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Datasheet for the decision of 11 March 2025

Case Number: T 0089/23 - 3.3.04

Application Number: 14721668.3

Publication Number: 2970875

IPC: C07K16/00, C12N5/00

Language of the proceedings: EN

Title of invention:
Cell culture compositions with antioxidants and methods for polypeptide production

Patent Proprietor:
F. Hoffmann-La Roche AG

Opponents:
Hoffmann Eitle Patent- und Rechtsanwälte Partnerschaftsgesellschaft mbB
Maiwald GmbH

Headword:
Hypotaurine/HOFFMANN-LA ROCHE

Relevant legal provisions:
RPBA 2020 Art. 13(1), 12(6)
EPC Art. 83, 87

Keyword:
Late-filed documents - should have been submitted in first-instance proceedings (yes)
Amendment to appeal case - suitability of amendment to resolve issues raised (yes)
Sufficiency of disclosure - (yes)

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Case Number: T 0089/23 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 11 March 2025

Appellant: (Opponent 1)	Hoffmann Eitle Patent- und Rechtsanwälte Partnerschaftsgesellschaft mbB Arabellastr. 30 81925 München (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
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Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Party as of right: (Opponent 2)	Maiwald GmbH Elisenhof, Elisenstrasse 3 80335 München (DE)
Representative:	Maiwald GmbH Elisenhof Elisenstraße 3 80335 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 11 November 2022 concerning maintenance of the European Patent No. 2970875 in amended form.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	O. Lechner
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 2 970 875 ("patent") was granted based on application No. 14721668.3, claiming priority of US 61/799,602 filed on 15 March 2013. The application was filed as an international patent application and published as WO 2014/145098 ("application as filed").

II. Opponent 1 (appellant) filed an appeal against the interlocutory decision of the opposition division that the patent, amended in accordance with the main request (set of claims filed on 11 June 2021), met the requirements of the EPC.

III. With its statement of grounds of appeal, the appellant raised objections under Articles 56, 83, 87 and 123(2) EPC against the main request and submitted new documents D28 to D30.

IV. In reply to the statement of grounds of appeal, the patent proprietor (respondent) resubmitted sets of claims in accordance with a main request (set of claims first filed on 11 June 2021), auxiliary requests 1 to 7 (first filed on 11 June 2021) and auxiliary request 8 (first filed on 12 August 2022).

V. The appellant and respondent each submitted a further letter in reaction. With its letter of 25 November 2024, the respondent filed new sets of claims in accordance with auxiliary requests 9 to 17.

VI. After the board issued its preliminary opinion pursuant to Article 15(1) RPBA, the respondent, in a letter dated 5 March 2025, withdrew its main request and

auxiliary requests 1, 3 to 12 and 14 to 17. It submitted a main request and auxiliary requests 1 and 2. The main request is identical to auxiliary request 13 as filed by letter dated 25 November 2024. Auxiliary request 1 is a new request. Auxiliary request 2 is identical to auxiliary request 2 filed by letter dated 11 June 2021 and resubmitted with the respondent's reply to the statement of grounds of appeal dated 14 July 2023.

VII. Opponent 2, who has made no submissions in appeal and did not attend oral proceedings either, is a party to the appeal proceedings as of right within the meaning of Article 107, second sentence, EPC.

VIII. Oral proceedings before the board took place on 11 March 2025.

During the oral proceedings, the respondent made an argument based on a comparison of the data in Figure 9 of the patent and Figure 4 of document D14, but withdrew this new line of argument after the appellant objected to it, and the discussion continued.

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

IX. Reference is made to the following documents:

D5 Vijayasankaran N. *et al.*, Biotechnol. Prog. (2013), 29(5):1270-1277 (Epub: 11 June 2013)

D14 Vijayasankaran N. *et al.*, Biotechnol. Prog. (2018), 34(5):1298-1307

D15 Qi P. *et al.*, J. Pharm. Sci. (2009), 98(9): 3117-3130

D25 Council of Europe, Strasbourg, European Pharmacopoeia, 7th edition (2010), 01/2008:20202, chapter "2.2.2. DEGREE OF COLORATION OF LIQUIDS":22-24

D26 Council of Europe, Strasbourg, European Pharmacopoeia, 7th edition, Supplement 7.3 (2012) 01/2012:2031, chapter "Monoclonal antibodies for human use":3815-3819

The bibliographic data for other documents mentioned by document number in this decision are not given here because those documents were not relevant to the board's decision.

