features which characterised the claimed compositions in paragraphs [00206] and [00208] were not "simply what was observed at the end of that step of the process". To the contrary, the skilled reader immediately appreciated that the process steps were designed so as to provide the desired product, not

vice versa. Said characteristic features were disclosed as "being something that is desirable per se" (see reply, page 7, fourth paragraph). In both paragraphs [00206] and [00208], the application disclosed the claimed compositions as a final product of a method which "can, but does not have to, be used", to obtain the composition (see reply, page 8, second paragraph). This understanding was in line with the fact that the method steps which were used to make the claimed compositions were described as "[n]*on-limiting examples of suitable purification procedures for obtaining greater purity and homogeneity of CTLA4-Ig*" in paragraph [00580] of the application as filed.

Paragraphs [00206] and [00208] took the two parameters out of the context of the process to a higher level. The desired product was disclosed as such, apart from the process.

Auxiliary request 1d

Article 84 EPC - claim 1

Claim 1 was amended to refer to the method disclosed in paragraph [00206] of the application as filed. A product-by-process claim was allowable because this was the only way to guarantee adequate protection for the claimed product, whereas including the features from Table 15 was not reasonable because it would have restricted the scope of protection with respect to the claims as granted.

Auxiliary request 22

Admittance into the appeal proceedings
(Article 13 RPBA 2007)

The amendment was introduced to address appellant III's objection under Article 123(2) EPC. The request was filed in response to the board's opinion on the higher-ranking requests. Only in the oral proceedings had appellant I learned that claim 1 of the main request did not meet the requirements of Article 123(2) EPC and that claim 1 of auxiliary request 1d did not meet the requirements of Article 84 EPC. The request reconciled the squeeze between Articles 123(2) EPC and 84 EPC. The arguments with respect to novelty and inventive step remained the same.

XIX. Appellant III's arguments, submitted in writing, are summarised as follows:

Main request, auxiliary request 1a - claim 2

Rule 80 EPC

The inclusion of "*and spectrophotometric detection*" in claim 2 was an attempt to improve clarity or support in accordance with Article 84 EPC and therefore had to be rejected under Rule 80 EPC.

Main request, auxiliary requests 1a, 1b and 1c - claim 1

Claim construction

The claim related to compositions comprising CTLA4-Ig molecules further defined by only two distinct features, (a) and (b).

Amendments (Article 123(2) EPC)

The compositions defined in claim 1 represented an inadmissible intermediate generalisation. The original application either described a generic CTLA4-Ig-containing composition (see paragraphs [0007] and [00201]) or described very specific CTLA4-Ig-containing compositions obtained by a combination of a variety of specific process steps (see paragraphs [00206] and [00208]).

According to established case law of the boards of appeal, an intermediate generalisation was only justified in the absence of any clearly recognisable functional or structural relationship among the features of the specific combination or if the extracted feature was not inextricably linked with those features. In this case, an intermediate generalisation was not justified.

Paragraphs [00206] to [00208] of the application described two different multi-step purification/work-up procedures, which both started from obtaining a soluble fraction of a liquid culture comprising mammalian cells that produced CTLA4-Ig and then subjecting this fraction to a variety of chromatographic purification steps. Accordingly, these paragraphs were essentially

about specific methods and not about compositions *per se*. The application then continued by describing the compositions as obtained from each purification step, using the NANA molar ratio and HMW CTLA4-Ig species content as exemplary parameters illustrating the enrichment and purification level achieved by the work-up procedure described in this section.

The skilled person would consider the described compositions only in the context of and closely associated with the production and subsequent work-up/ purification scheme disclosed in paragraphs [00206] to [00208].

The parameters characterising the CTLA4-Ig-containing composition were intimately tied to the production and work-up procedure described in these paragraphs. For example, if produced by mammalian cells and subjected to a series of purification steps, the skilled person would have expected certain maximum amounts of constituents of the mammalian cells that produced the CTLA4-Ig molecules not to be exceeded.

