



Submission in opposition proceedings

Representative:

HOFFMANN EITLE PATENT- UND RECHTSANWÄLTE PARTMBB
151
Arabellastraße 30
81925 Munich
Germany

Phone: 089/92409-0

Fax: 089/918356

80298 Munich

Germany

Tel. +49(0)89 2399-0 | Fax -4465

P.O. Box 5818

NL-2280 HV Rijswijk

Netherlands

Tel. +31(0)70 340-2040 | Fax -3016

10958 Berlin

Germany

Tel. +49(0)30 25901-0 | Fax -840

- representing the proprietor(s):

Halozyme, Inc.

Proprietor/representative's reference

225 788 m10/ann

The information given below is pertaining to the following patent in opposition proceedings:

Patent No.

EP3760715

Application No.

EP20186922.9

Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)

04 August 2021

Title of the invention

Large-scale production of soluble hyaluronidase

Proprietor of the patent

Halozyme, Inc.

Requests:

- Oral proceedings are hereby requested auxilarily.

Documents attached:

	Description of document	Original file name	Assigned file name
1	Reply of the patent proprietor to the notice(s) of opposition	Response to opposition - 2022-09-29.pdf	OBSO3.pdf
2	Auxiliary request in opposition	AR03 (clean).pdf	AUXREQ-5.pdf
3	Auxiliary request in opposition	AR03 (marked).pdf	AUXREQ-6.pdf
4	Auxiliary request in opposition	AR04 (clean).pdf	AUXREQ-7.pdf
5	Auxiliary request in opposition	AR04 (marked).pdf	AUXREQ-8.pdf
6	Auxiliary request in opposition	AR05 (clean).pdf	AUXREQ-9.pdf
7	Auxiliary request in opposition	AR05 (marked).pdf	AUXREQ-10.pdf

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8	Auxiliary request in opposition	AR06 (clean).pdf	AUXREQ-11.pdf
9	Auxiliary request in opposition	AR06 (marked).pdf	AUXREQ-12.pdf
10	Auxiliary request in opposition	AR07 (clean).pdf	AUXREQ-13.pdf
11	Auxiliary request in opposition	AR07 (marked).pdf	AUXREQ-14.pdf
12	Auxiliary request in opposition	AR01 (clean).pdf	AUXREQ-1.pdf
13	Auxiliary request in opposition	AR01 (marked).pdf	AUXREQ-2.pdf
14	Auxiliary request in opposition	AR02 (clean).pdf	AUXREQ-3.pdf
15	Auxiliary request in opposition	AR02 (marked).pdf	AUXREQ-4.pdf

Evidence filed subsequently:

D08	Other evidence	Declaration by Michael Labarre, Ph.D. original file name: D08 Declaration by Michael LaBarre, Ph.D..PDF attached as: Other-evidence-1.PDF
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Signatures

Place:	Munich
Date:	29 September 2022
Signed by:	/OGLE, James Matthew, PhD/
Association:	HOFFMANN EITL PATENT- UND RECHTSANWÄLTE PARTMBB
Representative name:	James M. Ogle, PhD
Capacity:	(Representative)

225 788 m10/ann



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HOFFMANN EITLE PATENT- UND RECHTSANWÄLTE PARTMBB
151
Arabellastraße 30
81925 Munich
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Phone: 089/92409-0

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Proprietor of the patent

Halozyme, Inc.

Evidence filed subsequently:

D07	Other evidence	Claims allowed by Board in T 1471-16 original file name: D07 Claims allowed by Board in T 1471-16.pdf attached as: Other-evidence-1.pdf
D09	Other evidence	Proprietor's observations of February 17, 2021 original file name: D09 P's observations of Feb. 17, 2021.pdf attached as: Other-evidence-3.pdf
D10	Non-patent literature - article	Furukawa et al., "Effect of culture temperature on a recombinant CHO cell line producing a C-terminal a-amidating enzyme" Cytotechnology, 1998 original file name: D10 Furukawa 1998.pdf attached as: Published-Evidence-1.pdf

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D11	Non-patent literature - article	Moore et al., "Effects of temperature shift on cell cycle, apoptosis and nucleotide pools in CHO cell batch cultures" Cytotechnology, 1997 original file name: D11 Moore 1997.pdf attached as: Published-Evidence-2.pdf
D12	Non-patent literature - article	Kaufmann et al., "Influence of Low Temperature on Productivity, Proteome and Protein Phosphorylation of CHO Cells " Biotechnology and Bioengineering, 1999 original file name: D12 Kaufmann 1999.pdf attached as: Published-Evidence-3.pdf
D13	Non-patent literature - article	Chuppa et al., "Fermentor Temperature as a Tool for Control of High-Density Perfusion Cultures of Mammalian Cells" Biotechnology and Bioengineering, 1997 original file name: D13 Chuppa 1997.pdf attached as: Published-Evidence-4.pdf
D14	Non-patent literature - article	Jahic et al., "Temperature limited fed-batch technique for control of proteolysis in Pichia pastoris bioreactor cultures" Microbial Cell Factories, 2003 original file name: D14 Jahic 2003.pdf attached as: Published-Evidence-5.pdf
D15	Non-patent literature - article	Inan et al., "Optimization of temperature-glycerol-pH conditions for a fed-batch fermentation process for recombinant hookworm (Ancylostoma caninum) anticoagulant peptide (AcAP-5) production by Pichia pastoris" Enzyme Microbial Technology, 1999 original file name: D15 Inan 1999.pdf attached as: Published-Evidence-6.pdf
D16	Non-patent literature - article	Li et al., "Expression of Recombinant Proteins in Pichia Pastoris" Appl. Biochem. Biotechnol., 2007 original file name: D16 Li 2007.pdf attached as: Published-Evidence-7.pdf
D17	Non-patent literature - article	Gupta et al., "Enhanced Expression of the Recombinant Lethal Factor of Bacillus anthracis by Fed-Batch Culture" Biochemical and Biophysical Research Communications, 2001 original file name: D17 Gupta 2001.pdf attached as: Published-Evidence-8.pdf
D18	Non-patent literature - article	Gawande et al., "Optimization of Cyclodextrin Glycosyltransferase Production from Klebsiella pneumoniae AS-22 in Batch, Fed-Batch, and Continuous Cultures" Biotechnol. Prog., 2003 original file name: D18 Gawande 2003.pdf attached as: Published-Evidence-9.pdf
D19	Non-patent literature - article	Yoon et al., "Effect of Low Culture Temperature on Specific Productivity, Transcription Level, and Heterogeneity of Erythropoietin in Chinese Hamster Ovary Cells" Biotechnology and Bioengineering, 2003 original file name: D19 Yoon 2003.pdf attached as: Published-Evidence-10.pdf

D20	Non-patent literature - article	Schatz et al., "Higher Expression of Fab Antibody Fragments in a CHU Cell Line at Reduced Temperature" Biotechnology and Bioengineering, 2003 original file name: D20 Schatz 2003.pdf attached as: Published-Evidence-11.pdf
D21	Non-patent literature - article	Chen et al., "Temperature Shift as a Process Optimization Step for the Production of Pro-urokinase by a Recombinant Chinese Hamster Ovary Cell Line in High-Density Perfusion Culture" Journal of Bioscience and Bioengineering, 2004 original file name: D21 Chen 2004.pdf attached as: Published-Evidence-12.pdf
D22	Non-patent literature - article	Wulhfard et al., "Mild Hypothermia Improves Transient Gene Expression Yields Several Fold in Chinese Hamster Ovary Cells" Biotechnol. Prog., 2008 original file name: D22 Wulhfard 2008.pdf attached as: Published-Evidence-13.pdf
D23	Non-patent literature - article	Dowd et al., "Increased t-PA Yields Using Ultrafiltration of an Inhibitory Product from CHO Fed-Batch Culture" Biotechnol. Prog., 2000 original file name: D23 Dowd 2000.pdf attached as: Published-Evidence-14.pdf
D24	Non-patent literature - article	Gong et al., "Fed-batch culture optimization of a growth-associated hybridoma cell line in chemically defined protein-free media" Cytotechnology, 2006 original file name: D24 Gong 2006.pdf attached as: Published-Evidence-15.pdf
D25	Non-patent literature - article	Bibila et al., "In Pursuit of the Optimal Fed-Batch Process for Monoclonal Antibody Production" Biotechnol. Prog., 1995 original file name: D25 Bibila 1995.pdf attached as: Published-Evidence-16.pdf
D26	Non-patent literature - article	Xie et al., "High Cell Density and High Monoclonal Antibody Production Through Medium Design and Rational Control in a Bioreactor" Biotechnology and Bioengineering, 1996 original file name: D26 Xie 1996.pdf attached as: Published-Evidence-17.pdf
D27	Non-patent literature - article	Thiry et al., "Optimizing scale-up fermentation processes" Trends in Biotechnology, 2002 original file name: D27 Thiry 2002.pdf attached as: Published-Evidence-18.pdf
D28	Non-patent literature - article	Castro et al., "Application of a statistical design to the optimization of culture medium for recombinant interferon-gamma production by Chinese hamster ovary cells" Appl. Microbiol. Biotechnol, 1992 original file name: D28 Castro 1992.pdf attached as: Published-Evidence-19.pdf