X. Claim 1 of the main request reads as follows:

"1. A method of producing a recombinantly produced antibody comprising the step of culturing a cell comprising a nucleic acid encoding the antibody in a cell culture medium, wherein the antibody is secreted into the cell culture medium, wherein the cell culture medium comprises hypotaurine at a concentration from about 2.0 mM to about 50.0 mM; and wherein the cell culture medium comprising hypotaurine reduces the color intensity of a composition comprising the antibody produced by the cell as compared to a composition comprising the antibody produced by the cell cultured in a cell culture medium that does not comprise hypotaurine."

XI. The appellant's arguments relevant to the decision are summarised as follows:

Main request

(a) Admission - Article 13(1) RPBA

No justification for admitting the main request had been provided by the respondent. Identical added-matter objections (Articles 100(c) and 123(2) EPC) had already been raised in the notice of opposition against claims 14 and 15 as granted, which were identical to claims 9 and 10 of auxiliary request 2 filed on 11 June 2021. The same objections were reiterated in the statement of grounds of appeal against claims 10 and 11 of the set of claims which the opposition division had found to comply with the EPC (main request filed on 11 June 2021). The main request could have been submitted with the reply to the statement of grounds of appeal, and did not *prima facie* overcome sufficiency objections under Article 83 EPC, which had been consistently raised. Under Article 13(1) RPBA, all outstanding issues had to be addressed, not just one.

(b) Admission of documents D28 to D30

Documents D28 to D30 had been filed in direct response to expert declaration D27 being filed just before the date set under Rule 116 EPC for making final written submissions, and to the respondent's arguments discussed during the oral proceedings before the opposition division, especially in response to the revelation that the data in Figures 1, 2, 5, 6, 9 and 10 labelled as referring to "*color intensity*" were actually obtained using the Normalised Intrinsic Fluorescence Tool for Yellow/brown proteins (NIFTY)

assay, which measured fluorescence intensity but not colour intensity. Thus these documents could not have been filed earlier.

(c) Disclosure of the invention - Article 83 EPC

(i) Method for measuring the colour intensity

Based on the very slight, if any, effect measured with 2.29 mM (25%) hypotaurine (HT) in Figure 5 of the patent, which, according to the respondent and document D27, was determined using the fluorescence-based NIFTY assay, there were serious doubts that a slight decrease in fluorescence intensity would translate to a measurable decrease in colour intensity. Furthermore, as the Colour, Opalescence and Colouration (COC), Total Colour (TC) and NIFTY assays did not always provide consistent results, and considering that fluorescence intensity measurements were orders of magnitude more sensitive than the COC or TC assays, it was doubtful whether the effect of HT on colouration during cell culture could be detected using these less sensitive assays.

It was also debatable whether the specific chromophores that lead to colour also lead to the fluorescence at the measured wavelength.

Reference was also made to documents D5 (page 1271, left-hand column, paragraph 2) and D14 (Figure 4) in this context.

Moreover, from the patent it was not clear which methods were used in the examples for determining the colour intensity. Only from document D27 and the respondent's explanations during oral proceedings in

opposition (point 9 of the minutes) did it become evident that only the more sensitive NIFTY assay was used in the experiments of the patent.

(ii) Technical effect shown over entire HT concentration range claimed

Based on Example 2, Figure 5 of the patent in suit — which showed that supplementation with 2.29 mM HT (25%) did not result in a statistically significant effect compared with the positive control — serious doubts remained as to whether a reduction in colour intensity could be achieved at the lower end of the claimed HT concentration range. The error bars for the 2.29 mM (25%) HT sample overlapped completely with those of the positive control, and one of the two data points in this group showed no effect at all. A possible linear trend of the mean values was not relevant, as scientific practice required considering standard deviations rather than comparing mean values in isolation. Furthermore, the data in Figure 5 required additional experiments to confirm any effect.