The lack of a reference to the production and purification process in claim 1 resulted in a product definition that represented an inadmissible intermediate generalisation since inherent additional product characteristics such as overall purity, galactose to CTLA4-Ig ratio, sialic acid content, and type of N-linked glycosylation were necessarily linked to the specific process described in paragraphs [00206] to [00208] and thus also linked to the concrete NANA molar ratio and HMW CTLA4-Ig species, but were not included in the definition of the composition of claim 1.

The skilled person could not derive clearly and unambiguously that a composition merely characterised by the two parameters ranges, NANA to CTLA4-Ig molar ratio of between 8.0 and 11.9, and the presence of less than or equal to 2 area% of HMW CTLA4-Ig species, had been envisaged in the application.

Appellant I's reference to paragraph [001073] describing the CTLA4-Ig production in general terms could not overcome this deficiency. Paragraph [001073] also mentioned further aspects influencing the final product quality, such as product purity (removal of other, i.e. non-CTLA4-Ig proteins and other contaminants) and virus inactivation.

Auxiliary request 1d

Article 84 EPC - claim 1

The claim included a product-by-process feature. The CTLA4-Ig composition was, *inter alia*, defined as being obtainable by a certain method. According to decision T 150/82, claims for products defined in terms of processes for their preparation (known as "product-by-process" claims) were admissible only if there was no other information available in the application which could enable the applicant to define the product satisfactorily by reference to its composition, structure or some other testable parameter.

In this case, it was highly questionable whether that condition, which was relevant for the clarity of the claims, was met, because the application provided ample

data about the characteristics of the composition obtained by said process; see Table 15 on page 397 of the application.

XX. Opponent 2, as party as of right to the appeal proceedings (see section VII. above), did not submit any arguments that were of relevance to the decision.

XXI. Opponent 1, a party as of right to the appeal proceedings, did not submit any arguments or requests.

XXII. Appellant I requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the set of claims of the main request filed with letter of 23 June 2017, or on the basis of the set of claims of auxiliary request 1a filed with letter of 23 June 2017; alternatively that appellant III's appeal be dismissed, amounting to a request that the patent be maintained in amended form on the basis of auxiliary request 2 [auxiliary request 1b] held allowable by the opposition division, or, further in the alternative, requested that the patent be maintained on the basis of one of auxiliary requests 1c or 1d, both filed during the opposition proceedings by letter of 23 June 2017, or, in the alternative, on the basis of the new auxiliary request 22 filed during the oral proceedings before the board.

XXIII. Appellant III requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

1. The appeals by appellant I and appellant III comply with Articles 106 to 108 and Rule 99 EPC and are admissible.

2. An amended version of the Rules of Procedure of the Boards of Appeal (RPBA 2020) came into force on 1 January 2020. The transitional provisions are set out in Article 25 RPBA 2020. In the case in hand, the parties were notified of the summons to oral proceedings before 1 January 2020. Therefore, Article 13(1) and (3) RPBA 2007 apply.

3. The duly summoned appellant III, opponent 1 and opponent 2 were, as announced in advance, neither present nor represented at the oral proceedings. The board continued the proceedings in their absence, in accordance with Rule 115(2) EPC. They were treated as relying on their written cases, in accordance with Article 15(3) RPBA 2020.

Introduction

4. The claimed invention relates to compositions comprising CTLA4-Ig molecules. These are fusion proteins of the ligand-binding domain of cytotoxic T lymphocyte antigen 4 (CTLA4) and an immunoglobulin (Ig) heavy chain constant region. They exert their physiological effect by binding to B7 antigens (CD80 and CD86) on the surface of various antigen-presenting cells, thus blocking the functional interaction of B7-1 and B7-2 with CD28 on the surface of T-cells. This blocking results in the suppression of

the immune response. The molecules are thus therapeutically useful in the regulation of the immune response; see paragraph [0005] of the application.