D29	Non-patent literature - article	Zhang et al., "Fed-batch culture of hybridoma cells in serum-free medium using an optimized feeding strategy" <i>Journal of Chemical Technology and Biotechnology</i> , 2004 original file name: D29 Zhang 2004.pdf attached as: Published-Evidence-20.pdf
D30	Non-patent literature - article	Rampalli et al., "Insulin Regulates Expression of c-fos and c-jun and Suppresses Apoptosis of Lens Epithelial Cells" <i>Cell Growth and Differentiation</i> , 1995 original file name: D30 Rampalli 1995.pdf attached as: Published-Evidence-21.pdf
D31	Non-patent literature - article	Kang et al., "Insulin can block apoptosis by decreasing oxidative stress via phosphatidylinositol 3-kinase- and extracellular signal-regulated protein kinase-dependent signaling pathways in HepG2 cells" <i>European Journal of Endocrinology</i> , 2003 original file name: D31 Kang 2003.pdf attached as: Published-Evidence-22.pdf
D32	Non-patent literature - article	Tanaka et al., "Insulin prevents apoptosis of external granular layer neurons in rat cerebellar slice cultures" <i>Neuroscience Letters</i> , 1995 original file name: D32 Tanaka 1995.pdf attached as: Published-Evidence-23.pdf
D33	Non-patent literature - article	Johnson et al., "Insulin protects islets from apoptosis via Pdx1 and specific changes in the human islet proteome" <i>Proceedings of the National Academy of Sciences</i> , 2006 original file name: D33 Johnson 2006.pdf attached as: Published-Evidence-24.pdf
D34	Non-patent literature - article	Iida et al., "Insulin Inhibits Apoptosis of Macrophage Cell Line, THP-1 Cells, via Phosphatidylinositol-3-Kinase-Dependent Pathway" <i>Arteriosclerosis, Thrombosis, and Vascular Biology</i> , 2002 original file name: D34 Iida 2002.pdf attached as: Published-Evidence-25.pdf
D35	Non-patent literature - article	Parham et al., "Optimization of transient gene expression in mammalian cells and potential for scale-up using flow electroporation" <i>Cytotechnology</i> , 1998 original file name: D35 Parham 1998.pdf attached as: Published-Evidence-26.pdf
D36	Non-patent literature - article	Hendrick et al., "Increased productivity of recombinant tissular plasminogen activator (t-PA) by butyrate and shift of temperature: a cell cycle phases analysis" <i>Cytotechnology</i> , 2001 original file name: D36 Hendrick 2001.pdf attached as: Published-Evidence-27.pdf
D37	Non-patent literature - article	Sidorenko et al., "Comparison of Metabolic Flux Distributions for MDCK Cell Growth in Glutamine- and Pyruvate-Containing Media" <i>Biotechnol. Prog.</i> , 2008 original file name: D37 Sidorenko 2008.pdf attached as: Published-Evidence-28.pdf

D38	Non-patent literature - article	Neermann et al., "Comparative Analysis of Glucose and Glutamine Metabolism in Transformed Mammalian Cell Lines, Insect and Primary Liver Cells " Journal of Cellular Physiology, 1996 original file name: D38 Neermann 1996.pdf attached as: Published-Evidence-29.pdf
D39	Other evidence	Background to T 1320/13: application as filed underlying T 1320/13 original file name: D39 T 1320-13 - appln as filed.pdf attached as: Other-evidence-4.pdf

Payment

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Annotations

() 1. Remark(Annotate) Remaining documents of the reply will follow in a separate submission.
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Signatures

Place: Munich

Date: 29 September 2022

Signed by: /OGLE, James Matthew, PhD/

Association: HOFFMANN EITLE PATENT- UND RECHTSANWÄLTE PARTMBB

Representative name: OGLE, James Matthew, PhD

Capacity: (Representative)

225 788 m10/ann



HOFFMANN EITLE

HOFFMANN EITLE | Postfach 81 04 20 | 81904 München

European Patent Office

80298 Munich

HOFFMANN EITLE
Patent- und Rechtsanwälte
Partnerschaftsgesellschaft mbB

Arabellastraße 30
81925 München
Deutschland | Germany

T +49. (0)89. 92 409. 0

F +49. (0)89. 91 83 56

pm@hoffmanneitle.com

www.hoffmanneitle.com

Dr. James Ogle
jogle@hoffmanneitle.com

Munich, September 29, 2022

Our Ref.: 225 788 m10/ann

Opposition proceedings concerning

European Patent 3 760 715 B1 / 20 186 922.9

LARGE-SCALE PRODUCTION OF SOLUBLE HYALURONIDASE

On behalf of the Proprietor

**Halozyme, Inc.
11388 Sorrento Valley Road
San Diego, CA 92121 / US**

MÜNCHEN
LONDON
DÜSSELDORF
HAMBURG
MILANO*
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Further to the Opposition Division's communication of May 19, 2022, we herewith provide the Proprietor's response to the opposition against the above-referenced Patent.

1 Requests

1. The Proprietor's Main Request is that the opposition be rejected and the Patent be maintained as granted.
2. Should the Opposition Division not allow the Proprietor's Main Request, it is requested that the Patent be maintained on the basis of one of Auxiliary Requests 1-7 as filed herewith. We file clean and marked-up copies of the Auxiliary Requests, indicating the differences to the claims as granted.
3. The Proprietor also requests the opportunity to file further auxiliary requests in order to address any further matter that may be identified in the course of the opposition proceedings.
4. As a precaution the opportunity is also requested to be allowed, in the interest of procedural efficiency, to combine two or more of the Proprietor's claim requests or amendments made therein, if that is expedient to the progress of the proceedings. The Auxiliary Requests filed by the Proprietor endeavour to address entirely distinct objections raised by the Opponents, and it is not foreseeable which, if any, of those objections in combination could be successful in these proceedings.
5. For example, it is requested if necessary to be allowed to combine AR7, in which the amendment relates to cells, with any of AR1-3 or AR5-6 in which the amendments relate to activities, or with AR4 in which the amendments relate to sequences. Likewise, for example, it is requested if necessary to be allowed to combine AR4 in which the amendments relate to sequences with any of AR1-3 or AR5-6 relating to activities. The opportunity is also requested to combine or delete claims in any of the Proprietor's claim requests, and to adjust the order of the Proprietor's claim requests.
6. Oral proceedings are requested if the Opposition Division does not reject the opposition in written proceedings and prior to any decision by the Opposition Division that is adverse to the Proprietor.

2 Introduction and summary

7. The claims of the Present patent relate to a starting material for the production of soluble human PH20 hyaluronidase (rHuPH20), a “harvested cell culture fluid” (“HCCF”)¹. This HCCF is improved over the prior art in that it contains significantly more active rHuPH20 for purification per ml than was expected to be achievable based on the closest prior art. Claim 1 thus defines that the HCCF contains rHuPH20 activity in the range of “*greater than 5000 and less than or equal to 24,000 units of hyaluronidase activity/mL of cell culture fluid as harvested*”.
8. The Patent describes in detail how to obtain the improved HCCF, i.e., by methods that are discussed and put into practice in the description and Examples of the Patent. Those methods involve a number of different cell culture parameters in combination, which work together to achieve the increase in active rHuPH20 in the HCCF.
9. Decision T 1471/16 of Boards of Appeal 3.3.08 concerned the parent application to the present case. The Main Request considered and allowed by the Board of Appeal in T 1471/16 is filed herewith as **D7**. Claim 1 in T 1471/16 was identical to present claim 1, except that the range of activity was defined as “*greater than 5000 and less than or equal to 18,000 units...*”. The Board of Appeal decided that this “18,000” subject matter met the requirements of Articles 83, 54, 56, 76(1) and 123(2) EPC.
10. Thus, the present opposition is concerned, with subject matter that, to its largest part, has already been considered in detail and found to comply with the requirements of the EPC at second instance, by the Board of Appeal. That subject matter is defined expressly in dependent claim 4 of the present Patent.
11. In the examination of present divisional case, however, it was established that range above 18,000 and up to 24,000 units/ml as defined in present claims 1-3 likewise meets the requirements of the EPC. There was otherwise no difference in subject matter or underlying evidence between the parent (T 1471/16) and divisional case, i.e., the cases were, in substance, otherwise identical in all respects. Dependent claims 2-4 as considered and held allowable by the Board of Appeal in T 1471/16 are identical to dependent claims 5-7 of the present divisional Patent. Therefore, only

¹ The fluid is clarified of cells, cell debris and aggregates, but otherwise “*as harvested*”; see claim 1 and the discussion in T 1471/16.

the present divisional case was taken forward to grant, instead of the parent, because double patenting needed to be avoided.