Claim 1 specified a reduction in colour intensity rather than reactive oxygen species (ROS) levels. Since different media may contain varying ROS, the required HT concentration to achieve the claimed reduction in colour intensity could differ depending on the medium used. Figure 6 of document D14 was irrelevant as it concerned unrelated data (with hydrocortisone) and lacked error bars. The burden to demonstrate an effect lay with the respondent, and the high variability suggested that the claimed effect had not been reliably achieved, imposing an undue burden on the skilled person.

(iii) Antibody concentration in the cell culture medium

The issue of increased colour intensity and the alleged reduction in colour intensity arose only in high-antibody-concentration formulations, as indicated in paragraph [0003] of the patent. Document D5 (page 1271, left-hand column, paragraph 2) supported this, stating that at lower concentrations (≤25-50 mg/ml) significant colouration is rare, and increasing antibody concentration leads to increased colour intensity.

However, the claims did not specify the antibody concentration(s) required to achieve the claimed reduction in colour intensity compared with HT-free cell culture. The patent itself mentioned antibody concentrations as low as 1 mg/ml (paragraphs [0056], [0164], [0165], [0172], [0174] and [0178]), raising doubts about the applicability of the claimed effect to low-concentration formulations. Examples 1 and 2 in the patent used concentrated antibody compositions, and Example 3 a composition comprising 150 g/l of the antibody.

(d) Priority - Article 87 EPC

The claims were not entitled to priority from US 61/799,602, as the priority document disclosed only the COC assay (paragraph [0173]) but not the TC or NIFTY assays described in paragraphs [0167] and [0168] of the patent. Document D5 (page 1271, left-hand column, paragraph 3), while disclosing a correlation between the TC, NIFTY and COC assays, did not demonstrate that the COC assay can measure changes in colour intensity due to the presence of HT in the cell culture medium. The appellant also relied on document

D14 (e.g. page 1300, left-hand column; Figure 1), which showed that the COC assay lacks the resolution required for such measurements.
The priority document contained no data demonstrating that the COC assay could detect these changes.

Thus the patent was not entitled to the claimed priority, and document D5 was consequently prior art under Article 54(2) EPC, citable as closest prior art and rendering the claimed subject-matter obvious within the meaning of Article 56 EPC.

XII. The respondent's arguments relevant to the decision are summarised as follows:

Main request

(a) Admission – Article 13(1) RPBA

The deletion of claims 9 and 10 from the former auxiliary request 2 addressed an objection under Article 123(2) EPC raised in the statement of grounds of appeal. The deletion of dependent claims did not result in a change in the factual or legal framework of the proceedings, and instead reduced the complexity of the proceedings by eliminating one of the matters in dispute. This was merely a restriction of the scope of an appeal and as such did not constitute an amendment of a party's case. It would be procedurally inefficient to file all possible permutations of claim requests addressing the different objections raised.

The main request combined amendments previously introduced in auxiliary requests 2, 3 and 4. It maintained the HT concentration range addressed in auxiliary request 2, and removed dependent claims 10

and 11 of the previous main request (main request first filed on 11 June 2021), corresponding to granted claims 14 and 15, as was also done in auxiliary requests 3 and 4, respectively. The main request addressed several of the appellant's objections without giving rise to any new ones.

(b) Admission of documents D28 to D30

The circumstances did not justify the admission of documents D28 to D30, filed only with the statement of grounds of appeal. The appellant should not have been surprised by the information in document D27 or the respondent's submission during oral proceedings in opposition regarding the use of the NIFTY assay in the experiments of the patent, as the patent clearly described the use of this assay for measuring colour intensity (paragraph [0168]). The use of the NIFTY assay was derivable for a skilled person from the specific wording in paragraph [0168] and the examples (e.g. paragraph [0180] or [0183]), which mentioned that the higher numerical value indicates higher colour intensity and the lower numerical value indicates lower colour intensity. Furthermore, documents D29 and D30, published after the priority date of the patent (15 March 2013), could not form part of the skilled person’s common general knowledge.