5. The application provides methods for obtaining compositions comprising CTLA4-Ig molecules based on the recombinant expression in mammalian cells followed by purification using a series of chromatography steps; see e.g. paragraphs [00206] to [00208] and Examples 14, 15, 28 and 29.

6. The compositions of the invention have certain characteristics, such as "*certain amounts of bacterial endotoxin, bioburden, a pI within a certain range (or certain IEF bands within a pI of a certain range), a certain amount of monomer (single chain), dimer or high molecular weight species (such as tetramer), a certain tryptic peptide profile, a certain set of major bands on SDS-PAGE, a certain DNA content, an amount of MCP-1 not exceeding a certain maximum, an amount of cell protein not exceeding a certain maximum, an amount of Triton X-100 not exceeding a certain maximum, an amount of Protein A not exceeding a certain maximum, a certain profile of N-linked carbohydrates, a certain amino monosaccharide composition (GlcNac, GalNAc), a certain neutral monosaccharide composition (galactose, fucose, mannose), a certain amount of B7 binding, a certain amount of activity in a IL-2 inhibition cell assay, and/or a certain sialic acid composition (NANA, NONA), in each case where said certain amounts can be a range or ranges.*" (emphasis added; see paragraph [0201] of the application).

Main request, auxiliary request 1a - claim 2

Rule 80 EPC

7. In these claim requests claim 2 has been amended to indicate that the percentage of CTLA4-Ig dimers is determined by size exclusion chromatography "*and spectrophotometric detection*".

8. Under Rule 80 EPC the description, claims and drawings may be amended, provided that the amendments are occasioned by a ground for opposition under Article 100 EPC, even if that ground has not been invoked by the opponent.

9. The opposition division held that the amendment to claim 2 aimed to address the requirements of Article 84 EPC and was thus not occasioned by a ground of opposition (see decision under appeal, paragraphs 16.4 and 17).

10. The application as filed discloses that the percentage of CTLA4-Ig dimers is determined by size exclusion chromatography and spectrophotometric detection; see e.g. paragraph [00314] and claims 88 to 92. As a result of the amendment, the wording of claim 2 matches this disclosure in the application as filed. The board is thus satisfied that the amendment in claim 2 aims to have claim 2 meet the requirements of Article 123(2) EPC.

11. Appellant III's argument that the amendment was an attempt to improve clarity or support in accordance with Article 84 EPC thus fails. The fact that an objection under Article 100(c) EPC with respect to the absence of the phrase "*and spectrophotometric*

detection" was not raised by the opponents is irrelevant. Indeed, such an objection is not required for the amendment to be admissible under Rule 80 EPC; see point 8. above.

12. For these reasons the board concludes that the amendment made to claim 2 of each of the main request and auxiliary request 1a complies with the requirements of Rule 80 EPC. The main request and auxiliary request 1a are admissible.

Allowability of the main request and auxiliary request 1a

13. Appellant I's appeal is against the opposition division's decision holding the main request and auxiliary request 1a inadmissible under Rule 80 EPC.

14. Appellant I submitted that as their appeal was successful (see point 12. above) and as there was no explicit request to dismiss their appeal, their appeal was to be allowed and the decision under appeal was to be set aside with the consequence that the patent was to be maintained on the basis of the set of claims of the main request. Allowability of the main request and auxiliary request 1a was not to be considered.

15. The board notes that appellant III requested that the patent be revoked; see section V. above. This request extends to the patent as granted and amended in any form, i.e. any claim request filed and admitted, or filed but not admitted, or still to be filed by the patent proprietor in the course of the appeal proceedings. The request to revoke the patent is indeed incompatible with any request to maintain it in amended form.

16. Appellant I's argument that the board was prevented from examining the allowability of the claims of the main request and of auxiliary request 1a because appellant III had not requested that appellant I's appeal be dismissed thus fails.