12. In summary, the opposition is to be rejected, because:

- It is *res iudicata* that a large part of the subject matter to which the Opponent objects – at least the scope of claim 4 – in fact meets the requirements of the EPC. The Opponent has not made out justified objections for any of the remaining subject matter. Moreover, much of the Board's reasoning clearly also applies to the present claims with the somewhat broader activity range.
- Under Article 100(b), the Opponent has not discharged its burden of proof for raising an objection. That is, the Opponent has not raised serious doubts, substantiated by verifiable facts, to support its allegations that the skilled faced any undue burden either (1) regarding various suitable cells for carrying out the invention or (2) the upper portion of the claimed activity range. To the contrary, the disclosure in the Patent is credible and that is only confirmed by **D8** as filed herewith.
- The Opponent's objections under Article 56 EPC are based only on hindsight bias. The Patent demonstrated for the first time, that very significantly higher yields than in the prior art could be achieved, namely above 5000 units/ml. Before this disclosure, the skilled person had no reasonable expectation that the use of such methods could achieve such improved yields. The claims comply with Article 56 EPC. This was the decision of the Board of Appeal in T 1471/16 regarding the lower activity of 5000 units/ml, which evidently applies all the more to HCCF with yet higher activities as claimed (including 24,000 units/ml).
- The claims clearly have basis in original disclosure, fully in line with the existing decision by the Board of Appeal in T 1471/16; the Opponent's objections are based on misinterpretations of both the original disclosure and the established case law, particularly on the basis for range definitions.

13. Thus, no ground of opposition has been made out, and the opposition is to be rejected.

3 Documents filed by the Proprietor

14. The Proprietor files the following documents herewith:
 - D7** Background to T 1471/16: claims assessed and allowed by the Board of Appeal in T 1471/16 on the parent application (claims designated “Main Request” in that decision).
 - D8** Sworn declaration by Michael LaBarre, Ph.D. including confirmatory data
 - D9** Proprietor’s observations of February 17, 2021, first filed in response to the first communication under Article 94(3) EPC in the examination of the application for the present Patent.
 - D10** Furukawa and Ohsusye (1998) Cytotechnology 26:153-164
 - D11** Moore et al. (1997) Cytotechnol. 23:47-54
 - D12** Kaufmann et al. (1999) Biotechnol Bioeng. 63(5):573-582
 - D13** Chuppa et al. (1997) Biotechnol. Bioeng. 55(2):328-338
 - D14** Jahic et al. (2003) Microb Cell Fact. 2(1):6
 - D15** Inan et al. (1999) Enzyme Microbial Technol. 24(7):438-445
 - D16** Li et al. (2007) Appl. Biochem. Biotechnol. 142(2):105-124
 - D17** Gupta et al. (2001) Biochem. Biophys. Res. Commun. 285(4):1025-33
 - D18** Gawande et al. (2003) Biotechnol. Prog. 19(6):1697-1702
 - D19** Yoon et al. (2003) Biotechnol. Bioeng. 82:289-298
 - D20** Schatz et al. (2003) Biotechnol. Bioeng. 84:433-438
 - D21** Chen et al., (2004) J. Biosci. Eng. 97(4):239-243
 - D22** Wulhfard et al. (2008) Biotechnol. Prog. 24(2):458-465
 - D23** Dowd et al. (2000) Biotechnol. Prog. 16(5):786-794
 - D24** Gong et al. (2006) Cytotechnology 52(1):25-38
 - D25** Bibila and Robinson (1995) Biotechnol Prog. 11(1):1-13
 - D26** Xie and Wang (1996) 51(6):725-729
 - D27** Thiry and Cingolani (2002) Trends Biotechnol. 20(3):103-105
 - D28** Castro et al. (1992) Appl. Microbiol. Biotechnol. 38(1):84-90

- D29** Zhang et al. (2004), J. Chem. Technol. Biotechnol. 79:171-181, 172
- D30** Rampalli and Zelenka (1995) Cell Growth and Differentiation 6:945-953
- D31** Kang et al. (2003) Eur. J. Endocrinol. 148:147-155
- D32** Tanaka et al. (1995) Neurosci. Lett. 199:3740
- D33** Johnson et al. (2006) Proc. Natl. Acad. Sci. USA 103:19575-19580
- D34** Iida et al. (2002) Arterioscler Thromb Vasc Biol 22:380-386
- D35** Parham et al. (1998) Cytotechnology 28(1-3):147-55
- D36** Hendrick et al. (2001) Cytotechnology 36(1-3):71-83
- D37** Sidorenko et al. (2008) Biotechnol. Prog. 24(2):311-20;
- D38** Neermann and Wagner (1996) J. Cell. Physiol. 166(1):152-69)
- D39** Background to T 1320/13: application as filed underlying T 1320/13 (EP application no. 08 798 791.3, published as WO 2009/035852)

4 Sufficiency of disclosure (Article 100(b) / Article 83 EPC)

15. The Opponent has presented two lines of argument under Articles 100(b)/83 EPC. One line objects to the entire range of activities in claim 1 (5000 to 24,000 units/ml), alleging that it was an undue burden for the skilled person to obtain suitable cells to produce an HCCF as claimed. The other line of argument is that HCCF having activity greater than 17,000 units per ml *“has not been produced”*, which thus relates only to an upper sub-range of activities in claim 1, >17,000 to 24,000 units/ml. Neither line of argument is well-founded. We will address each in turn.

4.1 Suitable cells are available to the skilled person without undue burden

16. The Opponent initially alleges incorrectly that *“the cells used in the patent to produce this product are not made available to the skilled person”*, and that only a deposit of particular clones or additional disclosure could have allowed the skilled person to produce the claimed HCCF without undue burden (paragraphs 3.2, 3.6 and 3.8 of the opposition). In essence, the Opponent alleges incorrectly that the reproducibility of the claim depends critically on the integration site of the sequence encoding rHuPH20 in the DG44 CHO cell genome, and that a functional integration site is allegedly so rare, unpredictable and critical that this defines the entire invention and

is a so-called “elite event” (paragraphs 3.3 and 3.7 of the opposition). The Opponent also alleges without evidence that “*the point on derivation of the cell lines was not considered by the Board in T 1471/16*”, and “*no consideration was given to whether those particular cell lines were available to the skilled person*”.

17. In fact, the Technical Board in T 1471/16 did already consider the entirety of the disclosure and data in the application in detail, including, of course, the method by which the various cells in the disclosure were obtained, i.e., by transfection. Technical Board 3.3.8 is well aware of the case law in its technical area, biotechnology, and if the present case depended on an “elite event” issue under Article 83 EPC, the Board would have raised it. T 1471/16 clearly shows that the Board did not consider itself bound to the objections raised at first instance and that it was minded to raise more objections of its own motion if they arose (see, e.g., point 6 of the reasons, last words).
18. However, the Board did not raise any such objection regarding availability of suitable cells or “elite events”, because the enablement of the present subject matter does not turn on an “elite event” within the meaning of that strain of case law. Instead, the Board held that the requirements of Article 83 are met. Points 11 and 12 of the reasons of T 1471/16 read as follows:

“11. Examples 4 to 8 of the patent application disclose the culture of several host cell lines - derived from DG44 CHO cells transfected with an expression vector comprising a nucleic acid encoding soluble rHuPH20 (Examples 1 to 3 of the patent application) - in several cell culture media and under various conditions (bioreactor volumes, with/without feeds, feed compositions, etc.). The resulting clarified harvested cell culture fluids comprise soluble rHuHP20 with hyaluronidase activities falling within the range defined in claim 1 (cf. Tables 13 to 15, 18, 20, 22 and 24 of the patent application). Although the highest hyaluronidase activity reported in these examples is 17.000 units/mL (cf. page 47, lines 52 and 53; Example 8 of the patent application), the board is convinced that, in the light of the technical teaching provided by the patent application, a skilled person can obtain a clarified HCCF with the upper-limit activity (18.000 units/mL) without undue burden or the exercise of inventive skill; the necessary increase falls within the levels of variation usually observed when changing the cell culture media and culture conditions.”

12. Therefore, the main request fulfils the requirements of Articles 84 and 83 EPC.

19. This finding that the requirements of Article 83 are met is thus *res iudicata* for the identical subject matter encompassed by present claim 1, i.e., certainly for embodiments up to 18,000 units/ml. Compliance of claim 1 with Article 83 EPC can therefore no longer be called into question for such embodiments. Indeed, this matter, being *res iudicata* by a final decision of a Board of Appeal, cannot even be examined again (see T 1155/13 point 6.2 of the reasons; T 51/08, Catchwords, point 3 of the reasons).
20. As the Board stated in T 51/08, point 3 of the reasons:

"In G 1/97 (OJ EPO 2000, 322, point 2(a) of the reasons) the Enlarged Board of Appeal stated that decisions of the boards of appeal become final as soon as they are issued. This means that the board's ruling becomes binding. This principle of res iudicata is generally accepted in the contracting states and acknowledged by the boards of appeal (see e.g. J 3/95, OJ EPO 1997, 493; T 167/93, OJ EPO 1997, 229). The meaning of the legal term res iudicata is old and well-established: it defines "...a matter finally settled by a Court of competent jurisdiction, rendering that subject matter conclusive as to the rights of the parties and their privies" (see Black's Law Dictionary, 5th Edition). Such a final judgement by a court of competent jurisdiction therefore constitutes an absolute bar to a subsequent legal action involving the same claim, demand or cause of action, and the same parties or privies (T 934/91, OJ EPO 1994, 184, point 3 of the reasons). Once a final judgement has been handed down, subsequent judges who are confronted with a suit that is identical to or substantially the same as the earlier one and between the same parties, are prevented from deciding on it a second time.