(c) Disclosure of the invention - Article 83 EPC

(i) Method for measuring the colour intensity

No evidence was presented to show that the skilled person would struggle to measure colour intensity reduction using any of the assays disclosed.

Using any of the assays, COC, TC or NIFTY, disclosed in the patent, the skilled person only needed to determine whether the colour intensity of one composition was reduced relative to another. It was not necessary to correlate results from different assays, and the patent did not require any specific numerical value to be achieved.

The appellant questioned whether the specific chromophores responsible for colour also contributed to fluorescence at the measured wavelength. However, the data in the patent (Figure 9) and post-published evidence (documents D5, p. 1271 and D14, Figures 4 and 6) confirmed that the TC and NIFTY assays reliably measured relative changes in colour intensity, demonstrating that fluorescence measurements were a valid proxy for colour intensity.

(ii) Technical effect shown over entire HT concentration range claimed

The patent explained that ROS cause protein oxidation, which increases colour intensity, while HT scavenges ROS, thereby reducing ROS-mediated oxidation and thereby colour intensity.

Examples 1 to 3 of the patent demonstrated this effect at varying HT concentrations and in different media, with Figures 5 and 6 showing a clear, concentration-dependent linear trend in colour intensity reduction. In Figure 5 of the patent, the 2.29 mM (25%) HT sample showed a mean reduction of around -5%, despite normal experimental variability, with all data normalised to the positive control. Claim 1 did not specify the magnitude of reduction, and stronger effects could be observed in other media.

Figures 4 and 6 of document D14 confirmed that all three methods, i.e. the COC, TC and NIFTY assays, could measure a reduction in colour intensity.
The appellant's argument that HT might preferentially react with specific ROS, rather than broadly reducing ROS levels, was unsubstantiated and purely speculative.

(iii) Antibody concentration in the cell culture medium

The appellant's argument that colour intensity reduction could not be measured below a concentration of 100 mg/ml antibody relied on paragraph [0003] of the patent, which merely explained why colour issues were more apparent at higher concentrations. However, this passage did not suggest that the invention was inoperative at lower concentrations. No evidence had been provided to show that a reduction in colour intensity could not be measured at lower antibody concentrations.

(d) Priority - Article 87 EPC

The priority document sufficiently disclosed the claimed invention, teaching that colour intensity reduction can be measured using the COC assay (paragraph [0173]), as per the European Pharmacopoeia (documents D25 and D26). Also document D15 described using a visual-based assay to detect changes in colour intensity of antibody formulations, similarly to the present invention - the colour comparison was made according to United States of America Pharmacopeia (USP) standards.

The appellant's argument, based on documents D5 and D14, that the COC assay lacked resolution was unconvincing. These documents only suggested a preference for more precise assays, not that the COC assay was unsuitable. The priority document (Figures 5, 6 and 9) provided evidence that HT reduced colour intensity - for Figure 9 two different assays independently reported a relative colour intensity reduction for the same sample. Therefore the claimed subject-matter validly claimed priority from 15 March 2013.

XIII. The parties' requests relevant to the decision were as follows:

(a) The appellant requested that the opposition division's decision be set aside and the patent be revoked. The appellant further requested that
- the claim sets on file (main request and auxiliary requests 1 and 2) not be admitted into the appeal proceedings;
- documents D28 to D30 be admitted;
- the new argument under Article 83 EPC that a reduction in colour intensity was not made credible by the opposed patent be admitted; and
- the respondent's new line of argument concerning the method used in the application as filed for determining the colour of the antibody-comprising solution and the newly defined objective technical problem not be admitted.

(b) The respondent requested that
- the appeal be dismissed and the patent be maintained on the basis of the main request or on the basis of one of the sets of claims in

accordance with auxiliary requests 1 or 2 as filed by letter dated 5 March 2025;

- the main request and auxiliary request 1 be admitted.

Reasons for the Decision

Main request

Admission – Article 13(1) RPBA

1. The set of claims 1 to 8 in accordance with the main request was first filed as auxiliary request 13 by letter dated 26 November 2024, i.e. prior to the issuance of the board's communication under Article 15(1) RPBA.