Main request, auxiliary requests 1a, 1b and 1c - claim 1

Claim construction

17. As noted above (see section VI.), claim 1 of the main request and claim 1 of auxiliary requests 1a, 1b and 1c are identical. They are directed to a composition comprising CTLA4-Ig molecules that is characterised by: (a) an average molar ratio of N-acetyl neuraminic acid (NANA) to CTLA4-Ig molecules of from 8.0 to 11.9, and (b) less than or equal to 2.0 area percent CTLA4-Ig high molecular weight (HMW) species.

18. The board agrees with appellant I and appellant III that the claims at hand cover various different compositions with a clear limit with respect to only two parameters, features (a) and (b).

Amendments (Article 123(2) EPC)

19. In the decision under appeal the opposition division considered that "*it is directly and unambiguously evident from the disclosure in e.g. paragraphs [0007] or [00201] (first sentence) that the application also envisages compositions as such of the purified CTLA4-Ig molecules. Therefore the OD considers that the composition described as end product in paragraphs [00206] and [00208] can be considered as disclosed as a composition as such, without being linked to the specific method by which it is produced nor to the*

mammalian cells wherein it is produced" (emphasis in the original; see decision under appeal, paragraph 19.3).

20. Appellant III contested this part of the decision under appeal and submitted that compositions defined as in claim 1, i.e. without reference to their production and purification process, represented an intermediate generalisation because inherent additional product characteristics necessarily resulted from the specific process described in paragraphs [00206] and [00208] and were thus also necessarily linked to the specific NANA to CTLA4-Ig ratio and amount of HMW species disclosed for the composition in these paragraphs.

21. The standard for assessing compliance with the requirements of Article 123(2) EPC is the standard set out in decision G 2/10 (OJ EPO 2012, 376, points 4.3 and 4.5.1 of the Reasons), also known as the "gold standard". Amendments are only permitted within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of the application as filed. It is not permitted for the skilled person to be presented with new technical information after the amendment. Subject-matter which is implicitly disclosed to the skilled person, using common general knowledge, in the application as filed is part of the content (*ibid.*, point 4.5.2). The concept of implicit disclosure refers to what any person skilled in the art would consider was necessarily implied by the application as a whole (see also Case Law of the Boards of Appeal of the European Patent Office, 2019, 9th edition, II.E.1.1, II.E.1.3.1 and 1.3.3).

22. According to paragraph [00206] "*the invention provides for a method for isolating CTLA4-Ig molecules, the method comprising: (i) obtaining a soluble fraction of a liquid culture comprising mammalian cells that produce composition comprising CTLA4-Ig molecules; (ii) subjecting the soluble fraction to anion exchange chromatography to obtain an eluted composition comprising CTLA4-Ig molecules; (iii) subjecting the composition of step (ii) to hydrophobic interaction chromatography so as to obtain an enriched composition comprising CTLA4-Ig molecules; (iv) subjecting the composition of (iii) to affinity chromatography to obtain a further enriched composition comprising CTLA4-Ig molecules; and (v) subjecting the composition of (iv) to anion exchange chromatography.*" The disclosure in paragraph [00208] is largely the same and no argument was made by appellant I that the considerations that applied to paragraph [00208] differed from those that applied to paragraph [00206]. While the board focuses on paragraph [00206] in the following, the same reasoning applies to paragraph [00208], *mutatis mutandis.*

23. As is evident from the previous point, paragraph [00206] describes a multi-step purification/ work-up procedure which starts from obtaining a soluble fraction of a liquid culture comprising mammalian cells that produce CTLA4-Ig and then subjecting this fraction to a variety of chromatographic purification steps with the aim of providing an enriched composition comprising CTLA4-Ig molecules.