3.1 The appellant was of the opinion that the principle of res iudicata could not be applied in the case of a divisional application when a decision on the same subject matter had been taken by a board of appeal in the case of the parent application. The board cannot share this view since it is inherent in the principle of res iudicata that subsequent proceedings should be avoided. The res iudicata maxim is based on the need for an end to all litigation. It provides legal certainty, while taking

account of the general public concern for the settlement of disputes (expedit rei publicae ut finis litium sit). It prohibits parties from challenging what has already been decided (J 3/95, supra, point 6 of the reasons). It must be avoided that the same case is decided twice, possibly with a different outcome. The divisional application gives the applicant, within certain limits, the possibility to pursue the same subject matter as in the parent application. Since the aim of the res iudicata maxim is to avoid relitigation of the same subject matter by the same parties, it must inevitably apply to a divisional application."

21. Thus, to the extent that the Opponent argues that claim 1 is not enabled in the area the claim relating to activities of 5000 to 18,000 units/ml, for alleged reasons relating to the transfection of cells or otherwise, it follows immediately that the Opponent has no arguable case, and that the Opponent's objections under Article 83 are to be rejected.
22. Further, nothing in the Opponent's incorrect line of argument concerning the transfection of cells and the alleged significance of the exact site of integration relates specifically to the subject matter ">18,000 to 24,000 units/ml", which we also discuss further below, as opposed to the range considered specifically by the Technical Board of Appeal. Generally, the Opponent has not substantiated any serious doubts with concrete, new evidence that was not before the Board in T 1471/16 and would relate specifically to the range 18,000 to 24,000 units/ml. Nothing on file calls into question the credibility of that upper subrange. Thus, nothing calls into question the conclusion by the Examining Division for the present Patent that the Board's positive assessment under Article 83 EPC also applies if the claim recites an upper limit of 24,000 units/ml.
23. The Board of Appeal in T 1471/16 was indeed correct, because the exact site of integration and role of chance in the transfection process for expression of the rHuPH20 protein clearly do not have the significance the Opponent alleges. Enablement of the claimed invention without undue burden does not depend on this so as to render this case comparable to the cases underlying the strain of jurisprudence that refers to "elite events". Even if integration of the expression vector is not targeted, there is no evidence to suggest that the success of the method depends so critically on a particular site of insertion that it would generate an undue burden for the skilled person to practise the present invention, taking into account

both the skilled person's common general knowledge and the disclosure in the Patent.

24. The evidence shows that various different cells created in the Examples of the Patent allow the skilled person to practice the claimed invention and renders credible that there is no undue burden for the skilled person to achieve a particular cell line with a particular integration site. See, e.g., Table 13 in Example 4 of the Patent, in which three different cell lines (out of four tested) provide levels of activity falling in the claimed range (see the values 6231, 11064 and 15684, for cells 2E10, 2G10 and 2B2, respectively). Table 14 in Example 5 shows that a further clone, 3E10B, also provided activity in the claimed range (up to 6772 in the conditions of Example 5, see the penultimate line).
25. Thus, while Example 4 indicates that 1st generation "Gen1" cells were further adapted to higher methotrexate levels to produce 2nd generation "Gen2" clones, success in obtaining an HCCF as presently claimed does not depend on the exact identity of the cell line, much less on any specific integration site that can only be obtained as a highly critical "elite event" that defines the entire invention as alleged incorrectly by the Opponent. The methotrexate-based methods taught by the patent for producing such cells were sufficiently well-understood – indeed commonly known – and predictable for the purposes of the skilled person desiring to carry out the subject matter of claim 1, i.e., a purpose that did not depend on any random but unique and critical outcome within the cells, but rather would predictably provide a number of different suitable cells, as has been seen above.
26. Thus, the skilled person provided with the teaching of the Patent and wishing to produce a HCCF as claimed indeed faces no undue burden with regard to the cells, just as there is no undue burden with regard to other aspects. Reproducibility of an HCCF as claimed, across the scope of the claim, does not depend on an "elite event" within the meaning of that strain of case law, rather the skilled person provided with the teaching of Patent will succeed in obtaining the HCCF as claimed credibly and predictably, not merely by chance.
27. Only if there are serious doubts, substantiated by verifiable facts, may a Patent be objected to for lack of sufficient disclosure (see T 19/90, OJ 1990, 476, point 3.3 of the Reasons and the large body of case law cited in the Case Law book, 10th ed. 2022, II-C, 7.1.4, p.417, i.e., T 612/92, T 309/06, T 617/07, T 351/01, T 21/05, T 1188/06, T 884/06 and T 364/06). In the present *inter partes* proceedings, the burden of proof

to establish such doubts lies with the Opponent. The Opponent has, however, not discharged this burden.

28. The Opponent has certainly not provided any convincing and sufficiently specific evidence to substantiate the allegation that, in the present case, for the expression of rHuPH20, the criterion of the “integration site” is so uniquely sensitive and variable that it presents a serious obstacle to the skilled person in the sense of an elite event. No serious doubt has been substantiated.
29. To the contrary, Examples 7 and 8 of the Patent teach the development and combined use of various method parameters other than the exact identity of the cells to achieve the levels of activity in the claimed range and both at small and larger scale. As the Board recognised in T 1471/16 (reason 11), such method parameters relate, *inter alia*, to different culture media, bioreactor volume, presence or absence / timing and number of feeds, feed compositions (see, e.g., Tables 17, 19, 21 and 23). Paragraph [0211] highlights the “*the addition of recombinant human insulin to the bioreactor medium to increase the growth rate and product expression levels*”. See also paragraph [0241]: “*The addition of the feed media was observed to dramatically enhance the production of soluble rHuPH20 in the final stages of production.*”
30. Table 25 provides an overview and comparison of first generation “Gen 1” and improved second generation “Gen 2” production methods. Differences and specific parameters associated with the improved Gen 2 approach are taught in many different aspects than the identity of cells (for which, as has been seen, various CHO cell lines will work):
 - MTX content of the medium at different stages
 - Operating volume of the 36 L spinner flask and rigour by which a number of parameters are controlled (presence of instrumentation for control of pH, dissolved oxygen, sparge and overlay gas flow rate)
 - Final operating volume in bioreactor
 - Insulin content in medium in final bioreactor
 - Media feed volumes
 - Number and content of media feeds

- Technique for filtration of bioreactor cell culture to produce the HCCF

31. As already assessed and decided by the Technical Board in T 1471/16, in view of this technical teaching in the Patent,

“a skilled person can obtain a clarified HCCF with the upper-limit activity (18.000 units/mL) without undue burden or the exercise of inventive skill”

(T 1471/16, point 11 of the reasons).

32. Indeed, we filed herewith **D8**, which contains a sworn declaration by Michael LaBarre, Ph.D. and additional confirmatory data to which Dr. LaBarre refers. **D8**, pages 10-11, in paragraphs 8 (a.) and (b.) and in Tables 3 and 4 further confirms that activity yields in the claimed range were obtained by fourteen different nonhomogeneous pools (mixtures) of various cells that were used instead of individual cell lines, before and without any selection of individual cell lines at all. Activities in the claimed ranges were achieved regardless of whether the cells were derived from GD44 CHO cells (Table 3) or from GS CHO cells (Table 4). Yields measured in these various pools are subject to a certain variability (as reasonably understood by the Board of Appeal in T 1471/16, point 11 of the reasons). But even without any selection, we note immediately that the normal spread is confirmed regularly to include activities beyond 18,000 (23,840 units/ml in Table 3, Pool 3; 18,895 units/ml in Table 4, Pool 2).
33. Thus, the reproducibility and enablement of the invention across the scope of the claims does clearly not depend on a particular cell line or otherwise on an “elite event”. A skilled person can obtain a clarified HCCF with the upper-limit activity of greater than 5000 and up to 24,000 units/mL without undue burden or the exercise of inventive skill.

4.2 No serious doubts substantiated regarding upper activity limits of claim 1-3

34. As is already indicated by the discussion above, the Opponent’s second line of argumentation specifically regarding activities beyond 18,000 units/ml is also clearly unfounded. As has been established during examination of the present divisional case and is discussed in further detail below, the Board’s finding that the subject matter of claim 1 fulfils the requirements of Article 83 EPC can also be extended to 24,000 units/ml, because the teaching of the Patent is also credible for this range. No objection is justified specifically in the upper range of claimed activities.

35. We note that in the above-cited conclusion under Article 83 EPC by the Board in T 1471/16, point 11, the Board continued to reason expressly that

“the necessary increase [i.e., beyond the value of 17.000 that is reported in the experiment of Example 8 of the Patent] falls within the levels of variation usually observed when changing the cell culture media and culture conditions.”