The claims are directed to a method of producing a recombinantly produced antibody. Claim 1 differs from claim 1 as granted in that the subject-matter has been restricted (a) to antibodies (thereby excluding antibody fragments), and (b) by specifying that the hypotaurine (HT) is present at a concentration of about 2.0 mM to about 50.0 mM.

The claims of the main request are identical to those of auxiliary request 2 as filed during the opposition proceedings by letter dated 11 June 2021, except for the deletion of dependent claims 9 and 10. The deletion of claims 9 and 10 is self-explanatory and serves to overcome added-matter objections under Article 123(2) EPC.

2. The appellant argued, *inter alia*, that, irrespective of the timing of the filing of the main request,

Article 13(1) RPBA, which applied in this case, required — due to the plural form of "issues" - that all outstanding objections raised by another party in the appeal proceedings be overcome. It would not be enough if only one of several pending objections were overcome. The main request did not *prima facie* overcome the objections regarding sufficiency of disclosure under Article 83 EPC, which had already been raised in the notice of opposition, the statement of grounds of appeal and the board's preliminary opinion pursuant to Article 15(1) RPBA.

3. The board does not interpret Article 13(1) RPBA as requiring an amended claim set to overcome all objections raised by another party in the appeal proceedings. Requiring that all alleged objections be addressed as a precondition for admission would unduly restrict the patent proprietor’s means to defend its case, particularly in the case of a multitude of objections to different claims, the relevance or persuasiveness of which is disputed and thus open for consideration by the board. The appellant's interpretation would require a patent proprietor as a precaution to file permutations of claim sets which address all the objections raised by the opponents individually and in combination in order to anticipate an adverse decision on one or more or possibly all of these objections. Otherwise a patent proprietor would have to overcome all objections irrespective of their merit in order not to lose the patent. A large number of requests would certainly not be in the interests of procedural expediency, but rather burden all parties and the board. Consequently, an amendment cannot necessarily be deemed inadmissible merely because it does not address all objections raised by an opponent.

4. In exercising its discretion under Article 13(1) RPBA, the board must assess whether the amendment *prima facie* at least resolves issues in a manner that promotes procedural economy, without giving rise to new objections. This assessment necessarily depends on the specific circumstances of the case.

5. As explained in point 1. above, the amendments to claim 1 do not introduce new matter: corresponding amendments to the (sole) independent claim 1 had already been filed during the opposition proceedings. The request does not give rise to issues which have not been considered so far. No new discussions were to be expected.

6. Consequently, the board exercised its discretion under Article 13(1) RPBA and admitted the main request into the proceedings.

Admission of documents D28 to D30 - Article 12(4) RPBA

Document D28

7. The cited passage on page 69, right-hand column, first full paragraph in document D28 (published in 2009) teaches that fluorescence is usually much more sensitive than absorbance spectroscopy.

The patent itself already lists the Normalised Intrinsic Fluorescence Tool for Yellow/brown proteins (NIFTY) assay, e.g. in paragraph [0168], as a suitable method to determine colour intensity, especially as a surrogate for colour when culture volume is limited.

8. The argument that different results can be obtained depending on whether one uses the Clarity, Opalescence

and Colouration (COC), Total Colour (TC) or NIFTY assay had already been raised in the appellant's notice of opposition. Moreover, spectrophotometry is only used in the TC but not the COC assay (patent, paragraphs [0166] and [0167]).

9. Thus document D28 was not admitted into the proceedings, as it should have been submitted during the opposition proceedings (Article 12(6) RPBA).

Documents D29 and D30

10. Documents D29 (published in 2018), on fluorescence and UV spectroscopy in food and beverage production, and D30 (published in 2015), practical customer information on fluorescence and UV spectroscopy, are post-published and not considered representative of the skilled person's common general knowledge at the filing date. Thus these documents were not admitted either (Article 12(6) RPBA).