24. Paragraph [00206] then continues by describing various embodiments of the method by referring to the compositions as obtained from each purification step (ii) to (v), using the NANA molar ratio and HMW

CTLA4-IG species content as exemplary parameters illustrating the enrichment and purification level achieved by the work-up procedure described in this paragraph. The final part of the paragraph, which discloses that "[i]*n another embodiment, the composition obtained in step (v) is characterized by: (a) an average of 8.0-11.9 moles of NANA per mole of CTLA4-Ig molecule; and (b) less than or equal to 2.0 area percent being CTLA4-Ig high molecular weight species as determined by size exclusion chromatography and spectrophotometric detection (SPD)*" (emphasis added by the board) is relevant for this decision.

25. The board concurs with appellant III that the skilled person considers the composition obtained in step (v) in the context of and closely associated with the production and subsequent work-up/purification scheme disclosed in paragraph [00206], including the starting material "*a liquid culture comprising mammalian cells*" and the various chromatographic steps. Using their common general knowledge and considering the whole of the application (see e.g. points 4. to 6. above), the skilled person immediately derives that the effects of the chromatographic purification steps (i) to (v) manifest themselves in the product characteristics of the composition obtained in step (v).

26. The board concludes that the composition disclosed in paragraph [00206] of the application is characterised by the explicitly mentioned features relating to NANA/ CTLA4-Ig molar ratio and HMW species content. In addition to that, as a necessary consequence of the starting material and the chromatographic purification steps disclosed, it possesses inherent features, which

are implicitly disclosed, such as a reduced amount of process-related impurities, e.g. mammalian cell derived products.

27. In the board's judgement, the fact that the application also envisages compositions as such does not change the disclosure conveyed to the skilled person by paragraph [00206] of the application. Since the skilled person derives from the application as filed that the composition obtained in step (v) has inherent additional product features necessarily conveyed on the product by the specific process described therein (see point 26. above), the board cannot concur with the reasoning given in the decision under appeal (see point 19. above).

28. The issue which remains to be decided is whether or not claim 1 lacking a reference to the production and purification process disclosed in paragraph [00206] results in a product definition that presents the skilled person with new technical information.

29. Appellant I did not dispute that the process disclosed in paragraphs [00206] and [00208] resulted in inherent additional product characteristics necessarily conveyed on the product by the specific process described therein. Indeed, when asked at the oral proceedings, they argued that the process left a "footprint" on the product.

30. However, appellant I submitted that paragraphs [00206] and [00208] had to be read with the teaching of the examples in mind, that the examples provided a pointer to the NANA/CTLA4-Ig molar ratio and HMW species content such that these and only these two values could be used to characterise the compositions of the present

invention, and that paragraphs [00206] and [00208] disclosed the composition as such, apart from the process.

31. Appellant I relied on Examples 28 and 29, paragraph [001073] and Table 15 and on Example 15 and paragraph [00880] as supporting their argument that a pointer was provided to the NANA/CTLA4-Ig molar ratio as well as a low CTLA4-Ig HMW species as a common definition for the improved CTLA4-Ig composition.

32. Example 28 relates to a CTLA4-Ig production process and paragraph [001073], in that example, discloses that "*CTLA4-Ig is produced as a secreted protein in large-scale cell culture using Chinese hamster ovary (CHO) cell line.* (...). *CTLA4-Ig is purified using a series of chromatographic and filtration steps. The downstream CTLA4-Ig production process includes two anion exchange chromatography steps, one hydrophobic interaction chromatography step and one affinity chromatography step. The purpose of these steps is to purify the CTLA4-Ig protein, to remove high molecular weight CTLA4-Iq material and to control the sialic acid content of the CTLA4-Ig drug substance.*" (emphasis added by the board).

33. Therefore, purification is explicitly mentioned as a purpose of the process and, contrary to appellant I's submission, it cannot be derived from paragraph [001073] that the NANA/CTLA4-Ig molar ratio as well as a low CTLA4-Ig HMW species content are the "overriding" common definition for the composition.