36. This reasonable consideration of the normal levels of experimental variation applies, in essence, likewise to the range beyond 18,000 and to 24,000, as claimed in the Patent (see below).
37. The Opponent argues that in the experimental Examples of the Patent *“HCCF having activity greater than 17,000 units per ml has not been produced”*. But that is not the relevant legal criterion. The correct criterion is whether it is credible, in light of the disclosure in the Patent as a whole and taking into account relevant common general knowledge, that the skilled person can produce HFFC as claimed without undue burden. That is presently clearly the case.
38. Only if there are serious doubts, substantiated by verifiable facts, may a Patent be objected to for lack of sufficient disclosure (see T 19/90, OJ 1990, 476, point 3.3 of the Reasons and the large body of case law cited in the Case Law book, 10th ed. 2022, II-C, 7.1.4, p.417, i.e., T 612/92, T 309/06, T 617/07, T 351/01, T 21/05, T 1188/06, T 884/06 and T 364/06). In *inter partes* proceedings, the burden of proof to establish such doubts lies with the Opponent. The Opponent has not presented any concrete, serious doubts, substantiated by verifiable facts, that would be capable of calling into question whether activities from beyond 18,000 to 24,000 units/ml can be obtained. To the contrary, it is entirely credible that such activities can be achieved.
39. Regarding the Board’s reference in point 11 of the reasons to the levels of variation usually observed in the area of cell culture, we note that the Patent, in different experiments and batches and for various cells and conditions that are all in accordance with the claims, reports values varying from, e.g., 6231 units/ml as the highest value for cells “2E10” in Table 13 (Example 4) to the above-mentioned “17,000 units/ml” of Example 8. See, overall, the diverse levels of activities throughout the claimed range as reported in Tables 13-15, 18, 20, 22 and 24 (as considered and cited by the Board in point 11 of the reasons).

40. These data points alone (taking only the highest per batch) thus span a range of more than 10,000 units/ml. Within Table 13 alone, the batch of “2B2” cells (15,684 units) corresponds to 252 % of (i.e., 2.52-fold) the 2E10 value. The result in Example 8 (17,000 units) corresponds to 273 % of (i.e., 2.52-fold) the 2E10 value. In contrast, the upper limit of the claim is only 41% (1.41-fold) higher than the data point of “17,000”.
41. The scope of the claimed range is also proportionate and justified in view of the scale of the contribution to the prior art (see also below, under Article 56 EPC). Compared to **D1**, which both the Board in T 1471/16 and the present Opponent take as the closest prior art, the data points in the Patent demonstrate that the yield of rHuPH20 activity after harvest can be increased beyond 1000 % (10-fold, i.e., consider the data point 17,000 as compared to the value of 1600 units/ml that was reported in **D1**, the closest prior art in the discussion of Article 56 EPC below). And even the lower endpoint of the claimed range is 313 % of (3.13-fold) the prior-art value 1600 units/ml that was reported in **D1**. The relative variation that is allowed for by “24,000” at the upper endpoint of the claimed range to which the Opponent objects is thus much smaller in proportion compared to the relative increases in activity yields achieved in the Patent over the prior art.
42. Thus, in view of all of the above, and as has been established in further examination leading to the grant of the present Patent, it is evidently credible and justified under Article 83 EPC not only to recite “18,000 units/ml” but also to allow for further variation beyond the highest reported data point. In particular, it is entirely justified under Article 83 EPC to recite the value 24,000 units/ml, which is specifically contemplated and thus called out on page 5, line 30, of the application underlying the Patent. In view of the data point of 17,000 units/ml in Example 8 and the spread and expected usual variation in the results of the cell culture, this value of 24,000 is evidently called out with good, credible reason. In such circumstances, there is no requirement under Article 83 EPC to provide experimental data including exactly the value of 24,000 units/ml. Again, the Opponent has made out no substantiated, serious doubt that could justify an objection to this value.
43. Further, declaration **D8** contains relevant additional data in this regard and further confirms that the above conclusion is indeed correct. **D8** further confirms both that

- activities well beyond 18,000 units/ml are achieved, just as anticipated expressly and reasonably on page 5, lines 29-30 of the application for the Patent, and
 - the levels of normal variation in the measured level of activity between different cell culture batches (either individual lines or pools without selection of cells) produced according to the teaching in the Patent are indeed sufficiently broad to justify a range up to 24,000 in view of the disclosure of both the data point “17,000” and the credible extrapolation to 24,000 on page 5, lines 29-30 of the application for the Patent.
44. See **D8**, paragraph 6, Tables 1 and 2 and Figure 1, which show that values above 18,000 and, e.g., approaching 21,000 units/ml have been achieved in historical clinical (GMP) and commercial batches, or homogeneous pools, of soluble rHuPH20 according to the methods described in the Patent. The clinical (GMP) and commercial batch or pool data of Table 2 and Figure 1 are spread between a minimum of 8,810 U/mL and a maximum of 20,880 U/mL, with a mean of 13,504 U/mL and a 3 σ interval range of 7,645 U/mL for the lower limit and 19,362 U/mL for the upper limit (see **D8**, page 10, Figure 1).
45. Further, see the separate data of **D8**, Tables 3 and 4, where, as mentioned above, for additional pools of mixed cells (without any selection of particular cell lines), exemplary activities as high as 23,840 units/ml (Table 3, Pool 3) and 18,895 units/ml (Table 4, Pool 2) were observed. The value of 23,840 units/ml confirms that the highest value in the dataset of Table 2 and Figure 1 (20,880 U/mL) is certainly not the limit of what the skilled person can achieve without undue burden following the teaching of the Patent.
46. **D8** thus further confirms that values sufficiently higher than 18,000 units/ml and ranging to 24,000 units/ml are reasonably and credibly contemplated on page 5, lines 29-30 of the application for the Patent, and thus duly and fairly need to be taken into account in practice, to allow the present invention reasonably to be defined and covered across its actual practical scope. The degree of variation of activity levels from batch to batch seen in **D8** confirms that, in the technical area of the Patent, it was entirely credible to recite the range now claimed. This is also fully in line with the background of the range of relevant results in Tables 13-15, 18, 20, 22 and 24 as well as the further data point at 17,000 units/ml in Example 8.

47. Merely as a precaution and the avoidance of all possible doubt, we herewith also re-file the following documents from the examination phase:

- As **D9**, the Proprietor's observations of February 17, 2021, which was filed in response to the first communication under Article 94(3) EPC in the examination of the application for the present Patent and in **section 4** focuses on Article 83 EPC in relation to the scope of the range ">5000-24.000 units/ml" as in present claim 1. **D9** further discusses the data in the application and the skilled person's common general knowledge in relation to the skilled person's ability to carry out the invention without undue burden across the scope of the claims specifically including the range ">18,000-24,000".
- As **D10-D38**, the literature references cited and discussed in observations **D9**, which provide evidence of the skilled person's common knowledge and ability to vary conditions and work the presently claimed invention across the scope of the claims.

48. We doubt that **D9-D38** will be necessary to reject the Opposition under Article 100(b) in the circumstances, given existing decision T 1471/16, the Proprietor's further observations herein, the confirmatory data in **D8**, and the failure of the Opponent to discharge its burden of proof under Article 100(b) EPC by raising serious, substantiated doubts in the opposition. However, we nevertheless provide **D9-D38** for completeness and purely as a precaution.

49. In conclusion, the range "*greater than 5000 and less than or equal to 24,000 units/ml*" in claim 1 of the Patent is justified and not objectionable under Articles 100(b) and 83 EPC. Thus, the Opponent's second line of argumentation is also unfounded.

50. The present claims as granted meet the requirements of Article 83 EPC.

5 Inventive step (Articles 100(a) / 56 EPC)

51. The Opponent's arguments under Article 56 EPC are also flawed and are thus to be rejected. While the claimed subject matter is enabled by the teaching in the Patent for the reasons discussed above, prior to the teaching of the present Patent it was not obvious that an HCCF as claimed could be obtained. The activity levels shown to

be possible in are significantly higher than reported in the prior art. Such high activities were unexpected in view of the prior art.

52. The conclusion that certainly the subject matter of claim 4 meets the requirements of Article 56 EPC is *res iudicata* by a Board of Appeal and thus not open to attack or a further decision, because it has already been decided in T 1471/16.
53. The reasons of the Board in T 1471/16 for acknowledging an inventive step do not change in light of the upper limits as recited in claims 1-3.
54. In **D1**, a mere 1600 U/mL was the highest yield of rHuPH20 achieved after cell culture and harvest directly in the clarified HCCF², i.e., in the unconcentrated intermediate that forms the starting material for subsequent concentration and purification of rHuPH20.
55. The clarified HCCF as claimed is significantly improved over that of **D1** in that it reflects a higher yield per cell culture and production process.
56. Starting from this, as decided by the Board in T 1471/16, an appropriate formulation of the objective technical problem is the “provision of an improved starting material (clarified HCCF) for the purification of soluble rHuHP20” (T 1471/16, points 20-21 of the reasons).
57. The different wording used by the Opponent to formulate the objective technical problem is evidently incorrect and indeed misleading in the present case. By trying to deviate from the existing decision on the same matter and introduce the words “*more concentrated*” into the formulation of the technical problem, the Opponent seems to be trying to re-introduce relatively trivial issues and misunderstandings into the present opposition that were in fact already clarified in the appeal proceedings in T 1471/16, which is neither in the interest of procedural economy nor should it be permissible formally. At best the Opponent is choosing language that is ambiguous in context, which seems avoidable on this central point if the case is properly understood and is in any case certainly incorrect when formulating the objective technical problem.