Disclosure of the invention - Article 83 EPC

Method for measuring the colour intensity

11. Sufficiency must be established based on the disclosure in the application as filed and the common general knowledge of the skilled person at the priority or filing date of the patent. Since documents D5 (an intermediate document published in 2013) and D14 (published in 2018) are post-published journal articles by the inventors that do not represent textbook knowledge (see also points 33. to 36. below), they cannot be used to show the skilled person's common general knowledge at the relevant date when assessing sufficiency.

Besides this, the authors of document D5 report on page 1273, right-hand column that results obtained with the TC assay and the NIFTY assay correlate reasonably well with actual COC measurements in the drug substance. Page 1302, right-hand column and Figure 4 of document D14 also report that cultures using the antioxidant additives produced protein compositions with significantly reduced colour, as measured by both NIFTY and TC assays.

12. Neither claim 1 nor any of the other claims specifies the method to be used for determining the colour intensity. Nor is there any requirement for a quantitative determination of colour intensity, but rather a relative assessment, comparing the colour intensity of a composition containing the antibody produced in a cell culture medium having one of the claimed concentrations of HT with the same composition without HT added.

13. To carry out the invention, the skilled person needs only to determine whether there has been a relative reduction in the colour intensity of a composition to which HT was added compared with one with no HT added. The skilled person would use one of the assays mentioned in the patent to measure the colour intensity of a solution and then compare it to another composition using the same assay. The essential point is that the skilled person has an assay at hand to compare the colour intensity of two samples. What matters is not that different assays may yield different absolute values, but that they consistently reflect the same relative relationship, i.e. that the addition of HT results in an observable reduction in colour intensity compared with a control without HT.

14. The patent, in paragraphs [0166] to [0168], provides instructions on three different methods for determining colour intensity: the COC, TC and NIFTY assays. While the patent does not specify which assay was used in the examples, it is clear that the skilled person could use any of the methods described in the patent to determine a relative reduction in colour intensity.

Example 3 reports results from two (unspecified) different colour assays for measuring colour intensity (paragraphs [0027], [0184] and Figure 9), both of which allow for the determination of a relative reduction in colour intensity in a sample to which HT was added compared with the control (no HT added). This makes it clear that the NIFTY assay was not the only method used in the patent's examples and that other methods are also suitable for determining a relative reduction in colour intensity.

15. The COC assay was a standardised, well-known method, as evidenced by document D25, to which the patent refers in paragraph [0166] when describing the method. The assay required by the European Pharmacopoeia D26 (page 3817, right-hand column, "*TESTS*") to determine whether antibody compositions are colourless or slightly coloured is the COC assay set out in document D25.

Document D15 also describes a visual-based assay to detect colour intensity changes in antibody formulations, with discolouration observed upon light exposure. The visual evaluation was conducted comparing the colour of the solution against United States of America Pharmacopeia (USP) colour standards A, H and

water, as outlined on page 3119 under the "Visual Appearance" section.

16. The appellant's argument that not all chromophores may lead to fluorescence does not undermine the reliability of the assays. The data in the patent demonstrate that both the chromophore-based TC assay and the fluorescence-based NIFTY assay reliably detected relative changes in colour intensity in the same samples, as evidenced by Figure 9. The correlation observed between the TC and NIFTY methods suggests that the chromophores responsible for colour also lead to fluorescence. This indicates that the NIFTY assay is a reliable method for measuring colour intensity changes of antibody compositions isolated from cell cultures grown in media supplemented with HT, even if not all chromophores fluoresce.

17. The board considers that, using the methods described in the patent, the skilled person would have been able to determine a relative decrease in colour intensity. If required, a skilled person would also have resorted to a more sensitive method alternative to the COC assay.

The appellant has not demonstrated that the fluorescence-based NIFTY assay (or any of the other methods mentioned in the patent) leads to an incorrect determination of colour intensity or a flawed assessment of the relative reduction in colour intensity.

18. Thus the patent sufficiently discloses methods suitable for determining the relative change in colour intensity for the claimed invention.