34. Example 29 concerns the purification of the material obtained in Example 28 and discloses that that process comprises several steps. The process parameters for the

last chromatography step in the process are summarised in Table 15. Action limits are set for various product related parameters such as "*Product Pool residual Recombinant A*", "*Product Pool DNA*", "*Product Pool Triton X-100*", "*Product Pool SA NANA Molar ratio*", "*Product Pool HMW*", "*Product Pool CHOP*" and "*Product Pool MCP-1*".

35. Contrary to appellant I's submission, Table 15 assigns action limits not only to the CTLA4-Ig molecules, i.e. "*Product Pool SA NANA Molar ratio*" and "*Product Pool HMW*", but also to "*Product Pool residual Recombinant A*", "*Product Pool DNA*", "*Product Pool Triton X-100*", "*Product Pool CHOP*" and "*Product Pool MCP-1*" and thus to process-related impurities, namely Chinese Hamster Ovary Protein (CHOP), MCP-1, residual recombinant Protein A, DNA and Triton X-100.

36. Example 15 also relates to purification of recombinant CTLA4-Ig and discloses in paragraph [00880] that the objective of the Q-Sepharose Fast Flow (QFF) chromatography step, the last step in the purification process, is "*to reduce residual Protein A levels and provide additional reduction of host cell DNA from the viral filtration step product pool. The QFF column step is also used to control sialic acid to CTLA4-Ig protein molar ratio of the QFF chromatography step product pool and to provide additional control of in-process CTLA4-Ig HMW material levels.*"

37. Therefore, paragraph [00880] also conveys to the skilled person that process-related impurities such as residual recombinant Protein A and host cell DNA are

controlled together with the NANA/CTLA4-Ig molar ratio and CTLA4-Ig HMW species content and are thus closely related in the final composition.

38. Neither paragraph [001073] nor Table 15 nor paragraph [00880] therefore point to the NANA/CTLA4-Ig molar ratio and the low CTLA4-Ig HMW species content as the "overriding" common definition for the CTLA4-Ig composition of the present invention.

39. Therefore, the skilled person cannot directly and unambiguously derive from paragraph [00206] and the relevant examples that the NANA/CTLA4-Ig molar ratio and low CTLA4-Ig HMW species content are not functionally and structurally linked to the other features which characterise the purified composition comprising CTLA4-Ig molecules.

40. Appellant I's further argument that the composition is disclosed as such in paragraph [00206], independently of the process, is not persuasive either, for the following reasons.

41. It is evident from points 22. to 24. above that paragraph [00206] of the application concerns a method and not compositions *per se*. Indeed, paragraph [00206] discloses the composition obtained in step (v) as an embodiment of the method. The method is also not disclosed as being a non-limiting example of a suitable purification procedure for obtaining the composition in step (v) and none of the steps is disclosed as being optional.

42. Contrary to the submission by the appellant, the method disclosed in paragraph [00580] of the application does not relate to a method "to make the claimed

compositions". Paragraph [00580] relates to the production of CTLA4-Ig in CHO cells and does not mention anything regarding the characteristics of the composition obtained. In the board's judgement, the skilled person thus has no reason to re-interpret the disclosure of paragraph [00206] in the light of paragraph [00580] of the application to come to the conclusion that the method disclosed in paragraph [00206] "can, but does not have to, be used" to obtain the composition.

43. The board concludes from the above that, while in the composition obtained in step (v) of the process disclosed in paragraphs [00206] and [00208] of the application, process-related impurities have been removed to a large degree, claim 1 allows for the presence of any amount of process-related impurities. Claim 1 lacking a reference to the production and purification process disclosed in paragraph [00206] and [00208] therefore results in added subject-matter.

44. As a consequence, claim 1 does not meet the requirements of Article 123(2) EPC.

Auxiliary request 1d

Clarity (Article 84 EPC) - claim 1

45. Claim 1 of auxiliary request 1d is drafted as a product-by-process claim and further defines the claimed composition by way of the method steps disclosed in paragraph [00206] of the application; see section VI. and point 22. above.