² I.e., in the cell culture fluid “*as harvested*”, merely “*as separated from cells, cell debris and aggregates*” (claim 1)

58. As the Board of Appeal has expressly decided, claim 1 excludes “concentrated HCCF”, thus clearly differentiating claim 1 from the prior art including **D1** (see T 1471/16, point 18.2 of the reasons, also, e.g., points 8, 16 and 17). “Concentration” of an HCCF as claimed would be a downstream procedure applied to the HCCF according to its normal use. The HCCF as claimed is “as harvested” and has thus not been “concentrated”. The concept of “concentrating” the starting material (or of a more or less “concentrated” starting material), as alluded to by the Opponent, is thus irrelevant and a mere distraction by the Opponent in the opposition proceedings.
59. In reality, the relevant point is not that the claimed cell culture fluid is “more concentrated”, but that it reflects a higher yield per cell culture. Considering that claim 1 clearly excludes “concentrated HCCF”, claim 1 relates unambiguously to a starting material that has a higher yield directly “as harvested” than had been achieved in the prior art.
60. As has already been decided by the Board of Appeal in T 1471/16, and as discussed further above under Articles 100(b) and 83 EPC, the objective technical problem of providing an improved clarified HCCF for the purification of soluble rHuHP20 was plausibly solved by the application for the Patent. The Board stated that
- “the results reported in the examples of the patent application, in particular in Examples 4 to 8 (cf. point 11 supra), show that the claimed subject-matter solves this technical problem.”*
- (T 1471/16, point 23 of the reasons).
61. The claimed solution was not obvious in light of the cited prior art, for the reasons as stated by the Board in T 1471/16, point 25 of the reasons). We note immediately that the same assessment and conclusion as in T 1471/16 necessarily applies across the scope of present claims 1-3, because the Board has already acknowledged that an HCCF at the lower endpoint of >5000 units/ml involves an inventive step over **D1**. That decision is significant, because it is the portion of the present claims that is, in relative terms, closest to **D1**.
62. All higher activity yields of present claims 1-3 – all of which are rendered plausible by supporting experimental data as discussed under Articles 100(b) and 83 EPC – must thus also be non-obvious, for the same reasons and “all the more”. That applies not only to the range of “>5000-18,000 units/ml” as in present claim 4, which was

already expressly before the Board, but of course also to the activity values up to 24,000 units/ml according to present claims 1-3.

63. Specifically, the skilled person, starting from **D1**, and having at their disposal a variety of known standard methods, alternatives and routine adaptations including those discussed by the Opponent, e.g., as in **D2**, **D3**, **D5** or **D6**, would not have had any reasonable expectation of success in obtaining an HCCF with activity yields that are improved to the extent that is demonstrated to be possible, made plausible, and thus claimed in the Patent.
64. Specifically, the skilled person would not have had any reasonable expectation of success in obtaining yields in activity "*as harvested*" that are increased beyond 1600 units/ml as far as >5000 units/ml. Even the lower endpoint of 5000 units/ml as claimed is 313 % of (3.13-fold) the yield reported in **D1**. Much less would the skilled person, with knowledge only of **D1** and standard methods as in the remaining cited prior art, but not of the results achieved and disclosed in the present Patent, reasonably have expected that improvements in yields could range yet higher, up to 18,000 units/ml and indeed plausibly up to 24,000 units/ml, i.e., up to 1,500 % of (15-fold) the yield reported in **D1**.
65. The Opponent's elaborations regarding the MTX-based methods of, e.g., **D2** and **D3**, do not change this assessment. We note that the skilled person considering **D1** would of course have been aware that methods as described in **D2** and **D3** on which the Opponent relies were also already available at the time of D1. Nevertheless, nothing in **D1** or elsewhere in the cited prior art suggested that improvements in yield "*as harvested*" to the extent that is shown in the present Patent and as claimed, i.e., of < 5000 units/ml (over 313 % of the result in **D1** and far beyond) can indeed be achieved.
66. Overall, in the circumstances, as decided by the Board in T 1471/16, the claimed subject-matter could only be regarded as obvious with the benefit of hindsight (see point 25 of the reasons). We emphasise once again that this decision by the Board under Article 56 EPC necessarily applies equally and all the more to the higher levels of activity as are now also claimed, having established their compliance with Article 83 EPC.

67. Only the teaching and experimental results provided by the disclosure of the Patent as a whole rendered plausible that the scale of improvements in yield "*as harvested*" as reflected in the present claims can indeed be achieved.
68. The claimed subject matter clearly meets the requirements of Article 56 EPC and the Opponent's attack under Article 100(a) EPC is to be rejected.

6 Basis in the original disclosure (Articles 100(c) / 76(1) / 123(2) EPC)

6.1 Basis for ranges of activities of claims 1-3

69. The Opponent has objected to the ranges of activities of claims 1-3 under Article 100(c) EPC. These ranges, however, have basis in the original disclosure of the parent and divisional applications as filed, for the reasons already considered and decided by the Technical Board in T 1471/16 (point 4 of the reasons). Those reasons apply likewise to present claims 1-3.
70. Specifically, the sentence at page 5, lines 28-30 of the original disclosure provides an activity range that is open at the upper end, namely "*an enzymatic activity of greater than 5000 units/mL*" and, directly in the same sentence, goes on to provide examples of such activities of "*greater than 5000 units/mL*", which thus also disclose subranges. The relevant part of the complete sentence reads

*"... greater than 5000 units/mL, **such as** 10,000, 12,000, 14,000, 16,000, 18,000, 20,000, 22,000 or 24,000 units/mL".*
71. Further, original PCT claim 20 also discloses "*A harvested cell culture fluid, comprising soluble rHuPH20 with an enzymatic activity that is greater than 5000 units/mL*", whereupon immediately subsequent dependent PCT claim 21 further discloses that this activity can be further defined, e.g., as "*about 10,000, 12,000, 14,000, 16,000, 18,000, 20,000, 22,000 or 24,000 units/mL*".
72. In line with the case law (cf. "Case Law of the Boards of Appeal of the EPO", 9th edition 2019, II.E.1.5.2, 455 as cited by the Board in T 1471/16) in this case the combination of the lower-end value of the open-range (5000 units/mL) with one of these exemplified specific activities falling within this range clearly provides a basis for the range "*greater than 5000 and less than or equal to 24,000*".

73. Specifically in the present circumstances, this is clearly all the more correct in view of the form of the original disclosure. If a single sentence in the original disclosure as on page 5 (lines 28-30) refers to a range of “greater than 5000 units/mL, *such as ... 20,000, 22,000 or 24,000 units/mL*”, then this sentence necessarily (directly and unambiguously) discloses all subranges for values above “5000” and up to and including each one of the exemplified values in this range such as “24,000” (inclusive). The first part of the sentence provides the range, beginning above 5000, and the second part of the sentence inevitably completes a disclosure of respective subranges, for each of the exemplified “*such as*” values from within that range, i.e., likewise for both, e.g., “18,000” and “24,000”.
74. This was the reasoning of the Board in T 1471/16 as applied to claim 1 then before it (identical to present claim 4, relating to the value “18,000”), and there indeed is no reasonable doubt that the skilled person would understand the sentence in question in this manner for each one of the values exemplified in the sentence, i.e., also for 20,000, 22,000 and 24,000.
75. In this regard, the Technical Board of Appeal expressly stated the following, i.e., expressly citing broader portions of the relevant sentence:

“In the same sentence, the specific activities of “such as 10.000, 12.000, 14.000, 16.000, 18.000, 20.000, 22.000 or 24.000 units/mL” are disclosed. In line with the case law [...] the combination of the lower-end value of the open-range (5.000 units/mL) with one of the exemplified specific activities falling within this range provides a basis for the closed-range”

(T 1471/16, point 4 of the reasons, emphasis added)

76. The Opponent in paragraph 5.5 of the opposition artificially and incorrectly attempts to re-interpret this use of the word “*exemplified*” by the Technical Board. Referring vaguely to “*other passages of the decision*”, the Opponent alleges in essence that the Board’s choice of the word “*exemplified*” in this reasoning should be taken to mean that the Board was thereby referring only in a very narrow sense to sections of the application that are experimental “Examples”. The Opponent further incorrectly alleges that these experimental Examples in turn mean that, of the values on page 5, lines 29-30, only the value “18,000” of claim 4 could have basis. All of this is plainly incorrect, for a multitude of reasons.

77. The Opponent initially ignores the fact that the phrase “*such as*” in the relevant sentence of the original disclosure is synonymous with phrases such as “*for example*” or “*exemplified by*”, and that Board evidently used the word “*exemplified*” in that context. That is, in the portion following “*such as*”, the basis in the original disclosure directly and unambiguously calls out examples of values of interest within the initially disclosed open-ended range, thus defining subranges of interest. The Board’s reasoning thus applies to each of the values recited and thus exemplified on page 5, lines 29-30.
78. We further note that this is entirely consistent with the further wording of the Board’s reasoning in its overall context. Evidently, when considering the subrange “5000 – 18,000” as recited in the claim then at issue, the Board did not limit its underlying reasoning to the specific value “18,000”. Instead, the Board related its reasoning more generally to “*the combination of the lower-end value of the open-range (5.000 units/mL) with one of the exemplified specific activities falling within this range*”. It was from this reasoning that the Board deduced the finding that the main claim before it had basis. That finding indeed follows logically from the reasoning, because 18,000 is “*one of the exemplified specific activities falling within this range*”. Notably, the Board also did not discuss other portions of the specification than the sentence of page 5, lines 28-30, in order to justify that finding.
79. The Board’s reasoning in this regard was moreover entirely in line with the case law, which has long clarified precisely the issue that the point value forming the end-point of the claimed range does not need to be disclosed “in an example” in the sense of an “experimental” or “worked” example section of a patent application. Rather, precisely rejecting arguments of the type now presented by the Opponent, the case law has clarified all that is required is that the skilled person be able to recognise the value in question “*as a singularity ... within or at the end of a range of possibilities which may mark an end-point for a particular sub-range*”, and thus the basis can also be in the general description (T 612/09, point 17 of the reasons, explaining T 201/83 in the context of more general fact patterns that are based on the general description, not necessarily on “worked” examples, also cited in Case Law book, 10th ed. 2022, II-E, 1.5.1, p.512).
80. The Opponent alleges that its distinct, narrow interpretation of reason 4 in T 1471/16 is supported by the title of the section of the Case Law book as cited by the Board in reason 4 of T 1471/16, “*Forming a range with isolated value taken from example*”

(section II-E, 1.5.2, in the 9th ed. 2019, p.455). The Opponent superficially overinterprets and indeed misinterprets the word “*example*” in that title just as it misinterprets the Board’s reasoning and the word “*exemplified*” in T 1471/16. In fact, that title in the Case Law book is clearly no more than a broad and general indication of jurisprudence that is mentioned and summarised in the section –that title is necessarily only a most general “summary of summaries”.

81. Indeed, on closer review, the reference to this jurisprudence and section of the Case Law book immediately disqualifies the Opponent’s present objections, because this section of the Case Law book expressly makes clear that, while various cases that are collected together in the section were simultaneously concerned with the separate issue of isolation of a point value from an experimental example, the Boards have clarified precisely that for a point value to form an endpoint of a range, it is not necessary for the point value to relate specifically to an experimental example. The cited passage of the Case Law book expressly states the following (II-E, 1.5.2, in the 9th ed. 2019, p.455):

*“In T 612/09 the board considered that in the case underlying decision T 201/83 the fact that the value was disclosed in an example [emphasis added³] was insofar of relevance as the board had first to establish that the value disclosed in the context of an example could be considered separately from the other features disclosed in the example. However, the board in T 612/09 **could not derive from decision T 201/83 the requirement that the value on which a sub-range was to be based had necessarily to be disclosed in an example. Rather** it appeared that what was required was that for the skilled person **the value had to be recognisable as a singularity**, as in decision T 201/83, **within or at the end of a range of possibilities which may mark an end-point for a particular sub-range.**”*

82. The Board was evidently aware of this when the Board expressly cited this passage of the Case Law book as part of its reasoning concerning the sentence of pages 5, lines 29-30 of the original disclosure.

³ The phrase “*in an example*” (as opposed to, e.g., “*as an example*”), i.e., use of the preposition “*in*” as opposed to “*as*”, as well as the general context, indicates that here reference is being made to a standard section of a patent application that is typically termed “example” (in the sense of a “worked example”), as opposed to an “example” in a more general sense, which may simply be a mention of a typical value, which has thus also “exemplified”.

83. Of course, as already discussed above in connection with the phrase “*such as*” in the original disclosure, a mention of a typical or representative value that falls within a broader range in the general description is also “*exemplified*” in a more general sense of the word. In light of all the circumstances, i.e., including the case law and corresponding passage of the Case Law book that the Board expressly cited, the Board thus evidently used the word “*exemplified*” only in this more general sense.
84. The Opponent’s reasoning and interpretation of the existing Appeal Board decision T 1471/16 is thus evidently incorrect.
85. Any “*other passages of the decision*”, on which the Opponent wishes to reply for its incorrect re-interpretation of point 4 of the reasons, are irrelevant to the Board’s reasons for finding compliance with Articles 76(1) and 123(2) EPC. In “*other passages*” of its decision, the Board was concerned neither with the relevant basis on page 5 of the original application, nor was the Board in “*other passages*” concerned with the same legal criteria as in point 4 of the reasons.
86. In fact, the only “*other passage*” of the decision that the Opponent refers to concretely is point 11 of the reasons, which concern Article 83 EPC. That passage of the Board’s reasoning does not support the Opponent’s allegations under Articles 76(1) and 123(2) EPC in the least.
87. Initially, contrary to what the Opponent’s arguments suggest, the Board in point 11 of the reasons does not use the term “*exemplified*”. Thus, not even a purely linguistic link between points 4 and 11 of the reasons exists in this regard.
88. Further, in the absence of any clearer explanation in the decision, the Board in point 4 cannot reasonably be assumed to have been cross-referring to any considerations under Article 83 EPC of point 11 of the reasons. In point 4, the Board had not yet discussed such considerations under Article 83 EPC at all – they follow only later in the decision in point 11.
89. Further, the Opponent’s individual arguments are inconsistent in substance with the Opponent’s proposition that the Board’s considerations under Article 83 in point 11 of the reasons could somehow be relevant to the separate assessment under Articles 76(1) and 123(2) EPC. Initially, the experimental Example 8 of the Patent with which the Board was concerned in point 11 of the reasons does not contain any reference to the value “18,000”, i.e., the feature the Board was concerned with in point 4 of

the reasons. Unlike the straightforward mention of “18,000” in the sentence bridging pages 5 and 6 of the description, Example 8 refers to the distinct value “17,000”, i.e., one particular experimental result. Also for this reason, considering the standard of disclosure of Articles 76(1) and 123(2) EPC, the Board in point 4 of the reasons cannot reasonably simply be assumed “silently” to have had experimental Example 8 and reasoning pertaining to Article 83 EPC in mind, as the Opponent alleges in essence.

90. Indeed, only point 11 of the reasons is concerned with the criteria of Article 83 EPC. That is, unlike point 4 of the decision, point 11 is concerned with the question of whether the experimental result of “17,000”, in the further context of the entire disclosure in the Patent, renders credible the distinct, and reasonably broader subject matter of the claims, or whether there are serious doubts, substantiated by verifiable facts, that might justify an objection under Article 83. These criteria are entirely distinct from the legal assessment with which the Board was concerned in point 4 of the reasons under Articles 76(1) and 123(2) EPC. The Opponent falls into grave legal error by attempting to combine the two passages of the Board’s reasoning into a self-serving interpretation of point 4 of the reasons to construct a flawed added matter objection.
91. For the avoidance of doubt, we further note that, even the Opponent’s dubious approach, in their attempt to modify the actual textual basis on page 6 of the application, of applying criteria of Article 83 to the assessment of basis under Articles 76(1) and 123(2) EPC does not change the conclusion that the ranges of present claims 1-3 have good basis. In the circumstances of the case, the Board in reason 11 of T 1471/16 when assessing Article 83 EPC, having considered the complete teaching in the application including the experimental data, found that this teaching (i.e., including but not limited to the value 17,000 units/ml of Example 8⁴) did render credible the broader subject matter “>5000-18,000”, and thus in the sense of Article 83 EPC certainly supported that range. As discussed in more detail above, that same reasoning and conclusion under Article 83 EPC in fact and in substance applies equally to the range “>5000-24,000”. As discussed, that range is also credible based on the content of the application for the Patent overall, that credibility is further confirmed by experimental data, and no serious doubts to the contrary have been

⁴ The Board highlighted Example 8 at page 47, lines 52 and 53 of the related publication EP 2 674 487 A2; i.e., page 44, lines 6-7 in paragraph [0241] of the present Patent and page 101, lines 22-23 of the underlying original disclosure.

made out by the Opponent. Thus, merely for the sake of argument and completeness, even if the Opposition Division ever considered following the Opponent's approach of applying criteria of Article 83 to the assessment of basis under Articles 76(1) and 123(2) EPC, then this would only confirm the conclusion that the range "<5000-24,000" has basis.

92. The Opponent has further argued that the selection of an upper limit of 20,000, 22,000 or 24,000 units/ml in the present case is akin to the situation from T 1320/13. That is incorrect, though, because the two disclosures on which the appellant in T 1320/13 wished to rely in combination as basis for the claimed range were completely disjunct in the application as filed. The application as filed underlying T 1320/13 is filed herewith for the OD's ease of reference as **D39**.
93. The broader range in case T 1320/13 was disclosed in original claim 5 on page 40 of **D39**. The claims as filed made no mention of the individual point values on which the appellant relied. The list of point values that the appellant wished to combine with the broader range was found on page 6 of the application (line 12), completely separately from any concept of a range as claimed. As the Board in T 1320/13 explained⁵, that list contained "*no pointers to a particular combination of ratio values.*"
94. That is not comparable to the sentence on page 5, lines 28-30 of the present application, which is a single disclosure of both a basic, open-ended range and example values that are expressly disclosed in the same sentence because they fall within that range. In contrast to the disjunct disclosure in T 1320/13 / **D39**, the single sentence on page 5, lines 28-30 of the present application expressly links the example values to the range by the term "*such as*".⁶ That clearly applies to all example values in that sentence, including 24,000, 22,000 and 20,000. The Opponent is thus mistaken to argue that T 1320/13 supports an added matter attack against present claims 1-3. To the contrary, the key differences between T 1320/13 and the present case regarding the nature of the disclosure in the applications in question in each case only underline that present claims 1-3 do have basis.
95. Finally, the separate listing of values from page 5, lines 29-30 in claim 6 also does not support the Opponent's argument. The Opponent alleges that "*it would be*

⁵ Apparently mistakenly referring to "page 5" instead of "page 6".

⁶ The direct dependency of PCT claim 21 from PCT claim 20 also provides such a direct link, which was evidently missing in T 1320/13 / **D39**.

inconsistent for these values to provide basis for both endpoints of the ranges in claims 1-3, and the individual activity values in granted claim 6". But the fact that claim 6 has basis is in no way inconsistent with the considerations above, because, even if the subranges have basis as discussed above, the individual endpoints are of course clearly also disclosed in page 5, lines 29-30. The Board considered the same claim in T 1471/16 (then claim 3) alongside the subrange recited in claim 4 (then claim 1), and evidently also saw no inconsistency of the type alleged by the Opponent.

96. Thus, none of the Opponent's arguments are well-founded. Claims 1-3 clearly find basis in the original disclosure just as claim 4 does, which has already been decided by the Board of Appeal in T 1471/16 (point 4 of the reasons).

6.2 Basis for rHuPH20 amino acid sequences of claims 1 and 5

97. The Opponent also alleges incorrectly that the rHuPH20 amino acid sequences specified in claim 1 and claim 5 add matter.
98. Initially, the definitions of the sequences to which the Opponent objects in this regard are *res iudicata* by the Board of Appeal in T 1471/16 (it defines claims 1 and 2 as examined and decided upon by the Board of Appeal) and is thus not open to an attack aiming to undo that decision. The Board of Appeal in T 1471/16 was concerned with exactly the same claim language and original disclosure as the Opponent now wishes to make the subject of the present proceedings. As discussed above in the context of Article 83 EPC, however, as a matter of general legal principle, the same issue must not be examined and decided twice, to avoid the possibility of conflicts and legal uncertainty. Thus, an issue that has already been decided at the Appeal Board level in a parent application cannot be unravelled again in a divisional application at first instance in the hope of obtaining a different, conflicting decision on the same issue.
99. The Opponent alleges that the present issues were not discussed in the Board's decision in T 1471/16, "*as they do not appear to have been considered in the examining division's decision that was under appeal*". The Board in T 1471/16, however, made expressly clear that it was not limited to matters considered in the examining division's decision that was under appeal, but that it was concerned with reviewing fundamentally whether the subject matter complied with the EPC, and was entirely prepared to raise objections of its own motion if there should be any issue

(see T 1571/16, e.g., under Articles 76(1) and 123(2) EPC, point 6 of the reasons *in fine*).

100. Moreover, the Opponent's arguments are ill-founded. They are once again based on a self-serving misinterpretation of the original disclosure. The Opponent's convoluted analysis of various polypeptide variants according to page 8, lines 19-26 of the original disclosure is not relevant to the definition of the rHuPH20 amino acid sequences in claim 1, because page 8, line 27 initially clearly discloses that "*other variants*" are also included in the umbrella term "*soluble rHuPH20*", and then in that context page 8, lines 29-31 expressly discloses "*other variants*", including variants with 96% or more sequence identity to SEQ ID NO:4 as claimed. Page 8, line 26 also expressly discloses polypeptides having the sequence of SEQ ID NOS:4-9, as claimed in claim 5.
101. In particular, the Opponent's discussion of whether the sequence is "*encoded by the cell*" or expressed such that it is "*present in the culture medium*" is entirely artificial and misguided, because, evidently, a polypeptide cannot be present in the culture medium if it is not ultimately encoded by the cell that expresses the polypeptide. No added matter arises in this regard. Claims 1 and 5 clearly specify polypeptides that have straightforward basis in the application as filed.
102. The clarification that sequence identity is determined over the length of the whole sequence does not present the skilled person with any new information in light of, e.g., page 14, line 11, of the original disclosure. The same applies regarding the recitation of variants having 96 % identity with SEQ ID NO:4 in the context of the remaining features of the claim, including the recited activity range, which is evidently central to the invention and a preferred feature and likewise cannot realistically generate new information.
103. None of claims 1-3 or 5 presents the skilled person with any new information that the skilled person cannot derive directly and unambiguously from the original disclosure.

7 Conclusion on the Opponent's submissions

104. The Opposition lacks merit and is to be rejected.

8 Auxiliary claim requests

105. Purely as a precaution, in case the Proprietor's Main Request should not be allowed, the following Auxiliary Requests (ARs) are also submitted:

8.1 Auxiliary Request 1

106. In AR1, claim 1 is limited to 22,000 units/ml (granted claim 2). This amendment is filed as a precaution in view of the Opponent's objection under Article 100(b) EPC alleging that the endpoint of 24,000 is not enabled. The range to 22,000 units/ml is clearly credibly enabled, for the same reasons as have already been set out above with respect to the Main Request.

8.2 Auxiliary Request 2

107. In AR2, claim 1 is limited to 20,000 units/ml (granted claim 3). This amendment is filed as a precaution in view of the Opponent's objection under Article 100(b) EPC alleging that the endpoints of 24,000 and 22,000 are not enabled. The range to 20,000 units/ml is clearly credibly enabled, for the same reasons as have already been set out above with respect to the Main Request.

8.3 Auxiliary Request 3

108. In AR3, claim 1 is limited to 18,000 units/ml (granted claim 4). All four claims in AR3 are thus exactly as examined and allowed by the Board in T 1471/16. This amendment is filed as a precaution in view of the Opponent's objections under Articles 100(b) and 100(c) EPC, alleging that endpoints above 18,000 are not enabled and/or not disclosed. The claims meet the requirements of the EPC for the reasons given by the Board of Appeal in T 1471/16.

8.4 Auxiliary Request 4

109. In AR4, claim 1 is limited to recite the sequences of granted claim 5. This claim is also in a form exactly as allowed by the Board in T 1471/16 (there: dependent claim 2).

This amendment is filed as a precaution in view of the Opponent's objections to the sequences according to claim 1 as granted under 100(c) EPC. The sequences of granted claim 5 have clear basis on page 8, lines 13 and 26 of the original disclosure. The significance of these sequences as rHuPH20 sequences of reference in the original disclosure is also clearly highlighted on page 9, lines 24, 26 and 29 of the original disclosure, as well as on page 36, line 22, and page 39, line 4.

8.5 Auxiliary Request 5

110. In AR5, claim 1 is limited to recite activities as disclosed on page 5, lines 29-30, of the original disclosure ("*10,000, 12,000, 14,000, 16,000, 18,000, 20,000, 22,000 or 24,000 units/mL*"). Claims 2-4 have been amended accordingly, with the same basis, and claim 6 as granted has been deleted for consistency.-This amendment is filed as a precaution in view of the Opponent's objections to the ranges of activities as recited in claim 1 as granted under 100(c) EPC.

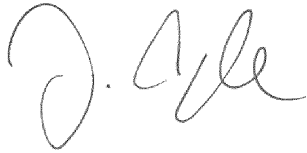
8.6 Auxiliary Request 6

111. In AR6, claim 1 is limited to recite the activities of granted claim 6. This claim is also in a form exactly as allowed by the Board in T 1471/16 (there: dependent claim 3). This amendment is filed as a precaution in view of the Opponent's objections under Articles 100(b) and 100(c) EPC, alleging that endpoints above 18,000 are not enabled and/or not disclosed, and the Opponent's objections to the ranges of activities as recited in claim 1 as granted under 100(c) EPC. The activities as recited in claim 1 of AR6 have express basis on page 5, lines 29-30, of the original disclosure. The activities are enabled for the reasons given by the Board in T 1471/16, point 11 of the reasons.

8.7 Auxiliary Request 7

112. In AR7, claim 1 is limited to recite that the cells that encode soluble human PH20 are DG44 CHO cells (granted claim 7), as in dependent claim 4 as allowed by the Board in T 1471/16. This amendment is filed as a precaution in view of the Opponent's objections under Article 100(b), alleging that it would be an undue burden for the skilled person to identify suitable cells to carry out the invention. The claims of AR7 reciting DG44 CHO cells are thus enabled for the reasons given by the Board in T 1471/16, point 11 of the reasons. The Patent contains ample teaching rendering credible that the skilled person can carry out the invention using DG44 CHO cells (Examples 1-8, as discussed herein above, in T 1471/16 and in **D9**), further taking into

account the evidence of the skilled person's relevant common general knowledge on file and as discussed in **D9**.

A handwritten signature in black ink, appearing to read 'J. Ogle'. The signature is fluid and cursive, with a large initial 'J' and a stylized 'Ogle'.

OGLE, James Matthew, PhD
European Patent Attorney
Hoffmann Eitle PartmbB
Association No. 151

Enc. Documents D7-D39
New Main Request and Auxiliary Requests 1-7. (clean and marked up copies)