Technical effect shown over entire HT concentration range claimed

19. Figure 5 forms the basis for the appellant's argument that there are substantiated doubts regarding the technical effect claimed in the patent. While the reduction in colour intensity observed with 9.16 mM (100%) and 4.58 mM (50%) HT is not disputed, the appellant specifically challenged whether the data point at 2.29 mM (25%) HT demonstrates a statistically significant or credible reduction in colour intensity. According to the appellant, the effect was therefore not convincingly shown across the full scope of the claim, particularly at the lower end of the claimed concentration range.

20. Sufficiency of disclosure within the meaning of Article 83 EPC must be assessed on the basis of the patent as a whole. While Figure 5 is highly relevant, it has to be considered in the context of the description.

21. The patent describes in paragraph [0056] that the presence of reactive oxygen species (ROS), formed through the use of certain media components, may produce oxidised polypeptides which may alter the quality of a protein product, such as colour intensity, which may be particularly significant for polypeptide products that are formulated at any concentration, such as greater than about 1 mg/ml. Based on the described oxidation of proteins by ROS, the addition of even small amounts of an antioxidant to a cell culture medium is expected to scavenge ROS, reduce ROS-mediated protein oxidation, and thereby decrease associated discolouration to a certain extent.

22. Example 1 and Figures 1 and 2 of the patent show that of the antioxidants tested for the ability to reduce colour intensity HT demonstrated the greatest effect. Figure 5 (9.16 mM, 4.58 mM or 2.29 mM HT tested) and Figure 6 (38.85 mM, 25.9 mM or 12.95 mM HT tested) of the patent show a concentration-dependent trend, where increasing amounts of HT are associated with a progressive reduction in colour intensity.

23. According to the brief description of Figure 5 provided in paragraph [0019], on page 6, lines 21 to 26 and in paragraph [0182], on page 41, lines 20 to 25 of the patent, Figure 5 is a graph showing colour intensity of antibody compositions isolated from cell cultures grown in media supplemented with HT. 100%, 50% or 25% indicates basal Media 1 supplemented with 9.16 mM, 4.58 mM or 2.29 mM HT, respectively. Filled circles indicate colour intensity values for cell culture experiments (Example 2). Empty circles indicate colour intensity values for incubation screening experiments (Example 1). Numerical results were normalised to the positive control, where the value for the positive control was set at 0% change in colour intensity. Values lower than 0% indicate reduced colour intensity.

24. In Figure 5, only the mean values and individual data points are clearly identifiable. As there are only two data points for the 25% and 50% HT groups, no meaningful statistical analysis is possible — only a general trend can be observed. The function of the diamond symbols and the upper and lower lines within the diamond symbols is not explained in the patent and cannot be deduced from the data, as they do not appear to correspond to the spacing between the individual data points. Additionally, it is not evident whether these graphical elements are intended to represent

standard deviations, error bars or confidence intervals. Such representations would not be statistically meaningful with only two data points per group. The patent in suit provides no further clarification regarding the content or interpretation of Figure 5.

25. The mean colour intensity reduction observed for the two data points with 2.29 mM (25%) HT is lower than the mean observed for the positive control (0% HT added), indicating that HT at this concentration reduces colour intensity. As far as the variability of results within a test group is concerned, the board considers that a certain variability is to be expected in any, and especially in biological, systems. Given the concentration-dependent trend in colour intensity reduction observed in Figure 5, there is no reason to assume that this effect would not continue at the lower end of the claimed HT concentration range. Even lower concentrations of this antioxidant can reasonably be expected to reduce ROS-mediated oxidation and, consequently, discolouration.

It is also worth noting that the colour intensity values obtained from the incubation screening experiments (Example 1; Figure 5, empty circles) correlated well with the results from cell culture experiments (Example 2; Figure 5, filled circles).

26. Based on the above assessment, the board considers that the patent as a whole provides sufficient information to enable the skilled person, using their common general knowledge, to carry out the claimed invention across the entire range of HT concentrations as claimed. No evidence to the contrary has been provided by the appellant.

27. Thus the claimed invention, specifically in so far as it relates to the effect of reducing the colour intensity of a composition comprising the antibody produced by a cell cultured in the claimed cell culture medium, is considered to be sufficiently disclosed within the meaning of Article 83 EPC.