46. Appellant III questioned whether a product-by-process claim was allowable in the circumstances of the present case.

47. According to the case law, "product-by-process claims" are allowable only where the product cannot be satisfactorily defined by reference to its composition, structure or some other testable parameters (see decision T 150/82, OJ EPO 1984, 309, see point 10 of the Reasons and Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019, II.A.7.1).

48. In this case, as is evident from Example 19 of the application, the product can be defined by reference to its structure and/or testable parameters. Table 15 on page 397 of the application provides process parameters defined by action limits; see point 34. above. These action limits correspond to testable parameters of the composition comprising CTLA4-Ig molecules.

49. Appellant I's argument that the product-by-process claim was allowable because this was the only way to guarantee adequate protection for the claimed product cannot succeed. The fact that claim 1 of auxiliary request 1d might provide adequate protection does not exempt it from having to fulfil the requirements of Article 84 EPC.

50. The board concludes that claim 1 of auxiliary request 1d does not comply with the requirements of Article 84 EPC.

Auxiliary request 22

Admittance into the appeal proceedings
(Article 13(1) RPBA 2007)

51. This request was filed during the oral proceedings after the board had expressed its view with respect to claim 1 of the main request and claim 1 of auxiliary requests 1a, 1b, 1c and 1d.

52. Claim 1 of auxiliary request 22 was amended with respect to claim 1 of the main request by further defining the composition based on the characteristics disclosed in Table 15 of the application as filed; see section XVI.

53. The board noted that the combination of features claimed had not been claimed before and represented an amendment to appellant I's case. Under Article 13(1) RPBA 2007, an amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at the board's discretion. The board, when exercising its discretion, considers, *inter alia*, the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy.

54. Appellant I argued that the amendment was introduced to address the objection under Article 123(2) EPC and that the request was a response to the board's opinion on the higher-ranking requests. Only in the oral proceedings had they learned that claim 1 of the main request and auxiliary requests 1a, 1b and 1c did not

meet the requirements of Article 123(2) EPC and that claim 1 of auxiliary request 1d did not meet the requirements of Article 84 EPC.

55. The board's findings with respect to the main request and auxiliary requests 1a, 1b, 1c and 1d were based on appellant III's objection contained in appellant III's statement of grounds of appeal (see section VIII.) and reply, respectively (see section X.). Therefore, the board's findings did not qualify as an unexpected development which could have justified the admittance of the new request.

56. Furthermore, appellant I was aware that appellant III maintained their objection under Article 123(2) EPC upon receipt of appellant III's statement of grounds of appeal and could thus have addressed this objection sooner. Appellant I's justification for only filing auxiliary request 22 at the oral proceedings could not be accepted, as parties should make their case at the beginning of the appeal proceedings; see Articles 12 and 13 RPBA 2007. Therefore, the board considered that the request, which aimed to address the issue of Article 123(2) EPC only at the oral proceedings, was filed late.

57. Finally, the board considered that including the composition parameters disclosed in Table 15 of the application led to an extensive change in the claimed subject-matter. This change would have necessarily extended the scope and framework of the discussion with regard to Article 123(2) EPC, but also with regard to novelty and inventive step with respect to that determined by the decision under appeal, the statements

of the grounds of appeal and the replies. Admission into the appeal proceedings would thus not have served the interests of procedural economy.

58. Accordingly, the board, exercising its discretion pursuant to Article 13(1) RPBA 2007, decided not to admit this request into the appeal proceedings.

Conclusion

59. The board concludes that the main request and auxiliary requests 1a, 1b, and 1c do not meet the requirements of Article 123(2) EPC, while auxiliary request 1d does not meet the requirements of Article 84 EPC. These are the sole claim requests to be considered by the board. Accordingly, the patent cannot be maintained in amended form based on these claim requests and, in the absence of another, allowable claim request, the patent must be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

B. ter Heijden G. Alt

Decision electronically authenticated