Antibody concentration in the cell culture medium

28. The board considers that the skilled person would recognise that the need to reduce colour intensity in an antibody composition arises only when the colouration of the composition presents a problem.

The patent addresses this issue by noting that increased colour intensity typically occurs in higher-concentration antibody formulations.
However, this does not exclude the possibility that, for specific antibodies or culture conditions, the problem may arise at lower antibody concentrations.

This is also acknowledged on page 1271, left-hand column, paragraph 2 of document D5, which states that "*Part of the reason for the lack of emphasis in the literature on this quality attribute could be that drug substance concentrations in the past have been relatively low (≤25-50 mg/mL) as most monoclonal antibody drug products have used the intravenous route of administration. At these protein concentrations, observations of significantly colored drug substance or drug product have been relatively rare.*"

In the "worst case", no colouring occurs, but this would fall outside the scope of claim 1, which requires a reduction in colour intensity.

Conclusion on disclosure of the invention

29. Based on the above, the board concludes that the patent discloses the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

Priority – Article 87 EPC

30. The sole objection concerning the priority claim relates to the method for measuring colour intensity, with the appellant arguing that the COC assay disclosed in the priority document was inadequate and that the NIFTY assay used in the patent was not disclosed therein.

31. The priority document explicitly describes the COC assay and states that it is suitable for measuring colour intensity (paragraph [0173]), as referenced in the European Pharmacopoeia (document D25, chapter 2.2.2) and its application to monoclonal antibodies for human use (document D26, page 3817, "*CHARACTERS*" and "*TESTS*").

The fact that the priority document does not include data specifically obtained using the COC assay does not imply that the skilled person would be unable to use it for the claimed invention. Particularly the above-cited entries in the European Pharmacopoeia support the COC being a standard considered suitable for measuring colour intensity changes in antibody formulations.

32. The priority document provides evidence showing that HT reduces colour intensity relative to controls (Figures 5 and 6), and also mentions that the colour

intensity data in Figure 7 were measured using two different (not further defined) assays which both measured a relative reduction in colour intensity due to the presence of HT (paragraph [0188], last 13 lines).
This indicates that the skilled person would understand from the priority document that the COC assay can be used for the claimed invention.

33. The appellant's reliance on documents D5 and D14 is unpersuasive. While these documents discuss certain limitations of the COC assay, they do not establish that it is fundamentally incapable of detecting relative changes in colour intensity. These studies aimed to identify specific components influencing colour intensity, rather than evaluating whether the COC assay could be used to assess relative reductions in colour intensity as required by the claimed invention.

34. Document D14 is a post-published document which is of no relevance to the issue of priority.

Document D5 was published after the claimed priority date but before the filing date of the patent. As such, it is a post-published document and may only be considered as prior art under Article 54(2) EPC if the priority claim is found invalid.
Document D5 states on page 1271, left-hand column, last full paragraph that "*Although the COC color method is commonly used for measuring color, it was impractical to use it in this work as it does not have sufficient resolution or precision for the purposes of these studies. Hence, the color of the samples was measured using two different surrogate assays, and it is shown that these assay results correlate well with COC*

measurements". However, impractical does not mean impossible.

35. There is no evidence on file that performing the claimed invention using the COC assay would be unfeasible.

36. Consequently, the board considers that the priority document enables the skilled person to perform a relative colour intensity measurement, the claimed subject-matter is entitled to the priority date of 15 March 2013, and document D5 is not state of the art pursuant to Article 54(2) EPC.

Further remarks

37. There were no further objections under Articles 123 and 54 EPC. As the main request was found to validly claim priority from 15 March 2013, document D5, the only document identified by the appellant in the statement of grounds of appeal as the closest prior art, does not qualify as state of the art under Article 54(2) EPC. Consequently, the objection of lack of inventive step based on document D5 must fail. Accordingly, the board is of the opinion that none of the grounds for opposition prejudice maintenance of the patent in amended form.

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 as amended in the following version:
Claims:
Claims 1 to 8 of the main request filed on 5 March 2025;
Description:
Paragraphs [0001] to [0187] of the patent specification;
Drawings:
Figures 1 to 10 of the patent specification.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated