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Leonard, Thomas Charles
Kilburn & Strode LLP
Lacon London
84 Theobalds Road
London WC1X 8NL
ROYAUME UNI

Formalities officer
Maier, Dagmar

Date
23.07.2025

Reference O238764EP	OPPO 02	Application No./Patent No. 23191930.9 - 1111 / 4269578
Applicant/Proprietor Halozyme, Inc.		

BRIEF COMMUNICATION

Subject: ☐ Your letter of
☐ Our telephone conversation of
☐ Communication of
☐

Enclosure(s): ☒ Letter from the proprietor of the patent of 17.07.2025
☐ Letter from the opponent of
☐ Copy (copies)

Communication:

All annexes to the letter as well as the consolidated list of all opposition citations are available for inspection via the European Patent Register at www.epo.org/register. Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (OJ EPO 2022, A28).



For the Opposition Division



☐ **Registered letter**
EPO Form 2911O 04.22 (18/07/25)

page 1 of 1



Letter accompanying subsequently filed items

Representative:

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

Phone: 089-92409-0

80298 Munich
Germany
Tel. +49(0)89 2399-0

P.O. Box 5818
2280 HV Rijswijk
Netherlands
Tel. +31(0)70 340-2040

10958 Berlin
Germany
Tel. +49(0)30 25901-0

The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number and/or Patent number

EP23191930.9 - EP4269578

Applicant's or representative's reference

257443_m10/m30/liw

Name of represented party

Halozyme, Inc.

	Description of document	Original file name	Assigned file name
1	Reply to notice of opposition	Response to opposition 2025-07-17_clean.pdf	OBSO3.pdf
2	Other document	D16 Declaration of Anna-Maria Putnam.pdf	OTHER-1.pdf
3	Other document	D17 Declaration Michael LaBarre.pdf	OTHER-2.pdf
4	Other document	D18 Decision Board of Appeal T 1471-16-3308.pdf	OTHER-3.pdf
5	Other document	D19 Preliminary opinion in opposition against EP 3 760 715.pdf	OTHER-4.pdf
6	Separate auxiliary request document	ARs 1-7_clean.pdf	AUXREQ-1.pdf
7	Separate auxiliary request document	ARs 1-7_marked.pdf	AUXREQ-2.pdf
8	Other document	Annex A - AR overview 2025-07-17.pdf	OTHER-5.pdf

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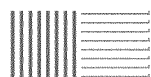
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1. Remark (Annotate)

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Place:	Munich
Date:	17 July 2025
Signed by:	/OGLE, James Matthew, PhD/
Association:	HOFFMANN EITLE PATENT- UND RECHTSANWÄLTE PARTMBB
Representative name:	OGLE, James Matthew, PhD
Capacity:	Representative
Function of person signing:	Representative



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, July 17, 2025

Our Ref.: 257 443 m10/m30/liw

Opposition proceedings concerning

European Patent 4 269 578 B1 / 23 191 930.9

SOLUBLE HYALURONIDASE COMPOSITION

On behalf of the Proprietor

**Halozyme, Inc.
12390 El Camino Real
San Diego, CA 92130 / US**

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Table of contents

1	Requests.....	3
2	Introduction and overview of the Proprietor's reply	4
3	Documents filed by the Proprietor.....	6
4	Claim interpretation: product-by-process claim format	6
5	Basis in the original disclosure (Articles 100(c) / 76(1) / 123(2) EPC)	9
5.1	The feature " <i>composition comprising a mixture of polypeptides</i> "	9
5.2	The feature " <i>mixture comprising the polypeptides set forth in SEQ ID NOs: 4-8</i> "	10
5.3	The feature " <i>wherein the composition is obtainable by the following method</i> ", ...	11
5.4	No unallowable intermediate generalisation	12
6	Novelty (Articles 100(a) / 54 EPC)	13
6.1	The Proprietor has demonstrated that the product as such is novel	15
6.1.1	Evidence in the Patent demonstrates that the product as such is novel	15
6.1.2	Evidence in D16 demonstrates that the product as such is novel	22
6.2	The opponents have not discharged their burden of proof for their allegations.....	25
7	Inventive step (Articles 100(a) / 56 EPC)	29
7.1	Problem-solution approach.....	31
7.2	Opponents' elaborations on table [0564] in D3 are not relevant.....	35
7.3	Opponents' remaining allegations are also not relevant	38
8	Sufficiency of disclosure (Articles 100(b) / 83 EPC).....	41
8.1	The skilled person can obtain the claimed composition without undue burden	41
8.2	Suitable cells are available to the skilled person without undue burden	43
8.3	Patent provides sufficient guidance to obtain the mixture as claimed.....	48
8.4	The claims comply with Art. 83 EPC	50
9	Conclusion on the Opponents' submissions.....	50
10	Auxiliary claim requests	51
10.1	Auxiliary Request 1	51
10.2	Auxiliary Request 2	51
10.3	Auxiliary Request 3	52
10.4	Auxiliary Request 4	52
10.5	Auxiliary Request 5	53
10.6	Auxiliary Requests 6 and 7	56

Further to the Opposition Division's communication of March 17, 2025, we herewith provide the Proprietor's response to the oppositions against the above-referenced Patent.

1 Requests

1. The Proprietor's Main Request is that the oppositions 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 (ARs) 1-95 as filed herewith, of which ARs 1-7 contain distinct individual amendments, and the remaining requests merely represent combinations of those same amendments. We file clean and marked-up copies of the ARs, 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 adjust the order of the Auxiliary Requests, to be allowed to combine or delete claims in any of the Proprietor's present claim requests, and/or to file further auxiliary requests.
5. Oral proceedings are requested if the Opposition Division does not reject the oppositions in written proceedings and prior to any decision by the Opposition Division that is adverse to the Proprietor.

2 Introduction and overview of the Proprietor's reply

6. The claims of the present Patent are product-by-process claims to a composition comprising a mixture of rHuPH20 polypeptides, wherein the mixture is obtainable by a method that is specifically defined by eight steps a) to h). The steps set out requirements for culture conditions, harvesting and purification.
7. Under **Article 100(c) EPC**, the Opponent's objections are based on misinterpretations of both the original disclosure and the established case law. The claims clearly have basis in original disclosure.
8. The **usual interpretation of product-by-process claims applies**, i.e., the claims are to the claimed composition as such, albeit that the composition is required to have technical features imparted to it by the process steps. In the present case, the structural characteristics and functional properties imparted on the claimed composition by the recited process render the claimed composition as such both novel and inventive.
9. Under **Article 100(a) EPC**, the Proprietor has demonstrated that the claimed composition is distinct from the prior art, in that the recited process imparts a distinctive molecular "fingerprint" on the composition. The Proprietor has also demonstrated that the claimed composition is unexpectedly improved over the prior art, in that it contains a significantly increased proportion of structurally and functionally intact, active rHuPH20 species (as opposed to inactive aggregated and hydrolysed species) than was achievable based on the closest prior art, i.e., an earlier production process mentioned in **D3** (US2004/0268425). The Proprietor has demonstrated these differences to the prior art based on the Patent, additional evidence filed during examination (**D6**) and further additional evidence filed herewith (**D16**).
10. The opponents' objections under Article 54 EPC are based in essence only on unsubstantiated allegations and hypotheses rather than direct and unambiguous disclosures. The opponents thus fail to discharge burden of proof that they carry in these opposition proceedings when alleging a lack of novelty over **D3** or **D4**.
11. By way of background to the invention and the prior art, **D3** (US2004/0268425) is an earlier patent application by the Proprietor and describes a distinct rHuPH20 composition that was produced by a preliminary production process ("generation 1" process, i.e., "Gen1" herein) on a small scale. The present Patent describes the

results of years of subsequent, careful further work that led to the presently claimed, improved composition. This composition is a successful commercial product.

12. The Patent describes and puts into practice how the improved composition can be obtained by means of a process as recited in claim 1. The process involves a number of different cell culture parameters in combination, which work together (i.e., synergistically) to produce the improved rHuPH20 composition (production process “generation 2”, i.e., “Gen2” herein).
13. The changes to the production process leading to the improved composition were not obvious. The same applies to the resulting composition as such, as claimed. Its structural differences and advantageous properties compared to the composition of **D3** provide a nonobvious solution to the separate technical problem of providing an improved hyaluronidase composition.
14. Moreover, these advantages are obtained only as a result of the non-obvious, unexpectedly advantageous changes to the process of the prior art. Board of Appeal decision **T 1471/16** has already decided that a composition as such resulting from the inventive production process according to claim 1 is also non-obvious.
15. The structural differences to the prior art that result from the production process as recited in claim 1 are thus not the result of an arbitrary variation; rather they are the result of an inventive step. The Opponent’s objections under Article 56 EPC are based only on hindsight knowledge of the present invention. Without such knowledge, it would not have been obvious to produce any composition having the distinctive molecular “fingerprint” of the presently claimed compositions, let alone the higher content in active molecular species compared to the prior art, without knowledge of the disclosure in the present Patent.
16. Under **Article 100(b) EPC**, the Opponents have also not discharged their burden of proof. No serious doubts, substantiated by verifiable facts, have been raised as to whether the skilled person could, without undue burden, obtain an rHuPH20 composition as claimed. To the contrary, the disclosure in the Patent is credible and enables the skilled person to carry out the invention as claimed. **D16** and **D17** filed herewith only further confirm that.
17. Thus, no ground of opposition has been made out, and the opposition is to be rejected.

3 Documents filed by the Proprietor

18. The Proprietor files the following documents herewith:

D16 Sworn declaration by Anna Maria Hays Putnam, Ph.D, including confirmatory data

D17 Sworn declaration by Michael LaBarre, Ph.D., including confirmatory data

D18 T 1471/16: Board of Appeal decision on an earlier application in this patent family

D19 Opposition Division's preliminary opinion on the subsequently withdrawn opposition against EP 3 760 715

4 Claim interpretation: product-by-process claim format

19. The claimed compositions are defined in part by structural features (SEQ ID NOS: 4-8) and in part by a process of production, i.e., in the product-by-process format. In view of the specific nature of the claimed invention, this is an appropriate format in the present case, in accordance with the long-established case law of the Boards of Appeal on product-by-process claims.

20. Both oppositions repeatedly confuse fundamental principles concerning the nature, subject matter, scope and patentability of product-by-process claims – flawed allegations are made in this connection under various aspects and headings. We thus initially set out the established law and practice concerning the interpretation of product-by-process claims.

21. Product-by-process claims are interpreted as claims to products as such, but the product is also limited by the technical product features that are imparted to the product as a result of the process by which it is produced. Taking account of any such imparted technical product features, it is the product as such that must fulfil the requirements for patentability.

22. The product-by-process claims is appropriate if the products themselves fulfil the requirements for patentability and there is no other information available in the application which could have enabled the applicant to define the product satisfactorily by reference to its composition, structure or some other testable

parameter (see, e.g., **T 150/82**, OJ 1984, 309, r.10, and its citation as the foundation of the established case law in **CLBA10**¹, II.A.7.1, and the express endorsement of **T 150/82** by the Enlarged Board of Appeal in **G 2/12**, IV(5) [page 35] along with five other foundational decisions applying these same basic criteria, **T 219/83**, **T 248/85**, **T 148/87**, **T 320/87** and **T 129/88**.

23. Generally, the established case law and practice acknowledges that the criterion of impossibility of achieving a satisfactory definition (solely) in terms of composition, structure or other testable parameter is satisfied – and thus that a definition in terms of a production process is appropriate – in cases of complex compositions involving a certain degree of structural heterogeneity and variation, and in which, from the perspective of the skilled person, it is particularly the choice of the production process that imparts the characteristic properties to the product. That is typically the case in technical areas concerning compositions of complex biological products or other polymers, including pharmaceutical preparations of proteins having novel and inventive product features that cannot be adequately defined by structural or parameter features alone (see, e.g., **T 130/90**, or **T 148/87**).
24. The nature of the present invention falls precisely within this case group, in which the product-by-process claims is appropriate to allow for a satisfactory definition of the invention.
25. Contrary to the opponents’ allegations, the product-by-process claim format is appropriate in the present case, because the process imparts a number of different properties on the product, each of which is affected by an extent of batch-to-batch variation. As will be shown herein, this variation is not merely limited to the relative abundances of SEQ ID NO: 4-8. Overall, is it clearly impossible to define a composition according to the present invention satisfactorily using a regular product claim format.
26. In its consideration of a “harvest cell culture fluid” (“HCCF”) intermediate product of the “Gen2” process as mentioned in step (g) of the present case, the Board of Appeal in **T 1471/16 (D18)** as filed herewith, point 10 of the reasons) has expressly confirmed that the definition of a product of the “Gen2” process in the product-by-process claim format is “fair and appropriate” in the present case:

¹ Herein, “CLBA10” refers to the book “Case Law of the Boards of Appeal”, 10th ed., 2022.

“10. In the board's view, the combination of features related to the method of production of the HCCF with the structural and functional features of the relevant component comprised in said HCCF, i.e. the soluble rHuHP20, define the claimed HCCF in a clear and unambiguous manner. In view of the whole content of the patent application, the claimed HCCF is seen as an intermediate product for use in the further purification of soluble rHuHP20. Taking into account the large number of possible cell culture media and culture conditions, the definition of such an intermediate product by a combination of features related to the method of production with (functional and structural) features of the relevant component comprised in said product is considered to be fair and appropriate by the board and in line with the case law (cf. "Case Law", supra, II.A.7.3, 318).”

27. As will be seen in more detail below, the present case is fully in line with principal requirements for the patentability of product-by-process claims as established in the case law. For example, in **T 205/83** relating to polymers, it was held that *“novelty of a product-by-process claim can be established only if evidence is provided that modification of the process parameters results in other products”* and that *“it is sufficient for this purpose”* to show that *“distinct differences exist in the properties of the products”* (see **T 205/83**, headnote). As a further example, in **T 748/98**, novelty of a product-by-process claim was accepted on the grounds that there were *“marked differences between the process steps of claim 1 [and the prior art]”*, which *“necessarily lead to the conclusion that the products of claim 1 are not identical to the products obtainable by wording according to [the prior art]”* (see **T 748/98**, reason 7).
28. As a general point, we note that any allegations by the opponents regarding the appropriateness or clarity of the claim format relate to Article 84 EPC and are thus not covered by any ground for opposition.
29. As demonstrated in detail below, the claimed compositions as such are directly and unambiguously – and reproducibly – distinguishable from any compositions according to the cited prior art in terms of structure and (functional) properties, involve an inventive step, find basis in the original disclosure and can be made without undue burden by the skilled person. The claims of the Main Request thus

satisfy the relevant criteria under the grounds of opposition. Any other alleged criteria brought forward by the opponents are irrelevant.

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

30. As noted by O1, except for the reproduction of originally disclosed claim language at the end of the divisional specifications, the divisional application as filed for the present Patent is identical to the earlier divisional applications and to the root (PCT) application as originally filed. Unless indicated otherwise, herein the term “Original Disclosure” thus refers to the identical content of the root (PCT) and divisional applications.
31. Claim 1 is directly and unambiguously derivable from the Original Disclosure. In particular, original claim 1 of the PCT application as filed provides verbatim basis for the method steps a) – h). The remaining features of claim 1 are also directly and unambiguously derivable from the Original Disclosure, as we will show in the following discussion.

5.1 The feature “*composition comprising a mixture of polypeptides*”

32. Regarding the feature “*composition comprising a mixture of polypeptides...*”, O2 has alleged incorrectly that the Original Disclosure does not disclose a composition comprising soluble rHuPH20 ([057] of O2’s opposition). In this context, O2 paradoxically refers to several passages in the description that refer to compositions provided by the invention – as presently claimed. Amongst passages cited by O2, for example, page 20, line 30, refers to “*compositions provided herein*”, and page 20, line 17, defines that “*as used herein, a composition refers to any mixture*”.
33. The Original Disclosure also provides basis for a product produced in cell culture that is a mixture of polypeptides, see, e.g., page 8, lines 24-26:

“As produced in the culture medium there is heterogeneity at the C-terminus so that the product includes a mixture of species that can include one or more of SEQ ID NOS 4-9 in various abundance”.

34. The Original Disclosure clearly discloses a product that comprises a mixture of polypeptides. Any such mixture is also directly and unambiguously a “*composition*”. That is the case both as a matter of fact and expressly according to the application

(e.g., as cited above from page 20, line 17: “*a composition refers to any mixture*”). The term “*composition*” in claim 1 does not present the skilled person with any new information that cannot be derived directly and unambiguously from the Original Disclosure.

5.2 The feature “*mixture comprising the polypeptides set forth in SEQ ID NOs: 4-8*”

35. The Opponents have alleged incorrectly that the Original Disclosure provides basis only for a mixture of polypeptides comprising the polypeptides set forth in SEQ ID NOs: 4-9, and not SEQ ID NOs: 4-8. This objection is also unfounded.
36. While, e.g., the above-cited passage on page 8, lines 24-26, of the Original Disclosure refers to SEQ ID NOs 4-9, this same passage provides direct and unambiguous basis also for a mixture of polypeptides that does not need to comprise each of those species: “...*the product includes a mixture of species that can include one or more of SEQ ID NOs 4-9 in various abundance*” (emphasis added). Thus, the Original Disclosure expressly foresees that one or more of those species are optional.
37. Against this background, the reference in claim 1 to SEQ ID NOs: 4-8 instead of SEQ ID NOs: 4-9 does not add matter, for the following reasons.
38. Firstly, according to established case law (**CLBA10**, II-E, 1.6.3 on “*Deletion of elements from lists*”), a shrinking of a generic group of compounds is not objectionable under Art. 123(2) EPC when it does not result in singling out of a particular combination of specific definitions which was not disclosed originally, but rather maintains the remaining subject-matter as a generic group of compounds differing from the original group only by its smaller size, without generating any invention that was originally disclosed (i.e., does not provide any technical contribution to the originally disclosed subject-matter).
39. Both the Original Disclosure in so far as it concerns a list of SEQ ID NOs: 4, 5, 6, 7, 8 and/or 9 and the reference in claim 1 to a mixture “*comprising SEQ ID NOs: 4-8*” constitute a generic group of compounds. Merely shrinking the list by removing reference to one of the compounds does not lead to a particular combination of specific meanings of the respective residues that was not disclosed originally, nor does it generate a new invention. This is especially so considering that the Original Disclosure explicitly discloses that fewer than all of SEQ ID NOs: 4-9 may be present in the mixture.

40. Secondly, the application in any case singles out mixtures of polypeptides from which precisely SEQ ID NO: 9 is absent, but SEQ ID NO: 4-8 are present. Such mixtures are disclosed, e.g., on page 36, line 18 - page 37, line 2, and on page 39, lines 3-16. These disclosures confirm that, against the background of the generalised disclosure of “*a mixture of species that can include one or more of SEQ ID NOs 4-9*” on page 8, lines 24-26, a reference to a mixture of species comprising SEQ ID NO: 4-8 cannot add matter.
41. In this connection, the disclosures of mixtures of species comprising, precisely, SEQ ID NO: 4-8 and not SEQ ID NO: 9 on page 36, line 18 - page 37, line 2, and on page 39, lines 3-16 also perform the role of a “pointer” within the meaning of the established case law of the EPO Boards of Appeal on selections and combinations.
42. In conclusion, a “*mixture comprising the polypeptides set forth in SEQ ID NOs: 4-8*” is directly and unambiguously derivable from the Original Disclosure when appreciated as a whole.

5.3 The feature “*wherein the composition is obtainable by the following method*”,

43. O2 has alleged that there is no original disclosure of a product obtainable by the method steps recited in the claims and no indication that the invention includes a product. O2 states that “*the disclosure of a method of producing the product does not amount to a direct and unambiguous disclosure of the product per se*” (O2’s opposition, paragraph [0038]). These allegations are manifestly incorrect.
44. The Original Disclosure as a whole is entirely focussed on disclosing a production process for rHuPH20, and thus evidently also discloses rHuPH20 obtainable by this production process.
45. Furthermore, the Original Disclosure also explicitly refers to a product (which is a “*Composition comprising a mixture...*” in line with claim 1), including in the above cited passage at page 8, lines 24-26, which includes the statement “*As produced in the culture medium there is heterogeneity at the C-terminus so that the product includes a mixture of species [...]*” (emphasis added).
46. O2’s incorrect allegation that the product-by-process claim format adds matter fails to appreciate that the product-by-process claim format is, precisely, the appropriate format for the composition at the heart of the invention that is disclosed in the Patent.

5.4 No unallowable intermediate generalisation

47. O1 also alleges that the combination of recombinant expression in “*Chinese Hamster Ovary (CHO) cells*” with the “*mixture comprising the polypeptides set forth in SEQ ID NOs: 4-8*” in claim 1 is an intermediate generalisation that adds matter. O1 incorrectly alleges that a mixture of polypeptides comprising SEQ ID NOs: 4-8 is inextricably linked to production by specific cell lines, as well as to exact values for numerical proportions allowing for no variation.
48. Supposedly in support of this allegation, paradoxically, O1 refers to disclosures in the application as filed providing exemplary productions of compositions comprising mixtures of SEQ ID NO: 4-8 by two different cell lines, using two different methods and resulting in different numerical proportions. This alone shows that O1’s allegation of an “inextricable link” specifically between the feature “*mixture comprising the polypeptides set forth in SEQ ID NOs: 4-8*” and specific cell lines and exact numerical proportions without variation is unfounded.
49. Production of the claimed composition comprising a mixture of SEQ ID NOs: 4-8 and obtainable from a process as claimed is, as a matter of scientific fact, not inextricably linked to one specific cell line. This can be seen in the data in the application as filed.
50. For example, in Table 13 in Example 4 of the Original Disclosure, four different cell lines (out of four tested) obtained by adaptation to higher methotrexate levels all provide improved levels of enzyme activity relative to the activity achieved in cell cultures using the 3D35M cells, on which O2 relies as a point of comparison. See in this regard the values 6231 U/ml, 3831 U/ml, 11064 U/ml and 15684 U/ml, for cells 2E10, 1G11, 2G10 and 2B2, respectively, relative to harvest titers consistently under 2000 U/ml for 3D35M cells in Table 3. Table 14 in Example 5 shows that a further clone, 3E10B, also provided improved levels of enzyme activity in cell cultures relative to levels of enzyme activity in cell cultures using 3D35M cells (up to 6772 U/ml in the conditions of Example 5, see the penultimate line). In this regard, see also below in section 8.2 concerning sufficiency of disclosure (“*Suitable cells are available to the skilled person without undue burden*”).
51. For the avoidance of doubt, the fact that the claimed composition comprising a mixture of SEQ ID NOs: 4-8 and obtainable from a process as claimed is not

inextricably linked to one specific cell line is further confirmed by post-filing data submitted herewith, e.g., as **D17**.²

52. Moreover, contrary to O1's allegation, the "*mixture of species that can include one or more of SEQ ID NOS 4-9*" (e.g., page 8, lines 24-26, of the Original Disclosure) is in fact disclosed directly and unambiguously in the context of production in CHO cells, on the same page of the application as filed. The relevant passage in its entirety provides (page 8, lines 19-26):

"As used herein, soluble rHuPH20 refers to a soluble form of human PH20 that is recombinantly expressed in Chinese Hamster Ovary (CHO) cells. Soluble rHuPH20 is encoded by nucleic acid that includes the signal sequence and is set forth in SEQ ID NO:47. Also included are DNA molecules that are allelic variants thereof and other soluble variants. The nucleic acid encoding soluble rHuPH20 is expressed in CHO cells which secrete the mature polypeptide. As produced in the culture medium there is heterogeneity at the C-terminus so that the product includes a mixture of species that can include one or more of SEQ ID NOS. 4-9 in various abundance." (emphasis added)

53. In conclusion, nothing in claim 1 presents the skilled person with any new information that cannot be derived directly and unambiguously from the Original Disclosure. Claim 1 finds basis in the Original Disclosure, and the Opponents' arguments under Article 100(c) EPC are to be rejected.
54. We note that the Opponents have not attacked any terms of the dependent claims under Article 100(c) EPC. O2 refers merely to their dependency on claim 1 without formulating any separate attack. Indeed, all claims as granted, including the dependent claims, comply with Articles 76(1) and 123(2) EPC.

6 Novelty (Articles 100(a) / 54 EPC)

55. The Opponents' novelty objections in view of **D3** and **D4** are based, in essence, on the incorrect allegation that a composition obtainable by the process as defined in

² For the avoidance of all possible doubt, to the extent that the proportions of different polypeptide sequences within the mixture of a composition as claimed are distinct from mixtures in the prior art, these differences are the result of the differences to the prior art in the recited method steps. These aspects are discussed below in the context of Articles 54 and 56.

present claim 1 cannot be distinguished from compositions obtainable by the process disclosed in **D3**. That is incorrect.

56. By the evidence discussed herein and filed herewith, the Proprietor demonstrates that a composition obtainable by the process recited in claim 1 is structurally and functionally distinct, as such, from any composition that is derivable from **D3**.
57. **D3** describes the Proprietor's earlier research on an expression construct for producing a soluble human hyaluronidase. **D3** demonstrated that a particular truncated coding sequence allows for the recombinant expression of human hyaluronidase in a form that is soluble and enzymatically active. The focus of **D3** is on the identification of the truncated coding sequence that allows for such expression. In terms of a production process in cell culture, **D3** only contains a single proof-of-concept study, on a small scale. The Proprietor also refers to this earlier work as the generation 1 or "Gen1" production process. Such a process does not directly and unambiguously result in a product that is also obtainable by the process of present claim 1.
58. The purpose of the work disclosed in the present Patent was to develop improvements beyond **D3**, both to the production process and to the resulting hyaluronidase composition as such, generally with a view to using the composition in pharmaceutical applications.
59. Example 3B of the Patent (which is not, as such, prior art) describes how simply scaling up the small-scale "Gen 1" process of **D3** to a somewhat larger scale did not significantly improve the hyaluronidase composition.
60. The Patent then shows that several aspects of the production process had to be modified such that they act together (i.e., synergistically) to provide an improved hyaluronidase composition. The Proprietor also refers to this improved process for producing soluble rHuPH20 as the generation 2 or "Gen2" production process.
61. The method steps recited in claim 1 are different from the production process disclosed in **D3** and result in a hyaluronidase composition that is demonstrably distinct from any composition disclosed in **D3** or obtainable by the small-scale "Gen 1" method that is disclosed in **D3**. The same distinction applies *vis-à-vis* **D4**, for which O1 has acknowledged that it "*describes essentially the same process as in D3*" (O1's opposition, page 27, paragraph 2).

6.1 The Proprietor has demonstrated that the product as such is novel

62. A product-by-process claim meets the criteria of Article 54 EPC if the product as such is novel. In this assessment, account is taken of all structural and functional features of the product, including any that result from the process of production that is recited in the claim. If those features are not present in prior art products, they confer novelty. According to the EPO Guidelines for Examination, F-IV, 4.12., for novelty of a product-by-process claim *“the question to be answered is whether the product under consideration is identical to known products”*, i.e., just as for any other product claim.
63. During the examination of the application for the Patent, the Proprietor has already provided evidence based on the data in the Patent and further post-filing data that the claimed composition is not identical to known products, due to structural features that are conferred upon the claimed composition by the method of production to which the claim refers. The Proprietor thus established convincingly that the claimed compositions as such are novel, and the Patent was granted on that basis.
64. The Opponents have, in their oppositions, not discharged the burden of proof that they then carry when making an allegation of lack of novelty, i.e., to show convincingly that a hyaluronidase composition of the prior art directly and unambiguously falls within the scope of claim 1.
65. Moreover, in reply to the oppositions, we herewith also file **D16**, which contains a sworn declaration by Anna-Maria Hays Putnam, Ph.D., and provides yet further, confirmatory evidence that compositions obtainable by the process of present claim 1 are demonstrably, verifiably and reproducibly distinct from compositions obtainable by the process of **D3** (or **D4**).
66. In the following sections, we discuss the evidence from the Patent and from post-filing data.

6.1.1 Evidence in the Patent demonstrates that the product as such is novel

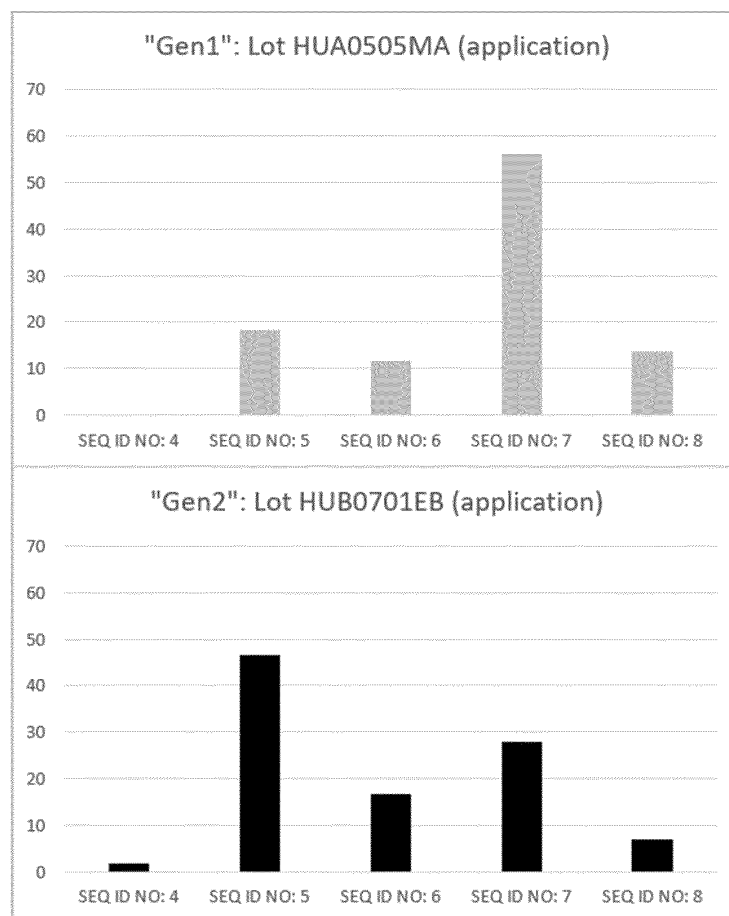
67. Regarding evidence in the Patent, we note that the Patent clearly refers to the relationship between the invention described therein and the earlier invention in **D3**. The Original Disclosure explicitly refers to **D3** on page 1, in line 21, stating that the present application *“is related to”* (page 1, line 6 of the application) *inter alia* **D3**.

68. As previously mentioned, **D3** is concerned with the identification of a coding sequence for an expression construct that allows for recombinant expression of a soluble and active form of a human hyaluronidase. The single short paragraph concerning a production process in **D3** describes a mere proof-of-concept study on a small-scale 5 L culture, using a method that employs a different feeding strategy from that reflected in the present claims.
69. It is clear that the focus of the present Patent is significantly different from **D3**, e.g., in view of the “Overview” section in the Patent ([0077]), which refers to “large scale production of soluble hyaluronidases”, a topic on which **D3** is silent.
70. The Patent includes the only production example from **D3** as Comparative Example 3A, which is entitled “5 L Bioreactor Process”. Comparative Example 3A is the first part of Comparative Example 3, which carries the overall title “Production and Purification of Gen1 soluble rHuPH20”. Example 3A is included in the present Patent as a comparative starting point for a sequence of further developments. In Example 3B (which is not, as such, part of the prior art although it is an embodiment of the Gen1 process), the Patent shows that, even when the Gen1 process of **D3** is scaled up, that alone does not achieve significant improvements over the method and composition of **D3**. Many further modifications to the production process were needed to enable production of a truly improved hyaluronidase composition.
71. Examples 7 and 8 of the Patent, e.g., describe how the production process was further modified to arrive at the improved “Gen2” process. In particular, the “Gen2” process according to the present claims differs from the process disclosed in **D3**, e.g., in the following culturing parameters:
- The claimed “Gen2” production process of the present Patent is a large-scale production process requiring at least 100 litres of cell culture. In contrast, the “Gen1” production process in [0588] of **D3** only discloses a 5 L culture.
 - In the claimed “Gen2” production process of the present Patent, the culture is fed four times with four distinct feed media. In contrast, in the “Gen1” production process in [0588] of **D3**, the culture is fed three times with two distinct feed media.
 - Each of the four feed media used in the claimed “Gen2” production process is different from any of the two feed media used in the “Gen1” production

process in [0588] of **D3**. The feed media used in the claimed “Gen2” production process contain more ingredients that are included in different amounts in each feeding step. Amounts of glucose, L-alanyl-L-glutamine, yeast extract and human insulin or sodium butyrate are specifically varied relative to amounts used in preceding steps. In contrast, the feed media used in the “Gen1” production process in [0588] of **D3** contain fewer ingredients, specifically, only CD CHO, glucose and sodium butyrate, and the amounts used in certain feeds had not yet been altered specifically for soluble rHuPH20 production.

- In the claimed “Gen2” production process of the present Patent, the temperature of the culture is gradually lowered at three specifically defined time points. In contrast, in the “Gen1” production process in [0588] of **D3**, the temperature is not lowered at any point.
- In the claimed “Gen2” production process of the present Patent, the cells are cultured until viability drops below at least 50%. In contrast, in the “Gen1” production process in [0588] of **D3**, the cells are harvested when viability is still above 50% (the Table under [0588] of **D3** shows a viability of 52% as the last measured value).

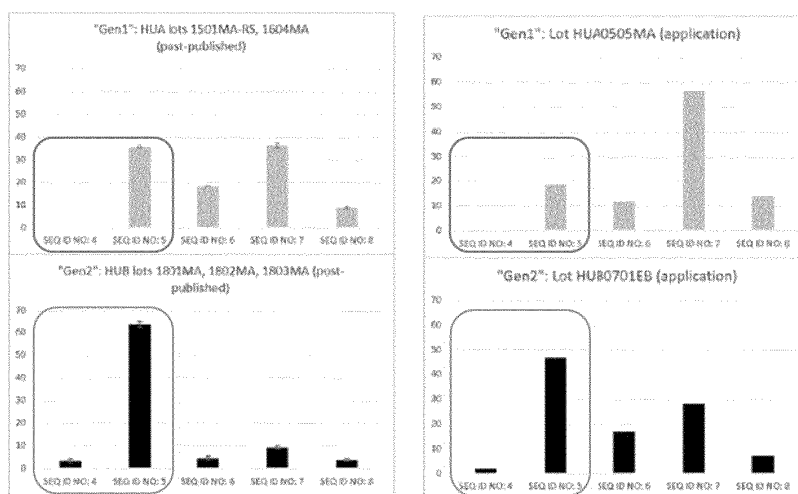
72. It is unambiguously clear that the process parameters of the “Gen2” rHuPH20 production process have been substantially modified compared to the process parameters of the “Gen1” rHuPH20 production process of **D3**. Allegations by the opponents that the method recited in the present claims is not substantially different from that of **D3** should be rejected.
73. The Patent also provides evidence that this modified “Gen2” rHuPH20 production process results in a distinct product. In particular, the Examples in the Patent include comparative data showing results obtained both with the earlier “Gen1” production process and with the “Gen2” production process according to the Patent. For example, the data shown in Tables 27 and 28 of the Patent show that the relative abundance of SEQ ID NOs: 4-8 within the obtained mixture of species is different. For clarity and illustration, the numerical data of Tables 27 and 28 on page 111 of the application as filed are represented in two following bar graphs:



74. The bar labelled SEQ ID NO: 4 indicates the abundance of the longest polypeptide species consisting of 447 amino acids. SEQ ID NOs 5-8 are successively shortened by one amino acid. SEQ ID NO: 8 thus indicates the abundance of the polypeptide species consisting of 443 amino acids. The data in Tables 27 and 28 of the Patent thus show that the "Gen1" method predominantly produces shorter polypeptide species, wherein SEQ ID NO: 7 is the most abundant. In contrast, the "Gen2" method recited in the present claims predominantly produces longer polypeptide species, with SEQ ID NO: 5 as the most abundant.
75. In other words, the method recited in the present claims results in a structurally different product (composition) having a higher proportion of longer polypeptide species. The data shown above reflect this in that, in the composition obtainable by the "Gen2" process, –

- the proportion of the longest polypeptide (SEQ ID NO: 4) has increased from 0.2% to 1.9%;
 - the proportion of the second longest polypeptide (SEQ ID NO: 5) has increased from 18.4% to 46.7%;
 - the proportion of the third longest polypeptide (SEQ ID NO: 6) has increased from 11.8% to 16.7%;
 - the proportion of the second shortest polypeptide (SEQ ID NO: 7) has decreased from 56.1% to 27.8%; and
 - the proportion of the shortest polypeptide (SEQ ID NO: 8) has decreased from 13.6% to 6.9%.
76. Thus, the disclosure in the Patent, including its experimental data, demonstrates that (i) the Gen2 process of production is different from the Gen1 process in **D3**, and (ii) the product resulting from the Gen2 method is structurally different (has a different composition) than products obtainable by the Gen1 methods according to **D3** and the present application.
77. This alone is sufficient to establish novelty of the product as such: the product is evidently distinct, and the difference is also identifiable, e.g., by analytical methods disclosed in the Patent. Neither of the opponents has discharged their burden of providing any evidence leading to a different conclusion.
78. Both O1 and O2 have alleged incorrectly that these data from the Patent, which were already submitted during prosecution, do not constitute appropriate evidence that the rHuPH20 compositions obtainable by the method recited in the Patent claims are structurally different from rHuPH20 compositions obtainable by the “Gen1” production process. The analyses presented by O1 and O2 in this regard are, however, flawed, as we will explain below, and are thus not suitable for discrediting the evidence provided by the Proprietor.
79. O1’s attack is incorrect from the outset, e.g., in that O1 artificially constructs an argument based on, in O1’s own words, “*hypothetical compositions*” (page 23, last paragraph of O1’s opposition) having SEQ ID NOs: 4-8 in certain abundances. These “*hypothetical compositions*”, however, have nothing to do with any real soluble rHuPH20 compositions obtainable by either the “Gen1” or “Gen2” production processes.

80. O1's attack is further fundamentally flawed in that it treats the above-described evidence regarding the relative abundances of SEQ ID NOs: 4-8 as if they were features explicitly required by the claims. Taken together with an allegation that there would be extreme effects of batch-to-batch variation, which is entirely unsupported by any data, O1 fabricates an argument alleging that the claimed compositions of the Patent are not novel because there is a theoretical possibility of certain compositions existing that may have particular features that are not even recited in the claims. The only evidence submitted for this allegation are O1's made up "*hypothetical compositions*".
81. The test for novelty, however, is whether there is an actual (direct and unambiguous) disclosure in the state of the art that is identical to the claimed invention. Clearly, O1's attack based on a non-existent "*hypothetical*" disclosure of features that are not even required in the claims must fail.
82. O2's attack in this regard is similarly flawed, because it alleges that the evidence provided by the Proprietor shows "*nothing more than batch-to-batch variation*" (page 19, [070] of O2's opposition), but fails to provide any evidence for this allegation. The only apparent attempt to substantiate their allegation in this regard is the below statement in [069] of O2's opposition, which, however, entirely misconstrues data submitted by the Proprietor during examination:
- "[...] the "Gen1" post-filing data (top left) and the "Gen2" data (bottom right) **look far more alike** than both the two top panels, which show the proportions of the polypeptides produced by the "Gen1" method, and the two bottom panels, which show the proportions of the polypeptides produced by the "Gen2" method"* (emphasis added)
83. Clearly "*look far more alike*" is not the appropriate legal standard for assessing novelty. In any case, O2's allegation merely misconstrues what is actually shown in the Proprietor's data. For ease of reference, an annotated version of the arrangement of data as relied on by O2 in their opposition is reproduced below:



84. For example, regarding the higher abundance of longer polypeptide species, the “Gen1” post-published data (top left) and the “Gen2” data in the Patent (bottom right) to which O2 refers do not “*look far more alike*”. To the contrary, all these data still support that the “Gen2” compositions have a higher abundance of longer polypeptide species than the “Gen1” compositions:

- In “Gen2” (post-published), bottom left: the longer polypeptides with the sequences of SEQ ID NOs: 4 and 5 together make up, on average, approximately **65%** of the polypeptide species in the composition
- In “Gen2” (Patent), bottom right: the longer polypeptides with the sequences of SEQ ID NOs: 4 and 5 together make up **48.6%** of the polypeptide species in the composition
- In “Gen1” (post-published), top left: the longer polypeptides with the sequences of SEQ ID NOs: 4 and 5 together make up, on average, only approximately **35%** of the polypeptide species in the composition
- In “Gen1” (Patent), top right: the longer polypeptides with the sequences of SEQ ID NOs: 4 and 5 together make up only **18.6%** of the polypeptides in the composition.

85. Thus, contrary to O2’s allegations, the data in the Patent and the post-filing data provided by the Proprietor during prosecution (see **D6**) both demonstrate that compositions according to the present claims are structurally different from

compositions obtainable by other methods. In particular, in “Gen2” compositions according to the claims, the abundance of longer polypeptides is increased, and the abundance of shorter polypeptides is decreased, relative to the “Gen1” composition. O2’s attempt to misconstrue the Proprietor’s numerical data using an unscientific and legally irrelevant standard that two datasets, allegedly, “*look far more alike*” clearly must fail.

86. The Patent provides evidence that clearly and unambiguously demonstrates that a composition obtainable by the method recited in the present claims is not identical to compositions obtainable by the “Gen1” method disclosed in **D3**, for example, in the abundances of the different polypeptide species. Already for this reason, the claimed composition is distinct from the prior art and thus novel.

6.1.2 Evidence in D16 demonstrates that the product as such is novel

87. Both opponents’ attacks under novelty attempt to cast doubt on the fact that the claimed compositions are different from compositions obtainable by the “Gen1” process using the unfounded allegation that there is an extreme extent of batch-to-batch variation that makes these compositions indistinguishable. No evidence supporting these allegations has been submitted by either of the opponents.
88. The sworn declaration and additional post-published data submitted herewith as **D16** provide further evidence that “Gen2” soluble rHuPH20 compositions are reproducibly different and distinguishable from “Gen1” soluble rHuPH20 compositions, even when taking into account batch-to-batch variation.
89. In particular, since both the “Gen1” and “Gen2” rHuPH20 production processes were developed by the same inventor and the Proprietor has used both processes to produce rHuPH20, the Proprietor has a large amount of internal data on certain structural and functional attributes that were monitored across many produced batches. Some of these internal data are reflected in the declaration that is submitted herewith as **D16**. Quality attributes that were regularly monitored include:
 - the structural quality attribute of protein aggregation
 - the structural quality attribute of protein degradation, and
 - the functional quality attribute of enzyme activity per volume of produced cell culture.

90. Regarding structural differences, the data on protein aggregation and degradation in **D16** provide additional evidence that the soluble rHuPH20 compositions obtainable by the “Gen2” process of the present Patent are structurally different from soluble rHuPH20 compositions obtainable by other methods, such as those disclosed in **D3**.
91. In particular, Figure 1 of **D16** shows that, across 33 batches of “Gen2” rHuPH20, the content of aggregated (“HMW”) rHuPH20 was consistently under 1% (average of 0.1%). In contrast, across five batches of “Gen1” rHuPH20, the content of aggregated (“HMW”) rHuPH20 ranged between approximately 2% and 4% (average of 2.8%). Thus, rHuPH20 compositions according to the present Patent are also structurally different from rHuPH20 compositions obtainable by the “Gen1” process, because the “Gen2” process causes less aggregation of rHuPH20. A composition obtainable by the “Gen2” process as claimed has a lower content of aggregated species.
92. Furthermore, Figure 2 of **D16** shows that, across 33 batches of “Gen2” rHuPH20, the content of rHuPH20 that was “hydrolyzed” between residues 311 and 312 was consistently $\leq$ 1% (average of 0.1%). In contrast, across five batches of “Gen2” rHuPH20, the content of such “hydrolyzed” rHuPH20 ranged between approximately 8% and 10% (average of 8.9%). Thus, rHuPH20 compositions according to the present Patent are further structurally different from rHuPH20 compositions obtainable by the “Gen1” process, because the “Gen2” process causes less hydrolysis of rHuPH20. A composition obtainable by the “Gen2” process as claimed has a lower content of hydrolysed species.
93. Moreover, as shown in Figure 3 of **D16**, the additional data on enzyme activity collected from 33 batches of rHuPH20 produced with the “Gen2” process demonstrates that, contrary to the opponents’ unfounded allegations, even when taking into account batch-to-batch variation, the “Gen2” composition obtainable by the method steps recited in present claim 1 reproducibly exhibits distinct, much higher enzyme activity per ml of culture than the “Gen1” composition obtainable by other methods, such as those in **D3**: even the lowest enzyme activity detected for a “Gen2” hyaluronidase batch was almost 7-fold higher than the lowest enzyme activity detected for “Gen1” hyaluronidase batches. A composition obtainable by the “Gen2” process as claimed thus has a higher content of active species compared to a composition obtainable by the “Gen1” process, per unit volume.
94. Such a difference in a (functional) property that is imparted on a product by its production process of course once again implies a structural difference and thus also

confers novelty to a product-by-process claim (T 205/83, r.3.2.1³). Indeed the difference in the functional property of a higher content in active species is consistent with the two above-mentioned structural differences, because both aggregated and hydrolysed species are inactive. In the product of the “Gen2” process as claimed, a lower proportion of (inactive) aggregated and hydrolysed species thus implies a higher proportion in active species.

95. Taken together, these data demonstrate that rHuPH20 compositions obtainable by the “Gen2” process according to the Patent are characteristically and reproducibly distinct from rHuPH20 compositions obtainable by the “Gen1” process. Importantly, this also holds true when considering batch-to-batch variation. The opponents’ unfounded allegations that batch-to-batch variation renders “Gen2” compositions indistinguishable from “Gen1” compositions are thus to be rejected.
96. In this regard, we also note, e.g., the assessment of the Board of Appeal in decision T 148/87 (r.6), in which the Board expressly rejected similar arguments, noting that an overlap with a claim feature due to statistical variation „could not be excluded“, but acknowledged novelty of a product by process claim because the overlap would not have been predictably reproducible („gezielt wiederholbar“).⁴

³ T 205/83, r.3.2.1: “... **To establish novelty**, it will be necessary to provide evidence that modification of the process parameters results in **other products**. In principle **such evidence could conceivably be provided in a variety of ways**, for example on the basis of conclusive considerations which accord with the general state of the art. It is also **sufficient, however, if distinct differences in the products’ properties are demonstrated**; this is **because**, according to an empirical principle in chemistry, **a products properties are determined by its structure, so that differences in the properties of products indicate a structural modification**.”

⁴ T 148/87, r.6: “Wie aus den Ausführungen unter Punkt 4.1 oben ersichtlich, enthält Dokument (3) keinerlei Angaben aus denen hervorgeht, daß die dort beschriebenen Zubereitungen eine FEIBA von wenigstens 60 Einheiten pro ml enthalten können.

Ebensowenig kann Dokument (2) die Neuheit des beanspruchten Gegenstandes in Frage stellen, da auch die Beipacktexte zu FEIBA-Immuno-Packungen, die bereits erwähnte Obergrenze von 50 FEIBA-Einheiten pro ml klar erkennen lassen. Diese leitet sich daraus ab, daß gemäß Anleitung trockene FEIBA-Immuno-Präparationen mit 250, 500 oder 1000 Einheiten mit jeweils 20 ml destilliertem Wasser aufzubereiten sind und die vorgeschriebene Dosierung somit 12.5, 25 oder 50 Einheiten pro ml beträgt. **Die zusätzliche Angabe der produktionstechnisch bedingten, maximal möglichen Schwankungsbreite von 30 % ändert daran nichts, da dies lediglich besagt, daß statistisch gesehen mit einer Streuung der Werte zu rechnen ist, wobei rein theoretisch ein Höchstwert von 65 Einheiten/ml nicht ausgeschlossen werden kann, ohne daß, wie von der Beschwerdeführerin ausgeführt, die Erzielung eines solchen Wertes in der Praxis gezielt wiederholbar wäre** (siehe Punkt VI oben). Dies steht nicht in Widerspruch zu der im Einspruchsverfahren vorgelegten eidesstattlichen Erklärung vom 28. Mai 1985, eingegangen am 4. Juni 1985, wonach die hergestellte Lösung aufgrund der produktionstechnisch bedingten Schwankungsbreite bis zu 65 Einheiten FEIBA pro ml enthält.

Da die Kammer keine Veranlassung hat, die Neuheit aus anderen Gründen anzuzweifeln, ist der Gegenstand der geltenden Ansprüche 1 und 2 daher neu.” (Emphasis added).

97. In the present case, even if, theoretically, due to statistical variation, there could in rare instances of “Gen1” compositions be any sporadic overlap with at least some of the features that are imparted by the “Gen2” process to “Gen2” compositions as discussed herein (which is denied):

- this would not directly and unambiguously concern all of the features discussed herein, and moreover,
- in any case the same assessment as in **T 148/87** (r.6) would apply: the overlap would not be predictably reproducible and would thus not meet the “direct and unambiguous” criterion.

6.2 The opponents have not discharged their burden of proof for their allegations

98. During opposition, each party bears the burden of proof for the facts they allege (Guidelines, III-G, 5.1.1). The Proprietor has unequivocally demonstrated that the claimed composition is inherently and reproducibly distinct from compositions obtainable by the method disclosed in **D3**, providing extensive evidence both from the Patent, and further in the form of the sworn declaration submitted herewith as **D16**.

99. In contrast, neither O1 nor O2 has provided any evidence for their speculations that certain method steps may or may not impart certain characteristics on the product. Both opponents’ objections under novelty hinge on the incorrect and unsubstantiated allegation that the method steps recited in granted claim 1 do not limit the claimed composition. Neither O1 nor O2, however, has discharged their burden of proof for these allegations.

100. Many of the opponents’ unfounded allegations relating more fundamentally to novelty have already been addressed above. Merely for completeness, we will also briefly address the various unsubstantiated speculations regarding the alleged relevance or lack thereof of certain process parameters in [075]-[085] of O2’s opposition.

101. In [075]-[076], O2 alleges that it is “*standard in the art*” to use multiple feeding steps in recombinant protein production, citing four documents **D11-D14** in addition to **D3**. It is not clear from O2’s allegation how disclosures in four separate documents, apparently to be read together with **D3**, amount to a valid novelty attack. Moreover, the passages cited by O2 across these four documents do not provide a direct and

unambiguous disclosure of the feeding strategy according to present claim 1. In any case, O2's references to alleged disclosures of feeding strategies in various prior art documents are not relevant for the assessment of novelty of the present product-by-process claims, because these claims must be construed as claims to the composition as such, and the legal question to be answered is simply whether any single prior art disclosure directly and unambiguously provides a composition according to claim 1. That is manifestly not the case.

102. In [077]-[080], O2 alleges incorrectly that the patent itself indicates that the presence of certain peptidases in the cell culture medium is responsible for producing the mixture of polypeptides, citing passages in paragraphs [0288], [0121] and [0126] of the patent. O2 further alleges incorrectly that the "*presence or absence of peptidases in the cell culture medium is not a feature of the method of claim 1*" ([079] of O2's opposition.
103. First, contrary to O2's allegations, none of the cited passages in the Patent provides any definitive explanations. All three passages cited by O2 in fact use the same hypothetical language that "*this heterogeneity is likely the result of [...]*" (emphasis added). Nothing conclusive can be derived from this merely hypothetical statement.
104. Second, even if it was assumed, *arguendo*, that peptidases had an impact on the mixture of polypeptides, it is not correct that the claim does not specify any features impacting on the presence or absence of peptidases in the cell culture medium. During protein production in cell cultures, peptidases are released from cells in the culture. Granted claim 1 explicitly requires that the soluble rHuPH20 is recombinantly expressed in CHO cells, contrary to O2's allegation in [080] of their opposition that the "*cells used in the production method recited in claim 1 may be any type of cell*". The claims being limited to CHO cells impacts on the type of peptidases that may be present, since the peptidases are limited to those inherently present in CHO cells. Furthermore, granted claim 1 also specifies particular culture conditions that impact, e.g., on cell lysis, which in turn results in release of peptidases into the cell culture medium. Thus, O2's allegations regarding any effects of peptidases are also inherently flawed.
105. In any case, O2 in this regard submits mere speculation that is not relevant for the assessment of novelty of the present claims directed to the composition as such, because the Proprietor has already provided extensive evidence that this composition as such is novel.

106. In [081]-[082] of O2's opposition, O2 speculates about potential impacts that certain purification steps may have on the obtained composition. In particular, O2 alleges that hydrophobic interaction chromatography would alter the ratio of polypeptides in the final mixture, because of alleged "*differences in hydrophobicity of each of SEQ ID NOs: 4-8*". The rHuPH20 polypeptides with the sequences of SEQ ID NOs: 4-8 are between 447 and 443 amino acids long. Any differences in relative hydrophobicity between polypeptides of this length differing by only one amino acid are, however, negligible when using standard hydrophobic interaction chromatography techniques. In any case, this mere speculation is not relevant for the assessment of novelty of the present product-by-process claims, because the Proprietor has already provided extensive evidence that the composition as such is novel.
107. Similarly, O2's hypothetical deliberations in [083] of their opposition that the cells may contain one or more nucleic acids, each encoding a rHuPH20 polypeptide of a different length, which could be one way to achieve a mixture of different polypeptides in the final product, are not relevant for novelty of the present claims. O2 has provided no evidence for this assumption. This allegation merely amounts to another attack based on a hypothetical composition that is not actually part of the state of the art. In contrast, the Proprietor has already demonstrated, on the basis of extensive evidence, that the claimed product as such is novel.
108. In summary, all these speculations regarding different factors that may hypothetically affect production of a composition comprising rHuPH20 are unfounded. The case law has unambiguously established that mere speculation does not amount to a substantiated novelty objection. See, e.g., the following excerpt from CLBA10, III-G, 5.1.1:
- "It is not sufficient in opposition proceedings for the opponent to impugn a granted patent with an assertion which cannot be substantiated. And if the EPO is unable to establish the facts of its own motion, the proprietor is given the benefit of the doubt (T 219/83, OJ 1986, 211, 328; see also T 293/87 and T 459/87). According to T 200/94 (following established case law), if a board's investigation does not enable it to verify beyond reasonable doubt the facts alleged, this goes to the detriment of the party needing to prove them, i.e. the party who relies on these facts."*
109. The various aspects relating to production methods contemplated by the opponents in the context of their novelty objections are not even relevant for assessment of

novelty of the present product-by-process claims. The Proprietor has already provided conclusive evidence that the process has been modified and that the product as such is distinct from prior art products, as measured by many different parameters.

110. It is, in any case, not the Proprietor's burden to delineate precisely which method steps produce a specific effect on the product. The effect of the various modified process parameters on the product is of a synergistic nature, and it is neither required nor even possible to precisely delineate which changes in the method are causally associated with the characteristics of the resulting product.
111. Both opponents' attacks under novelty rely extensively on experimental data that the Proprietor provided in the Patent and in post-filing data. These data, however, relate only to one structural difference between the claimed compositions and compositions obtainable using the earlier "Gen1" process: the relative abundances (proportions) of polypeptides in compositions obtained using the "Gen2" process in comparison to compositions obtained using the "Gen1" process.
112. The Proprietor has shown herein that, moreover, this is not the only characteristic that distinguishes a composition obtainable by the "Gen2" process from a composition obtainable by other methods, such as that disclosed in **D3**. The claimed compositions are distinct also according to other structural and functional characteristics, including protein aggregation, protein degradation and the content of active enzyme per unit volume of a product obtained from the recited "Gen2" method. The Proprietor has further shown that these differences are reproducible, also when taking into account the natural batch-to-batch variation that is inherent to biotechnological processes for the production of proteins. Both opponents' analyses alleging that the differences to the prior art do not go beyond such batch-to-batch variation must be rejected in view of the Proprietors evidence in conjunction with fact that the opponents objections are based on nothing more than hypotheticals and speculation.
113. Indeed, the conclusion that the product-by-process claim format is the appropriate claim format for "Gen2" rHuPH20 compositions is strongly supported in the present case by the considerations that:

- the invention relates to complex compositions of biological products,

- a natural degree of batch-to-batch variation is observed both in the prior art and according to the claimed invention,
- but there are a number of clear, reproducible differences in terms of structure and functional properties between compositions as claimed that are obtainable by a “Gen2” process versus compositions obtainable by a “Gen1” process of the prior art.

The naturally variable character of the numerous differences cannot, within the meaning of the established case law, be accurately and satisfactorily defined by reference to specific product features alone (i.e. by specific composition, structure, parameters). Nevertheless, a composition of the invention in the Patent is reproducibly distinct from the compositions of the cited prior art.

114. The claimed subject matter clearly meets the requirements of Article 54 EPC and the Opponents’ attacks under Article 100(a) EPC are to be rejected.

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

115. The Opponent’s arguments under Article 56 EPC are also flawed and are thus to be rejected. Prior to the teaching of the present Patent, it was not obvious to obtain a composition as claimed. The composition as such is demonstrably improved relative to compositions obtainable by the methods of **D3**, e.g., in terms of the increased proportion of structurally and functionally intact rHuPH20 within rHuPH20 compositions as claimed, in comparison to rHuPH20 compositions obtainable by methods disclosed in the prior art. The increased content of enzymatically active forms of rHuPH20 within compositions according to the present invention was unexpected in view of the prior art. The skilled person would not have had any reasonable expectation of success in obtaining such a high content of active species by making the specific modifications to the “Gen1” production process that are reflected in the “Gen2” production process as recited in claim 1.
116. We note that in this regard the same reasoning applies as was set out by the Board of Appeal in **T 1471/16** (reason 25) and the Opposition Division in its preliminary opinion (**D19**, point 9.3.1) in the opposition against EP 3 760 715 B1, both of which concerned previous divisional cases based on the same Original Disclosure, with

claims directed to another composition that is a product of the “Gen2” method, the “harvest cell culture fluid” of present step (g).

117. As acknowledged by the Board of appeal in **T 1471/16**, the high levels of rHuPH20 activity in the intermediate HCCF product not obtainable by the “Gen1” production process of the prior art, and thus confers an inventive step over that prior art. The Board found that, as mentioned above, the skilled person would not have had any reasonable expectation of success in obtaining such a high content of activity. The Opposition Division in **D19** (point 9.3.1) came to the same conclusion.
118. The unexpected advantages in terms of a higher content in active species in compositions obtained from the “Gen2” as compared to the prior-art “Gen1” method are explained further herein below. These advantages over products of “Gen1” methods as considered by the Board of Appeal will likewise be reflected in the purified composition as presently claimed – the only additional processing step in the process of claim 1 after obtaining the HCCF in step (g) is the final purification step (h).
119. Therefore, the presently claimed compositions are, as such, and in their own right, a non-obvious solution to a technical problem. In such a case, an inventive step is acknowledged for the subject matter of a product-by-process claim (see, e.g., **T 219/83**, r.11-13; **T 148/87**, r.7.1-7.5; **CLBA10**, II.A.7.2).
120. Moreover, even leaving aside the unexpected advantages of the claimed compositions for the sake of argument, it was not obvious to make these compositions, with their characteristic molecular “fingerprint” or “signature” (e.g., with respect to the relative proportions of different C-terminally truncated chain lengths) without knowledge of the disclosure in the patent.
121. This structural “fingerprint” as such is not an arbitrary modification of the prior art, rather it results from a non-obvious development. Under Article 56 EPC it is not relevant whether the skilled person “could”, hypothetically and artificially, have put together compositions having at least some of the features that result from the “Gen2” method as claimed with hindsight knowledge of the disclosure in the Patent. The relevant point is that the skilled person would not have done so without knowledge of the Gen2 method.

122. Indeed, the skilled person in practice would not have been able to do so in an obvious manner, because the molecular “fingerprint” found “Gen2” in compositions results only from the “Gen2” process that is recited in claim 1. The development of that process – and thus the skilled person’s access to its products as such – was non-obvious. That finding of non-obviousness, both with respect to the process and its products as such, has been acknowledged previously,

- initially by the grant of the patent from the root application with claims directed to the “Gen2” process as such, and then
- by decision **T 1471/16** of the Technical Board of Appeal concerning a previous divisional case from the root application and the non-obvious products (as such) that result from the “Gen2” process (in that case specifically the harvested cell culture fluid resulting from the “Gen2” process).

123. Thus, in the present case, the claimed compositions as such involve an inventive step. The skilled person would only have made compositions having structural “fingerprints” as discussed herein with hindsight knowledge of the invention.

124. The case law of the Boards of Appeal in the area of product-by-process claims has held that a product that is novel does not automatically also involve an inventive step only because it has been made by an inventive process – the claimed product as such also has to be non-obvious in light of the state of the art (e.g., **CLBA10**, II.A.7.2, **T 219/83**, r.11-13). But an inventive step will only be denied by that principle if the skilled person would have made the novel product in an obvious manner by other (known) processes, instead of the inventive process. That is not presently the case, compositions having the “Gen2” molecular signature result only from the “Gen2” process, and it would not have been obvious to make such products without knowledge of the “Gen2” process. Thus, the presently claimed compositions are, as such, and in their own right, a solution to a technical problem which was not obvious in the light of the state of the art. In such a case, the product of an inventive process also involves an inventive step (see, e.g., **T 219/83**, r.11-13; **T 148/87**, r.7.1-7.5).

7.1 Problem-solution approach

125. Both opponents consider that **D3** is closest prior art. In any case, the arguments presented herein also apply in view of **D4**, which, in O1’s own words “*describes essentially the same process as in D3*” (page 34, fourth paragraph of O1’s opposition).

126. Claim 1 of the Patent is **distinguished from D3** at least by the specific features of the product that result from the process recited in the claim.
127. Contrary to the opponents' allegations, these differences in specific product features are not limited to the relative abundances of certain polypeptide species in the mixture. The Proprietor's submissions in this regard during prosecution merely discuss the differences in abundances of individual polypeptide species as one exemplary structural difference between compositions comprising rHuPH20 obtainable by the method steps recited in claim 1, in comparison to compositions comprising rHuPH20 obtainable by the method disclosed in the prior art, and in particular, in **D3**. Taking into account all evidence presented by the Proprietor, both from the patent and post-published data, the composition according to the present claims is distinguished from **D3** at least by the following structural features:
- The relative abundances of the components of the claimed mixture are different: longer, more complete polypeptide sequences, in particular SEQ ID NO: 4 and 5, are relatively more abundant;
 - The composition contains less aggregated rHuPH20 polypeptide; and
 - The composition contains less rHuPH20 polypeptide that is hydrolysed (between residues 311 and 312);
128. All of these features of the composition are the inevitable result of the process recited in claim 1.
129. Contrary to the opponents' allegations, the product characteristics are associated with the **technical effect** of providing rHuPH20 compositions that contain a significantly increased proportion of structurally and functionally intact rHuPH20.
130. This is demonstrated, e.g., by the data in the Patent on enzyme activity and on the total amount of obtained rHuPH20 per culture. For example, comparing enzyme activity per volume of culture at the same production stage in the prior art process and the claimed process demonstrates that the claimed composition contains more active enzyme than compositions obtainable by the "Gen1" production process disclosed in **D3** or scaled-up versions thereof described in the Patent: enzymatically active enzyme per volume of culture is increased more than 10-fold from 1,600 Units per ml ([0588] of **D3**) to 17,000 Units per ml ([0270] of the Patent). Furthermore, the total amount of rHuPH20 obtained is increased at least 15-fold from approximately 400-700 mg (i.e., 0.4-0.7 g) soluble rHuPH20 obtainable by the large-scale adaptation

of the “Gen1” method in Example 3B of the Patent (see [0214] of the Patent) to approximately 11 and 15 grams soluble rHuPH20 obtainable by the “Gen2” production process recited in the claims ([0279] of the Patent).

131. In addition to the data in the Patent demonstrating the obtainable increased quantity of structurally and functionally intact rHuPH20, we also refer to the sworn declaration submitted herewith as **D16**, which provides a further detailed explanation of the changes made to the rHuPH20 production process relative to the process disclosed in **D3**, as well as additional evidence that the rHuPH20 compositions obtainable by the modified production process as reflected in the claims are reproducibly improved, e.g., in terms of the higher proportions of active enzyme, as well as lower proportions of aggregated rHuPH20 and lower proportions of hydrolysed rHuPH20.
132. This dramatic improvement in the proportions of structurally and functionally intact rHuPH20 within rHuPH20 compositions that are obtainable by the method set out in the present claims has important real-life implications. The prior art methods did not produce enough active enzyme to be suitable for use in a pharmaceutical context. In contrast, the method recited in the present claims for the first time enabled production of soluble rHuPH20 at a yield that was suitable for pharmaceutical applications. The Proprietor indeed uses the methods according to the present claims to produce soluble rHuPH20 that is combined with other drugs for real-life pharmaceutical applications, e.g., as a spreading agent in conjunction with chemotherapy. Being able to obtain a high quantity of structurally and functionally intact rHuPH20 is essential for utility of rHuPH20 in these applications.
133. Thus, the claimed subject matter **solves the objective technical problem** of providing an improved hyaluronidase composition.
134. The solution provided in the present claims would also **not have been obvious** in view of **D3**. For this analysis, it is again important to be clear about what constitutes prior art, and what does not. In terms of the production process in cell culture, **D3** only contains a single paragraph ([0588] of D3) disclosing one small-scale, 5 L proof of concept study demonstrating that the engineered protein of **D3** can be produced in a recombinant expression system and is soluble and enzymatically active. Contrary to O1’s allegations in the passage bridging pages 33-34 of their opposition, the culture process disclosed in **D3** differs from the process steps recited in claim 1 of the

Patent in many parameters. As detailed under novelty, these parameters include, e.g.:

- The scale of the culture
- The number of feeding steps that are carried out
- The compositions of each of the feeds
- The gradual lowering of the temperature at specific time points
- The point at which the culture is harvested.

135. **D3** provides no motivation or suggestion that would have led the skilled person to the “Gen2” method, not even in terms of merely scaling up as reflected in Example 3B of the Patent, and certainly not in terms of leading the skilled person directly to modify the above-listed aspects of the process disclosed in **D3**. **D3** provides no pointers towards modifying any of the above-mentioned culture parameters in any way, let alone all of these culture parameters together.
136. As was noted by the Board of Appeal in **T 1471/16** (reason 25) and the Opposition Division in its preliminary opinion (**D19**, point 9.3.1) in the opposition against EP 3 760 715 B1 with respect to another composition that is a product of the “Gen2” method – the intermediate product termed “harvest cell culture fluid” in present step (g) – the skilled person would not have had any reasonable expectation of success in obtaining a significantly increased content in active species by modifying the various culture parameters of the “Gen1” process, in combination, as defined in the “Gen2” production process of present claim 1.
137. Thus, the skilled person would (not merely could, but would) **not** have arrived at a composition obtainable by the process recited in the claims in an obvious manner. The required enabling teaching and experiments are disclosed only in the present application.
138. The invention as defined in the present claims is the result of years of careful work constituting a complex research project carried out by the Proprietor, specifically with the aim of obtaining compositions comprising rHuPH20 that are improved relative to compositions comprising rHuPH20 that are obtainable by the method disclosed in **D3** or **D4**.
139. The claimed product as such is inventive.

140. Nothing in the opponents' speculations provided with their discussions of aspects of Art. 56 EPC plausibly discredits that the claimed composition is a non-obvious improvement over compositions obtainable by methods disclosed in the prior art, in particular **D3** or **D4**, as shown below.

7.2 Opponents' elaborations on table [0564] in **D3** are not relevant

141. Both opponents' interpretations of the table in paragraph [0564] in **D3** are fundamentally flawed and must thus be disregarded. In their discussions of technical effect, both opponents provide detailed speculations regarding supposed enzyme activities of individual polypeptide species that are allegedly derivable from the table in paragraph [0564] of **D3**. This attack already lacks relevance for inventive step of the claimed composition, because the relative abundances of individual polypeptide species are not the only distinguishing feature of the presently claimed composition, which needs to be considered as a whole for assessing inventive step. Furthermore, as we will show below, the opponents' allegations are, in any case, not supported by the data in the table in paragraph [0564] of **D3**.
142. In particular, both opponents allege incorrectly that reduced cleavage of SEQ ID NO: 4 is not advantageous. To support their allegations in this regard, both opponents rely on a particular data set in the table in paragraph [0564] of **D3** that shows certain levels of activity of C-terminally truncated versions of rHuPH20 polypeptides. The opponents both analyse levels of activity of certain polypeptides that they (without evidence) equate with SEQ ID NOS: 4-8, and use these data to conclude that "*SEQ ID NO: 4 does not display higher levels of hyaluronidase activity compared to the other polypeptides shown in any of SEQ ID NOS: 5-9*" ([099] of O2's opposition), and even that "*the table of paragraph [0564] of D3 also makes it abundantly clear that a polypeptide corresponding to SEQ ID NO:4 of the patent in suit, i.e. of the longest and uncleaved (!) polypeptide species has the lowest hyaluronidase activity of all six polypeptide species*" (page 31, penultimate paragraph of O1's opposition).
143. The activity assay used to obtain the data in the table in paragraph [0564] of **D3**, however, is not accurate enough to support the conclusions the opponents wish to infer on the alleged differences in activity of the polypeptides equated with SEQ ID NOS: 4-8. In this regard, we refer to paragraphs 39-47 of the declaration submitted herewith as **D16**, which confirm the following explanation of the actual disclosure of table in paragraph [0564] of **D3**.

144. The context of the data in the table in paragraph [0564] of **D3** is entirely unrelated to the presently claimed composition. As already mentioned herein, the focus of the work described in **D3** was optimisation of the expression construct for producing a soluble hyaluronidase. In particular, **D3** describes in detail how several C-terminal truncations of hyaluronidase were generated to produce a soluble recombinant human hyaluronidase product. Example 4 of **D3** describes how these truncation mutants were generated ([0546]-[0562]) and how hyaluronidase activity of these C-terminally truncated mutants was measured individually by microtiter assay ([0562]). The “*Results*”-section of this same Example 4 of **D3** contain the data in the table in paragraph [0564] to which the opponents refer. The purpose of the assay in the context of Example 4 was to determine at which position truncation results in loss of activity, as stated in [0564] immediately above the table:

*“Hyaluronidase activity was measured in sHASEGP [i.e., rHuPH20] truncation mutants **to identify the minimally active domain** for secreted neutral active hyaluronidase activity.” (emphasis added)*

145. In other words, the aim of the activity assay was to find out which of the C-terminally truncated mutants no longer exhibit any significant levels of hyaluronidase activity. This assay was not used to, nor was it suitable for being used to, decipher small differences in activity between the individual C-terminally truncated mutants.
146. The sworn declaration provided herewith as **D16** testifies that the assay that was used to generate the data in the table in paragraph [0564] of **D3** is associated with a variability of up to $\pm 50\%$. The assay is thus only suitable for distinguishing between variants with high enzyme activity, and variants with little or no enzyme activity. Indeed, the only conclusion that is made in **D3** from the data shown in the table in paragraph [0564] is in line with this level variability, see [0565] of **D3**:

“The results showed that all six one amino acid deletion mutants ending at indicated amino acids from Y 482 to E 477 gave higher secreted activity than GPI anchored sHASEGP [i.e., rHuPH20].” (emphasis added)

147. The “*mutants ending at indicated amino acids from Y 483 to E 477*” gave activity readings between 0.329 and 0.750. The “*GPI anchored*” rHuPH20 terminating at position 509 only gave an activity reading of 0.044. In their own analyses both opponents (artificially) equate the mutant ending at Y482 with SEQ ID NO: 4, the mutant ending at F481 with SEQ ID NO: 5, the mutant ending at I480 with SEQ ID NO:

6, the mutant ending at Q479 with SEQ ID NO: 7, the mutant ending at P478 with SEQ ID NO: 8, and the mutant ending at E477 with SEQ ID NO: 9. The only conclusion that **D3** draws on mutants ending at amino acids from Y482 to E477 is that all of these mutants gave higher secreted activity than the GPI-anchored hyaluronidase. D3 does not present any conclusions on the, according to the opponents, allegedly relevant differences in activities between the polypeptides terminating at positions Y482 to E477. The reason for this is that the assay used to generate this data is not suitable for supporting any such conclusions. This is supported by the sworn declaration submitted herewith as **D16**.

148. That the assay used to generate the data in the table in paragraph [0564] has such a high degree of variability is, indeed, also derivable from the values in this table. In particular, O1's allegation that SEQ ID NO: 4 has the lowest hyaluronidase activity of all six polypeptide species evidently cannot be supported by these data. Even if SEQ ID NO: 4 is equated with the data provided for the hyaluronidase having amino acids 1-482, although this is a hyaluronidase with a different N-terminus, and even if one were to accept the opponents' analysis that the data for C-terminal truncations in this region show meaningful differences, the conclusion would be that:

- Hyaluronidase 1-481 (seen by the opponents as equivalent to SEQ ID NO: 5) has higher enzyme activity than hyaluronidase 1-482 (seen by the opponents as equivalent to SEQ ID NO: 4); and
- Hyaluronidase 1-483 also has higher enzyme activity than hyaluronidase 1-482 (seen by the opponents as equivalent to SEQ ID NO: 4)

149. This can be seen from the below excerpt of the table in [0564] of D3:

Amino acid 1 to:	Enzyme activity (U/ml/24 h)	Alleged equivalence to SEQ ID NO:
481	0,740	5 + 35 aa signal sequence
482	0.392	4 + 35 aa signal sequence
483	0.800	N/A

150. There is no meaningful scientific explanation why only the truncation at amino acid 482 would have a lower enzyme activity than the truncations at amino acid positions 481 and 483, aside from the explanation provided herein: the assay used in Example 4 of **D3** produces data with a variability of up to +/- 50%.

151. Thus, the data shown in [0564] of **D3** is not accurate enough to support the opponent's allegations on alleged differences of enzyme activities of individual polypeptide species.
152. In contrast, the question that is relevant for assessing inventive step of the presently claimed composition is whether the claimed composition as a whole constitutes an improvement over any compositions obtainable by methods disclosed in the prior art. The Proprietor has already provided extensive data that rHuPH20 compositions as a whole that are obtainable by the method steps recited in the present claims are improved over compositions obtainable by other methods disclosed in **D3**, e.g., in that the composition as a whole contains an increased quantity of structurally and functionally intact rHuPH20.

7.3 Opponents' remaining allegations are also not relevant

153. Both opponents allege incorrectly that the Proprietor has argued that the claimed composition is inventive due to inventiveness of the production method (page 33, fifth paragraph of O1's opposition; [101]-[103] of O2's opposition). This clearly and deliberately misconstrues the actual submission made by the Proprietor. The Proprietors argument in their submission of December 6, 2023, in the relevant context was (page 9, paragraphs 2-3, **D6** in the present opposition proceedings):

"We note immediately that a novel product produced by that method must necessarily involve an inventive step for the same reasons as the method that allows the product to be made.

Further, as has been explained in detail and acknowledged by the EPO during prosecution of the parent case EP 3 760 715, the "Gen 2" method is in turn also associated with additional underlying advantages, such as that the harvested cell culture fluid in which the novel mixture of species of polypeptides is obtained has an increased enzymatic activity per volume compared to that obtained in D1 (cf. Examples 4-8 of the present and root applications)."

154. As explained in detail herein, the rHuPH20 composition obtainable by the method recited in the claims is improved with respect to rHuPH20 compositions obtainable by prior art methods. In particular, the presently claimed composition contains an increased amount of structurally and functionally intact rHuPH20. Thus, in this patent family, the fact that the composition obtained by the method is improved supports

inventive step of both the method and the product: for both types of claims, the subject matter is inventive, because it was not obvious to arrive at the improved method or the improved product. The opponents' attempts to misconstrue certain submissions made by the Proprietors during prosecution, in any case, are immaterial to inventive step assessment of the present case. It is only relevant for inventive step of the present case that the product as such is inventive, which has already been shown above.

155. Both opponents' incorrect allegations that the claimed composition does not have improved enzyme activity must clearly also be discarded. As explained above, e.g., the Patent provides evidence that enzymatically active enzyme per volume of culture is increased more than 10-fold from 1,600 Units per ml ([0588] of **D3**) to 17,000 Units per ml ([0270] of the Patent). The reproducible increase in enzyme activity of rHuPH20 obtainable by the method recited in the present claims is further corroborated by post-filing data submitted herewith in **D16** and **D17**. In contrast, the opponents have merely provided unsubstantiated allegations.
156. Both opponents incorrectly allege that any improvement in enzyme activity of the harvested cell culture fluid would not be reflected in the composition according to the present invention. Essentially, both opponents insinuate, without evidence, that even the improvement as evidenced by the more than 10-fold improvement in enzymatic activity per volume of harvested cell culture fluid would inevitably be lost from a composition that is further subjected to a step (g) of "*obtaining the harvest cell culture fluid*" and a step (h) of "*purifying the rHuPH20 from the harvest cell culture fluid*". The data in the Patent, however, disproves this. As already explained above, the composition obtained after purification contains an increased proportion of structurally and functionally intact rHuPH20. Specifically, the amount of rHuPH20 is increased at least 15-fold from approximately 400-700 mg (i.e., 0.4-0.7 g) soluble rHuPH20 obtainable by the large-scale adaptation of the "Gen1" method in Example 3 of the Patent ([0214] of the Patent) to approximately 11 and 15 grams soluble rHuPH20 obtainable by the "Gen2" method recited in the present claims (see Example 8 of the Patent ([0279] of the Patent). Thus, the Patent provides evidence for an improvement also after purification of the rHuPH20 from the harvested cell culture fluid.
157. O2 attempts to diminish the technical contribution of the Patent by focussing on values of specific activities to support their allegation in this regard. This objection is

fundamentally flawed in that, as explained above, what is relevant for assessing whether the claimed composition is improved with respect to compositions in the prior art is that there is an increased quantity of structurally and functionally intact rHuPH20 in the composition as a whole. To convert enzyme activity to specific activity, the evidently increased enzyme activity is divided by the evidently increased amount of obtained rHuPH20 in mg. In essence, this only serves to artificially diminish the technical contribution of the claimed subject matter: that more active protein is obtainable using the modified production process reflected in the claims.

158. This can also be demonstrated by calculating the total obtainable units of rHuPH20 activity for each method: The Patent reports in [0279] that the exemplary “Gen2” process in Example 8 yields 11 and 15 grams (i.e., 11,000 and 15,000 mg) soluble rHuPH20 with specific activities of 95,000 units/mg and 120,000 units/mg, i.e., a total of 95,000 units x 11,000 mg and 120,000 units x 15,000 mg, i.e., a total of 1,045,000,000 units and 1,800,000,000 units of rHuPH20 activity are evidently obtainable by the “Gen2” process. In contrast, regarding the exemplary scaled-up “Gen1” process in Example 3B, the Patent reports in [0214] that a yield of 400-700 mg soluble rHuPH20 with a specific activity of 96,000-144,000 units/mg is obtainable, i.e., a total of 96,000 units x 400 mg and 144,000 units x 700 mg, i.e., a total of only 38,400,000 to 100,800,000 of rHuPH20 activity are evidently obtainable by the “Gen1” process. Thus, the total units of rHuPH20 activity obtainable by the claimed “Gen2” process is up to **46.9 times increased** relative to the total units of rHuPH20 activity obtainable by the claimed “Gen1” process ($1,800,000,000 / 38,400,000 = 46.9$). Focussing only on specific activity deliberately obscures the technical contribution of the Patent. O2’s attack in this regard must thus be discarded.
159. O2’s further allegation that the same composition could be produced by obtaining individual polypeptides and combining them in a single composition only highlights their lack of understanding of product-by-process claims. Product-by-process claims define products obtainable by a specific process, because this process imparts certain properties on the product that cannot be accurately described in a traditional product by process claim. Contrary to O2’s interpretation, the claimed composition does not only differ from prior art compositions by the relative abundances of SEQ ID NOs: 4-8. In reality, the process recited in claim 1 imparts a number of characteristics on the obtained rHuPH20 composition, such as the relative abundances of polypeptides, a reduced amount of aggregation, a reduced amount of degradation, as well as increased enzyme activity. Merely taking individually produced

polypeptides and combining them would not, in fact, result in a composition that is the same as compositions obtainable by the process recited in claim 1.

160. Nothing in either of the opponents' submissions disproves that the claimed composition is a non-obvious improvement relative to what is actually disclosed in the prior art, in particular **D3** and **D4**.
161. Thus, 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.

8 Sufficiency of disclosure (Articles 100(b) / 83 EPC)

162. The Opponents have presented two lines of argument under Articles 100(b)/83 EPC. One line, presented by O1, objects that the method recited in the present claims does not result in a structurally different composition having a higher abundance of longer polypeptide species, alleging on this basis that the Patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The other line of argument, presented by O2, objects to reproducibility of the method recited in the claims, alleging that it was an undue burden for the skilled person to obtain suitable cells to produce a composition as claimed, and further objecting that the patent lacks information on certain peptidases allegedly required for production of a mixture of polypeptides of SEQ ID NOs: 4-8.

163. Neither of these lines of argument is justified. We will address each in turn.

8.1 The skilled person can obtain the claimed composition without undue burden

164. O1's incorrect allegation that the composition that is obtainable by the method steps recited in the claims is not structurally different is based on a misunderstanding of the structural data presented in the Patent and in Proprietor's submission of December 6, 2023 (**D6**). O1 objects that the claimed composition allegedly does not have a higher abundance of longer polypeptide species, e.g., because "*the longer sequence SEQ ID NO: 4 is less prevalent than its shorter counterpart SEQ ID NO: 5*" in the data in table 28 of the Patent (paragraph bridging pages 27-28 of O1's opposition).

165. It is immediately evident that O1's analysis in this regard is inherently flawed: in attempting to support an argument that a "Gen2" composition according to the claims (table 28 of the Patent) is allegedly not different from a "Gen1" composition (table 27 of the Patent), O1 only compares abundances of polypeptides within the "Gen2" composition, and separately from that, within the "Gen1" composition.
166. The correct approach to determine whether there is a difference between two compositions, however, is to make a comparison between those two compositions. As already explained in detail under inventive step, the composition as a whole is claimed and thus the composition as a whole needs to be considered for any valid comparison. Nevertheless, for the sake of argument, even when looking at abundances of individual polypeptides in the composition to compare between compositions, this indeed demonstrates that the claimed composition is structurally different from rHuPH20 compositions obtainable by the "Gen1" method used in Example 3 of the Patent. For example, for the data shown in tables 27 and 28 of the Patent:
- The proportion of the longest polypeptide (SEQ ID NO: 4) has increased from 0.2% to 1.9%
 - The proportion of the second longest polypeptide (SEQ ID NO: 5) has increased from 18.4% to 46.7%
 - The proportion of the third longest polypeptide (SEQ ID NO: 6) has increased from 11.8% to 16.7%
 - The proportion of the second shortest polypeptide (SEQ ID NO: 7) has decreased from 56.1% to 27.8%
 - The proportion of the shortest polypeptide (SEQ ID NO: 8) has decreased from 13.6% to 6.9%.
167. Thus, contrary to O1's allegation, the data in the Patent demonstrates that the exemplary composition according to the claims as shown in table 28 is structurally different from the composition as shown in table 27 that is obtained by other methods. In particular, in this "Gen2" composition according to the claims, the abundance of the longer polypeptides is increased, and the abundance of the shorter polypeptides is decreased, relative to the "Gen1" composition. The differences between "Gen1" and "Gen2" rHuPH20 compositions are even further supported by post-filing data submitted during prosecution and also with this submission, as explained in detail under novelty and inventive step. Moreover, the Patent provides

extensive disclosure of the method steps according to the claims that are required for obtaining this specific, structurally different composition.

168. Thus, O1's line of argumentation is unfounded. The patent provides sufficient guidance for a skilled person to obtain the claimed composition having, e.g., a higher abundance of longer polypeptide species.

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

169. O2 alleges incorrectly that the patent does not provide sufficient disclosure for the subject matter of the claims, because *"the skilled person would not be able to reproduce the method of Example 8 because the starting material of this method, the 2B2 cells, were not available at the filing date of the patent"*, and that only a deposit of this particular clone or additional disclosure could have allowed the skilled person to reproduce the method recited in the present claims (paragraphs [116]-[121] of O2's opposition). In essence, O2 alleges incorrectly that the reproducibility of the claim depends critically on a rearrangement of the integrated DNA 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 *"chance event"* (paragraph [120] of O2's opposition). O2 also alleges that *"it could not be guaranteed that the skilled person would be able to produce a different CHO cell line expressing soluble rHuPH20 that behaves like 2B2 cells, and be able to produce the composition of claim 1 by substituting the 2B2 cells in Example 8 for that cell line"* (paragraph [121] of O2's opposition).
170. Nothing in O2's incorrect line of argument concerning the alleged significance of an allegedly particular gene arrangement event relates specifically to the claimed subject matter *"composition comprising a mixture of polypeptides, said mixture comprising the polypeptides set forth in SEQ ID NOs: 4-8"*, obtainable by a method as claimed. Nothing on file calls into question the credibility that the claimed composition is obtainable by the method steps recited in the claims.
171. 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 **CLBA10**, 10th ed. 2022, II-C, 7.1.4, p.417). 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.

172. 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 a particular “*rearrangement*” is even required. Indeed, O2’s objection as presented in their submission is already flawed in that it is based entirely on an incorrect linguistic interpretation of one passage within [0123] of the Patent cited by O2 ([119] of O2’s opposition), which states:

“Therefore, by increasing the concentration of methotrexate in the culture media, the hyaluronidase-expressing cells are forced to produce more mouse dihydrofolate reductase to remain viable. This can be effected by, for example, gene amplification or rearrangement of the integrated DNA to a more stable and productive arrangement.” (emphasis added)

173. This sentence merely provides an open-ended list of examples of possible causes for increases in production of mouse dihydrofolate reductase in the context of the DHFR/methotrexate selection system. O2 artificially merges this with the observation that the 2B2 cell line used in certain examples in the Patent has a lower copy number compared 3D35M cells, and incorrectly concludes that “*increased production must, therefore, have been caused by rearrangement of the integrated DNA to a more stable and productive arrangement*” ([120] of O2’s opposition). Already from a purely linguistic perspective, the Patent does not support O2’s allegation in this regard, because this conclusion cannot reasonably be arrived at by isolating one example from an open-ended list of possibilities.
174. In fact, the data in the Patent support the conclusion that an alleged specific and reproducible “*rearrangement*” and role of chance in the transfection process for expression of the rHuPH20 protein clearly do not have the significance O2 alleges. Enablement of the presently claimed invention does not depend on chance to the extent that it would render this case comparable to the cases underlying the strain of jurisprudence that refers to “*elite events*”. Based on the disclosure in the present Patent, the skilled person would have been able to carry out the invention as defined by the terms of the claims without undue burden.
175. The evidence in the Patent indeed shows that various different cells created in the Examples of the Patent allow the skilled person to practice the claimed invention. The same evidence also renders credible that there is no undue burden for the skilled person to obtain a particular cell line with a suitable expression level of functional rHuPH20.

176. For example, in Table 13 in Example 4 of the Patent, four different cell lines (out of four tested) obtained by adaptation to higher methotrexate levels all provide improved levels of enzyme activity relative to the activity achieved in cell cultures using the 3D35M cells, on which O2 relies as a point of comparison. See in this regard the values 6231 U/ml, 3831 U/ml, 11064 U/ml and 15684 U/ml, for cells 2E10, 1G11, 2G10 and 2B2, respectively, relative to harvest titers consistently under 2000 U/ml for 3D35M cells in Table 3. Table 14 in Example 5 shows that a further clone, 3E10B, also provided improved levels of enzyme activity in cell cultures relative to levels of enzyme activity in cell cultures using 3D35M cells (up to 6772 U/ml in the conditions of Example 5, see the penultimate line).
177. Thus, while Example 4 indicates that cells used in the “Gen1” process were further adapted to higher methotrexate levels to produce the cells used in “Gen2” experiments, success in obtaining a composition comprising rHuPH20 polypeptides as presently claimed does not depend on the exact identity of the cell line, much less on any specific “*rearrangement*” event that can only be obtained as a highly critical “*chance event*” that defines the entire invention, as alleged incorrectly by O2. 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 or unique and critical outcome within the cells, but rather would predictably provide a number of different suitable cells, as has been seen above.
178. Thus, the skilled person provided with the teaching of the Patent and wishing to produce a composition comprising a mixture of rHuPH20 polypeptides 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 a composition 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 the Patent will succeed in obtaining the composition as claimed credibly and predictably, not merely by chance.
179. 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 obtain an improved composition comprising a mixture of rHuPH20 polypeptides. Such method parameters relate, *inter alia*, to different culture media,

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.”*

180. Additionally, from a legal perspective, we note that the aspect of sufficiency of disclosure has already been considered and positively assessed in two other cases in this patent family: first, decision **T 1471/16** by Technical Board 3.3.8, and second, the preliminary opinion in opposition proceedings against EP 3 760 715 (also EP ‘715 herein). The claims in both of these cases were directed to the harvested cell culture fluid comprising rHuPH20 and recited specific levels of enzyme activity.

181. Briefly, in view of the technical teaching in the Patent, the Technical Board in **T 1471/16** decided:

“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”

(point 11 of the reasons).

182. Notably, the method for producing the harvested cell culture fluid in these earlier cases only differs from the method for producing the composition claimed in the present Patent in that the composition has further been subjected to the step h) of purifying the rHuPH200 from the harvested cell culture fluid. Thus, absent any verifiable facts to the contrary, the finding that the disclosure in the description is sufficient within the meaning of Art. 83 EPC for obtaining the improved harvested cell culture fluid of these earlier cases must be seen as *res iudicata* for obtaining the composition of the present Patent.

183. Furthermore, in view of the technical teaching in the Patent and facing similar objections from an opponent as presently raised by O2 relating to the alleged critical relevance of one specific cell line for sufficiency of disclosure, the preliminary opinion in the opposition proceedings against EP ‘715 indicated that the requirement of Art. 83 EPC is met, stating as part of their reasoning, e.g.:

“The Opposition Division considers that the gold standard for sufficiency of disclosure in opposition is T19/90: Serious doubts must be

substantiated by verifiable facts. The teaching of D2 stating that the site of integration of a vector in the host cell genome has a profound influence on expression levels does not qualify as verifiable fact convincing enough to invalidate the disclosure of the present patent: 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. Success has not only been achieved in e.g. examples 4,5; rather, in examples 7 and 8 the 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."

(Preliminary opinion in opposition proceedings against EP 3 760 715, November 30, 2022, point 8.3 of the reasons).

184. After issuance of this preliminary opinion, the opposition against EP '715 was withdrawn, so that no final decision could be reached. EP '715 was maintained as granted. Importantly, though, two instances have considered the issue of sufficient disclosure, and both instances have already found the requirements of Art. 83 EPC to be met.
185. Furthermore, we file herewith **D17**, which contains a sworn declaration by Michael LaBarre, Ph.D. and additional confirmatory data to which Dr. LaBarre refers. **D17** was already filed in response to the opposition against EP '715. **D17** is thus focussed on confirming that rHuPH20 with improved enzyme activity, which is a feature recited in claim 1 of EP '715, is obtained by different cells when following the teaching in the Patent. The declaration however also generally supports that improved production of rHuPH20 is not limited to the 2B2 cell line used in Example 8, contrary to O2's allegations in this regard in the present opposition. More specifically, **D17**, pages 10-11, in paragraphs 8 (a.) and (b.) and in Tables 3 and 4 confirm that activity yields within an improved range relative to those obtainable by the "Gen1" production processes 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 this same improved range were achieved even 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 also 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 improved activities, even beyond 18,000 units/ml (23,840 units/ml in Table 3, Pool 3; 18,895 units/ml in Table 4, Pool 2). As explained under inventive step, this constitutes a more than 10-fold improvement in enzyme activity in comparison to that achieved in **D3**.

186. Thus, O2's line of argumentation regarding the 2B2 cell line is unfounded. The reproducibility and enablement of the invention across the scope of the claims clearly does not depend on a particular cell line or otherwise on a "*chance event*". A skilled person can obtain the claimed composition based on the information provided in the patent, without undue burden or the exercise of inventive skill.

8.3 Patent provides sufficient guidance to obtain the mixture as claimed

187. O2 further alleges incorrectly that the patent is insufficient, because it allegedly "*provides the skilled person with no information as to the peptidases present when carrying out the methods of Example 3 (comparative) and Example 8, which the patent teaches led to the production of mixtures of polypeptides of SEQ ID NOs: 4-8*" ([123] of O2's opposition).
188. O2's objection in this regard is already flawed in that the Patent does not support O2's interpretation that "*peptidases present in the culture medium and in other solutions used in the production and purification steps is what causes the heterogeneity in the soluble rHUPH20 preparations*" ([124] of O2's opposition, emphasis added). Indeed, similar to O2's incorrect interpretation of the disclosure relating to obtaining suitable cell lines, O2's objection relating to peptidases is also already flawed in that it is based entirely on an incorrect linguistic interpretation of the actual disclosure of the patent. O2 has cited [0121], [0126] and [0288] of the patent as alleged evidence that it is the presence of peptidases that definitively "*is what causes*" the heterogeneity in the soluble rHuPH20 compositions. None of these paragraphs, however, support this interpretation. In fact, all of these paragraphs mention the presence of peptidases merely as a hypothetical "*likely*" cause:

[0121]

“[...] Such heterogeneity in the soluble rHuPH20 preparation is likely a result of C-terminal cleavage by peptidases present during the production and purification methods provided herein.” (emphasis added)

[0126]

“[...] As noted for soluble rHuPH20 produced from 3D35M cells, the heterogeneity in the soluble rHuPH20 preparation from 2B2 cells is likely a result of C-terminal cleavage by peptidases present during the production and purification methods provided herein.” (emphasis added)

[0288]

“This heterogeneity is likely the result of C-terminal cleavage of the expressed 447 amino acid polypeptide (SEQ ID NO:4) by peptidases present in the cell culture medium or other solutions during the production and purification process.” (emphasis added)

189. Already from a purely linguistic perspective, these sentences merely providing a hypothetical indication for one factor that might contribute to the observed C-terminal heterogeneity does not constitute verifiable evidence for O2’s incorrect conclusion that the presence of peptidases that definitively “is what causes” the heterogeneity in the soluble rHuPH20 compositions ([124] of O2’s opposition). Thus, O2 has not even discharged their burden of proof for this objection, because O2 has failed to provide anything that would constitute the serious doubts, substantiated by verifiable facts, that would allow a Patent to 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 **CLBA10**, II-C, 7.1.4, p.417). In the present *inter partes* proceedings, the burden of proof to establish such doubts lies with the Opponent.
190. Even if it was to be assumed that peptidases would make an essential contribution to the observed C-terminal heterogeneity in the claimed composition, although we deny that this can be derived from the Patent, O2’s objection in this regard still does not hold up. The person skilled in the art of protein expression and purification knows, from their common general knowledge, that peptidases are present during the expression and purification process, because they are released from cells during cell culture. Thus, peptidases are inherently present during production of the claimed composition. O2’s allegation that the “*patent provides no guidance whatsoever as to*

how to control peptidases present in the culture medium or other solutions used in the production or purification steps of the method” is incorrect. The patent provides extensive guidance on the culture method for obtaining the claimed composition, and particularly on how CHO cells should be cultured to maximise productivity.

191. Thus, O2’s line of argumentation regarding the peptidases is also unfounded. the reproducibility and enablement of the invention across the scope of the claims does clearly not depend on the presence of particular peptidases or any “*chance event*” related thereto. A skilled person can obtain a composition comprising a mixture of rHuPH20 polypeptides according to the present claims without undue burden.

8.4 The claims comply with Art. 83 EPC

192. As can be seen from the detailed discussion above, neither of the opponents have provided any verifiable arguments, let alone any evidence, why it would not be possible to obtain the claimed composition based on the teaching in the Patent. O1’s allegations are based on an incorrect interpretation of data. O2’s allegations are based on an incorrect interpretation of the language in the patent. Neither of these approaches of misconstruing the true disclosure of the Patent constitute the serious doubts, substantiated by verifiable facts, that would allow a Patent to 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 **CLBA10**, II-C, 7.1.4, p.417). The Opponents have thus failed to discharge their burden of proof.
193. In contrast, the Patent provides extensive teaching that demonstrably enables the skilled person to practice the invention over the entire claim scope without undue burden. This is further supported, e.g., by the declaration submitted with the response to the opposition against EP ‘715 (herein **D17**).
194. The present claims as granted meet the requirements of Article 83 EPC.

9 Conclusion on the Opponents’ submissions

195. The Oppositions lack merit and are to be rejected.

10 Auxiliary claim requests

196. Purely as a precaution, in case the Proprietor's Main Request should not be allowed, Auxiliary Requests (ARs) are also submitted. The opponents have raised various entirely distinct objections, which the individual amendments in ARs 1-7 endeavour to address. It is not foreseeable which, if any, of those objections, alone or in combination, could be successful in these proceedings. ARs 8-95 thus simply contain combinations of the individual amendments in ARs 1-7. ARs 8-95 do not introduce any further claim amendments compared to ARs 1-7.
197. For ease of reference, an overview of all ARs filed herewith is provided in the table of Annex A to this submission.
198. The individual amendments in ARs 1-7 are discussed in more detail below.

10.1 Auxiliary Request 1

199. In AR1, claim 1 is limited to rHuPH20 that is encoded by the nucleic acid set forth in SEQ ID NO: 47 (granted claim 16). This amendment is filed as a precaution in view of O2's objections under Article 100(c) EPC alleging that a soluble rHuPH20 preparation containing polypeptides having amino acid sequences set forth in SEQ ID NO: 4-8 would be inextricably linked to the length of the polypeptide encoded by the cell line, and under Art. 54 EPC that the cells may contain one or more nucleic acids, each encoding a rHuPH20 polypeptide of a different length. Neither Opponent has substantiated or even raised such objections against granted claim 16, e.g., its basis has not been contested. rHuPH20 encoded by the nucleic acid set forth in SEQ ID NO: 47 is disclosed in the application as filed and a composition obtainable according to amended claim 1 of AR1 is novel, for the same reasons as have already been set out above with respect to the Main Request.

10.2 Auxiliary Request 2

200. In AR2, the cells used for the recombinant expression of soluble rHuPH20 according to claim 1 are limited to DG44 CHO cells, as in granted claim 15. This amendment is filed as a precaution in view of O1's objections under Article 100(c) EPC alleging that claim 1 amounts to an intermediate generalisation, because the CHO cells are not further specified or defined, and as a precaution in view of O2's objections under Art. 100(b) EPC that the skilled person would be unable to reproduce the claimed composition. Neither Opponent has substantiated or even raised such objections against granted claim 15, e.g., its basis has not been contested. rHuPH20 expressed

by DG44 CHO cells is credibly enabled, for the same reasons as have already been set out above with respect to the Main Request.

10.3 Auxiliary Request 3

201. In AR3, the specific activity of rHuPH20 according to claim 1 is limited to at least 100000, 120000, 140000, 160000 or 180000 units/mg, as in granted claim 13. This amendment is filed as a precaution in view of O1's and O2's objections under Article 56 EPC alleging that the composition of claim 1 does not have improved hyaluronidase activity and/or is not inventive with respect to the prior art composition. Neither Opponent has substantiated or even raised objections against granted claim 13, e.g., its basis has not been contested. rHuPH20 with these levels of specific activity is improved with respect to rHuPH20 compositions disclosed in the prior art, and is credibly inventive, for the same reasons as have already been set out above with respect to the Main Request.
202. Amended claim 1 of AR3 yet further reflects the advantages in rHuPH20 compositions that are achieved by the use of the "Gen2" process, in terms of a higher content in active rHuPH20 species and lower content in inactive (e.g., aggregated or hydrolysed) rHuPH20 species. Compositions with such high specific activities are neither disclosed in the cited prior art (Art. 54 EPC), nor would they have been achievable in an obvious manner and with a reasonable expectation of success without knowledge of the nonobvious "Gen2" production method (Art. 56 EPC).

10.4 Auxiliary Request 4

203. In AR4, claim 1 is limited to the amount of soluble rHuPH20 produced being at least 1, 5, 10, 15, 20, 25, 30, 35 or 40 grams per 100 L of cell culture (based on granted claim 12). This amendment is filed as a precaution in view of O1's and O2's objections under Article 56 EPC alleging that the composition of claim 1 is not improved or inventive with respect to the prior art composition. Neither Opponent has substantiated or even raised such objections against granted claim 12, e.g., its basis has not been contested. rHuPH20 with such high yields was not obtainable by methods known in the prior art, and is involves an inventive step for the same reasons as have already been set out above with respect to the Main Request and AR3 above.

10.5 Auxiliary Request 5

204. In AR5, claim 1, step (g) is limited to require that the harvest cell culture fluid ("HCCF") comprises soluble recombinant human PH20 (rHuPH20) with an enzymatic activity that is greater than 5000 and less than or equal to 24,000 units of hyaluronidase activity/mL of cell culture fluid as harvested, wherein an assay to determine said hyaluronidase activity, and further aspects of the HCCF are also defined. This amendment is filed as a precaution in view of O1's and O2's objections under Article 56 EPC alleging that the composition of claim 1 is not improved or inventive with respect to the prior art composition.
205. The amendments in AR5 were also contained in the main claim considered and held allowable by the Board of Appeal in **T 1471/16**, with the exception that in that decision the upper limit of the hyaluronidase activity was 18,000 units/mL rather than 24,000 units/mL. The corresponding upper-limit feature of 24,000 units/mL was however granted subsequently, after detailed consideration of that difference, in claim 1 of divisional case EP 3 760 715 B1, which was previously opposed. In that regard the reasoning in **D19**, the preliminary opinion of the OD in that opposition, applies, specifically the reasoning in point 7.3.3 (middle / lower half of page 5) under Articles 100(c), point 8.3 (second paragraph of page 7) under Articles 100(b), and point 9.3.1 under Articles 100(a)/56. As mentioned above, after the issuance of that preliminary opinion, the opposition to EP 3 760 715 B1 was withdrawn.
206. Specifically, the amendments find basis in the Original Disclosure on pages 5, lines 28-30 and PCT claim 20 (activity range), page 10, lines 12-17 (definition of HCCF), and page 62 in combination with page 107, lines 3-15 (the generalised description at the beginning of Example 9) – see reasons 4-6 of **T 1471/16**.
207. The higher activity value "24.000" was not as such a claim feature before the Board in **T 1471/16** but was considered to find basis in the Original Disclosure by the OD with strong reasons in **D19** (point 7.3.3 (middle / lower half of page 5)). The value "24.000" could not conceivably represent or contribute toward any added matter in the context of the Gen2 method or its products, for the following reasons:
208. 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".*

209. 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".
210. 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".
211. In the present circumstances, this is clearly the case 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".
212. 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 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.
213. 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)

214. Further, as noted by the Opposition Division in D19, point 7.3.3 of its reasoning:

"As the application aims to maximise the large scale production of hyaluronidase (see page 42, lines 17-21; the production is measured via its activity), the skilled person will infer that the higher the activity, the more preferred it is. As said before, as the enzyme activity cannot be infinite, from the list of converging values in the par. bridging pages 5 and 6, the skilled person will inevitably contemplate selecting the highest upper value mentioned i.e the value of 24,000 U/ml. The associated advantage is not unwarranted, because it is what the application explicitly aims for."

215. Thus, the amended features of AR5 find basis in the Original Disclosure.

216. AR5 underlines yet further that the claimed invention meets the requirements of Articles 54 and 56 EPC. The HCCF is an intermediate product of the "Gen2" method for use in the further production of soluble HCCF (see **T 1471/16**, r. 10, already cited above in section 4). The fact that the HCCF in step (g) has the high activity levels that are imparted only by the "Gen2" production process, yet further underlines the distinctions between the presently defined "Gen2" compositions and "Gen1" compositions of the prior art, as have been discussed in the context of the Main Request.

217. As acknowledged by the Board of appeal in **T 1471/16**, the high content of rHuPH20 activity in the intermediate HCCF product not obtainable by the "Gen1" production process of the prior art, and thus confers an inventive step over that prior art. The skilled person would not have had any reasonable expectation of success in obtaining such a high content of activity. The Opposition Division in **D19** (point 9.3.1) came to the same conclusion.

218. The advantages in terms of a higher content in active species in compositions obtained from the "Gen2" as compared to the prior-art "Gen1" method have been explained further herein in the context of the Main Request and by reference to the additional evidence in **D16**. By specifying the high activity in the "Gen2" HCCF of

process step (g), the amendments in AR5 underline that these advantages are achieved. These advantages over products of “Gen1” methods will likewise be reflected in the purified composition as presently claimed – the only additional processing step in the process of claim 1 after obtaining the HCCF in step (g) is the final purification step (h).

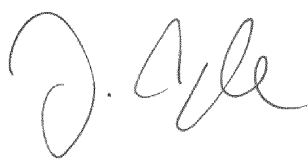
219. In conclusion, AR5 meets the requirements of the EPC.

10.6 Auxiliary Requests 6 and 7

220. In AR6 and AR7, claim 1 is limited to more specifically defined method steps as in granted claims 10 and 11, respectively. In particular, this includes more specific requirements regarding the temperature of the cell culture, the concentrations of feed media components, the volume of feed media added, and the types of purification methods used. Both claims 10 and 11 as granted have been removed as dependent claims from AR6 and AR7, in accordance with the respective amendments to claim 1 of each of these requests.

221. These amendments are filed as a precaution in view of O1’s allegation under Art. 56 EPC that the method is not sufficiently distinguished from the method disclosed in the prior art, and as a precaution in view of O2’s allegations under Art. 54 EPC that the method steps are too broadly defined, it would be standard in the art to use multiple feeding steps and that claim 1 does not specify and particular purification steps.

222. Claim 1 according to either of AR6 or AR7 is novel and inventive for the same reasons as have already been set out above with respect to the Main Request.



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

Enc. Documents D16-D19
Auxiliary Requests 1-95 (clean and marked up copies)
Annex A (overview table of Auxiliary Requests)

ANNEX A - OVERVIEW OF AUXILIARY CLAIM REQUESTS (ARs)

Amendment AR	1 SEQ ID NO: 47	2 DG44 CHO	3 Specific activity	4 g/100L	5 HCCF activity	6 granted claim 10	7 granted claim 11
1	X						
2		X					
3			X				
4				X			
5					X		
6						X	
7							X
8	X	X					
9	X		X				
10	X			X			
11	X				X		
12	X					X	
13	X						X
14		X	X				
15		X		X			
16		X			X		
17		X				X	
18		X					X
19			X	X			
20			X		X		
21			X			X	
22			X				X
23				X	X		
24				X		X	
25				X			X
26					X	X	
27					X		X
28	X	X	X				
29	X	X		X			
30	X	X			X		
31	X	X				X	
32	X	X					X
33	X		X	X			
34	X		X		X		
35	X		X			X	
36	X		X				X
37	X			X	X		
38	X			X		X	

Amendment AR	1 SEQ ID NO: 47	2 DG44 CHO	3 Specific activity	4 g/100L	5 HCCF activity	6 granted claim 10	7 granted claim 11
39	X			X			X
40	X				X	X	
41	X				X		X
42		X	X	X			
43		X	X		X		
44		X	X			X	
45		X	X				X
46		X		X	X		
47		X		X		X	
48		X		X			X
49		X			X	X	
50		X			X		X
51			X	X	X		
52			X	X		X	
53			X	X			X
54			X		X	X	
55			X		X		X
56				X	X	X	
57				X	X		X
58	X	X	X	X			
59	X	X	X		X		
60	X	X	X			X	
61	X	X	X				X
62	X	X		X	X		
63	X	X		X		X	
64	X	X		X			X
65	X	X			X	X	
66	X	X			X		X
67	X		X	X	X		
68	X		X	X		X	
69	X		X	X			X
70	X		X		X	X	
71	X		X		X		X
72	X			X	X	X	
73	X			X	X		X
74		X	X	X	X		
75		X	X	X		X	
76		X	X	X			X
77		X	X		X	X	
78		X	X		X		X
79		X		X	X	X	
80		X		X	X		X
81			X	X	X	X	

Amendment AR	1 SEQ ID NO: 47	2 DG44 CHO	3 Specific activity	4 g/100L	5 HCCF activity	6 granted claim 10	7 granted claim 11
82			X	X	X		X
83	X	X	X	X	X		
84	X	X	X	X		X	
85	X	X	X	X			X
86	X	X	X		X	X	
87	X	X	X		X		X
88	X	X		X	X	X	
89	X	X		X	X		X
90	X		X	X	X	X	
91	X		X	X	X		X
92		X	X	X	X	X	
93		X	X	X	X		X
94	X	X	X	X	X	X	
95	X	X	X	X	X		X

Declaration by Anna-Maria Hays Putnam, PhD

I am Anna-Maria Hays Putnam, declare as follows:

(1) I am familiar with the subject matter of the European Patent 4 269 578 (hereinafter: EP'578), which granted June 5, 2024.

(2) Vice President of Development and Manufacturing at Halozyme in San Diego, USA. I was awarded a PhD degree in Biochemistry at the University of California, Riverside (USA) in the field of Protein Engineering and Design. I have been employed by Halozyme since 2012. I have been responsible for analytical testing and characterization of Halozyme's hyaluronidase product (also referred to as "soluble recombinant human PH20" or "soluble rHuPH20") since 2012, and subsequently held roles with increasing responsibility in process development and manufacturing of soluble rHuPH20 at Halozyme.

(3) I have been asked by the patent attorneys of Hoffmann Eitle to comment on technical questions arising in opposition proceedings at the European Patent Office concerning Halozyme's EP'578, which concerns aspects of Halozyme's hyaluronidase products and production platform.

(4) I am competent and authorised to make this declaration, because I have been involved in the development and improvement of Halozyme's hyaluronidase production platform since 2012. The development of Halozyme's hyaluronidase production platform initially led to the invention described in US 2004/0268425 A1 (hereinafter: D3 in accordance with its numbering in the opposition proceedings against EP'578). Subsequent developments at Halozyme over a period of several years later led to the invention described in EP'578. Internally, we designate the earliest hyaluronidase production process, which corresponds to the process essentially as mentioned in D3, as "Gen1" (i.e., Generation 1), and the hyaluronidase production process first described in EP'578 as "Gen2" (i.e., Generation 2). I have been working closely with the inventors listed on both these patents. I am also highly experienced in working with the improved "Gen2" hyaluronidase production process as part of my current role and previous roles I held at Halozyme.

(5) Specifically, the patent attorneys of Hoffmann Eitle have informed me that the opponents of EP'578:

- i. question whether the "Gen2" hyaluronidase production process and resulting hyaluronidase compositions are significantly different from the "Gen1" hyaluronidase production process and the hyaluronidase compositions it produces,

- ii. question whether a hyaluronidase composition produced by the “Gen2” process is an improved product relative to a hyaluronidase composition produced by the “Gen1” process, and
- iii. hypothesize that the data in D3 demonstrates that the hyaluronidase of SEQ ID NO: 4 has lower enzyme activity than, e.g., the hyaluronidase of SEQ ID NO: 5

(6) As an introductory remark, I note that EP’578 describes the results of years of careful work that was undertaken at Halozyme with the aim of providing a further improved hyaluronidase product. The further improvement was, specifically, relative to the hyaluronidase product described in D3.

(7) D3 describes early foundation work on the hyaluronidase expression construct, in particular, the achievement of a soluble recombinant human hyaluronidase product by introducing C-terminal truncations to remove the GPI anchor and modifying the signal peptide. In terms of the production process, D3 only contains one small-scale proof-of-concept study demonstrating that the engineered protein of D3 can be produced in a recombinant expression system and is soluble and enzymatically active. The early version of the “Gen1” hyaluronidase production process as described in D3 was not suitable for commercial applications, because it was not developed specifically for large-scale production.

(8) The improved hyaluronidase production process of EP’578 differs from the process in D3 in several steps, which were all specifically altered to increase the relative content of active enzyme in the resulting composition. The improved “Gen2” large-scale production process described in EP’578 enabled production of hyaluronidase with an improved product profile at a larger scale and with a higher content of active enzyme. The hyaluronidase produced by the process in EP’578 is a successful commercial product that is used in co-administration of several commercialized drugs, where it helps to enable rapid, high-volume subcutaneous delivery of the co-administered drugs.

(9) Herein I explain and illustrate that the “Gen1” and “Gen2” hyaluronidase production processes differ in many aspects, and that a hyaluronidase composition produced by the “Gen2” process has an improved product profile and a higher content of active enzyme relative to that produced by the “Gen1” process. Moreover, I explain the enzyme activity data shown for different C-terminally truncated variants in D3.

The “Gen1” and “Gen2” hyaluronidase production process are different

(10) There are many differences between the small-scale proof-of-concept expression study of the early version of the “Gen1” manufacturing process mentioned in D3 and the improved production “Gen2” manufacturing process of EP’578. For example, the culturing process in EP’578 was changed relative to that of D3 by the following modifications:

1. Gradually reducing the temperature by specific amounts at specific times throughout the culturing process,
2. Modifying the composition of the feed media,
3. Modifying the number of feeds, and
4. Identifying the ideal time for harvesting.

(11) Changing such cell culture parameters to enable large-scale production of a specific protein product is not trivial. Each of the steps needs to be improved to maximize productivity individually, and it also needs to be ensured that enhanced productivity in one step does not have a negative effect on productivity in other steps. The development of the “Gen2” hyaluronidase production process was therefore a long-term research project that took several years to complete.

(12) Together, the various altered cell culture parameters act synergistically to produce an improved hyaluronidase product. Representative data generated at Halozyme to compare “Gen1” and “Gen2” hyaluronidase at different stages during the production process are summarized below. All these data show that “Gen2” hyaluronidase is a distinct and better product than “Gen1” hyaluronidase, in terms of both structural quality attributes and the maximally achievable titer of active hyaluronidase.

Structural differences

(13) While there is of course a certain extent of batch-to-batch variation when producing recombinant proteins, hyaluronidase compositions produced by the “Gen1” and “Gen2” processes are significantly and reproducibly different in terms of several structural attributes. In effect, hyaluronidase compositions have one of two distinct structural “fingerprints”, comparable to a “process-specific I.D.”, depending on whether it is the product of the “Gen1” or the “Gen2” process. These structural “fingerprints” involve characteristic C-terminal truncation patterns and product-related impurity patterns, which are distinctive of each process.

Distinct C-terminal truncation fingerprints

(14) Each product of these processes is, in effect, a composition in the sense that it comprises a mixture of hyaluronidase polypeptides that are C-terminally truncated at different positions. Compared to the “Gen1” process, the “Gen2” process gives rise to a distinct pattern of proportions of the individual C-terminally truncated polypeptides within such a mixture. These characteristic patterns of C-terminal truncations and their abundancies thus each amount to a structural “fingerprint” or “I.D.” that distinguishes these two types of hyaluronidase products. Overall, less C-terminal truncation is observed in hyaluronidase batches produced by the “Gen2” process than in hyaluronidase batches produced by the “Gen1” process, such that, in summary, the longer polypeptide species are more abundant in the “Gen2” product than in the “Gen1” product.

(15) It is my understanding that these data concerning the distinct pattern of proportions of the individual C-terminally truncated polypeptides in the compositions both as reflected in EP '578, as well as in two further “Gen1” batches and three further “Gen2” batches have already been presented separately in these opposition proceedings, e.g., in the document included as D6. To avoid unnecessary duplication, these data are thus not shown again herein, but I declare that all statements made on behalf of Halozyme regarding these data are of my own knowledge true.

“Gen2” hyaluronidase has lower levels of aggregation than “Gen1” hyaluronidase

(16) The structural “fingerprints” of hyaluronidase compositions obtained by the “Gen2” and “Gen1” production processes also include distinctive structural quality attributes, such as reproducibly different contents in product-related impurities. One relevant type of product-related impurity is the amount of aggregated protein material, also referred to as “high molecular weight” or “HMW” species. The presence of this aggregation impurity after “Gen1” and “Gen2” production processes was measured using size exclusion high-performance liquid chromatograph (SE-HPLC). This technique identifies aggregated HMW species, because the retention time of the aggregated HMW peak on the HPLC elution profile is shifted relative to the main peak for the intact hyaluronidase.

(17) The content of aggregated “HMW” hyaluronidase impurity was calculated using SE-HPLC to determine the % area under the respective peaks in the elution profile, i.e.:

$$\text{HMW (\% area)} = (\text{area under HMW aggregate peak}) / (\text{area under monomer peak} + \text{area under HMW aggregate peak}) \times 100$$

“Gen2” hyaluronidase has lower levels of degradation than “Gen1” hyaluronidase

(22) Another structural quality attribute of the hyaluronidase products concerning product-related impurities is the amount of degraded protein material, specifically hyaluronidase that has been hydrolyzed between residues 311 and 312 (also referred to as “hydrolyzed” species). Hyaluronidase has a natural protease cleavage site on the C-terminal side of arginine 311. The more active proteases are present in a given batch, the more cleavage at this site will be observed. This type of protein degradation is thus also an indicator of quality of the hyaluronidase product.

(23) The presence of this hydrolyzation impurity was measured by using reverse phase high performance liquid chromatography (RP-HPLC). This technique identifies hydrolyzed species, because the retention time of the hydrolyzed peak on the HPLC elution profile is shifted relative to the main peak for the intact hyaluronidase.

(24) The content of hydrolyzed hyaluronidase impurity was calculated by using RP-HPLC to determine the % area under the respective peaks in the elution profile, i.e.:

hydrolyzed (% area) = (area under hydrolyzed peak) / (area under monomer peak + area under hydrolyzed peak)) x 100

(25) The following graph shows the % area under peak corresponding to the degraded “hydrolyzed” species detected in 5 exemplary acceptable batches of “Gen1” hyaluronidase (red, circles) in comparison to 33 exemplary acceptable batches of “Gen2” hyaluronidase (green, triangles). Each marker represents an individual batch:

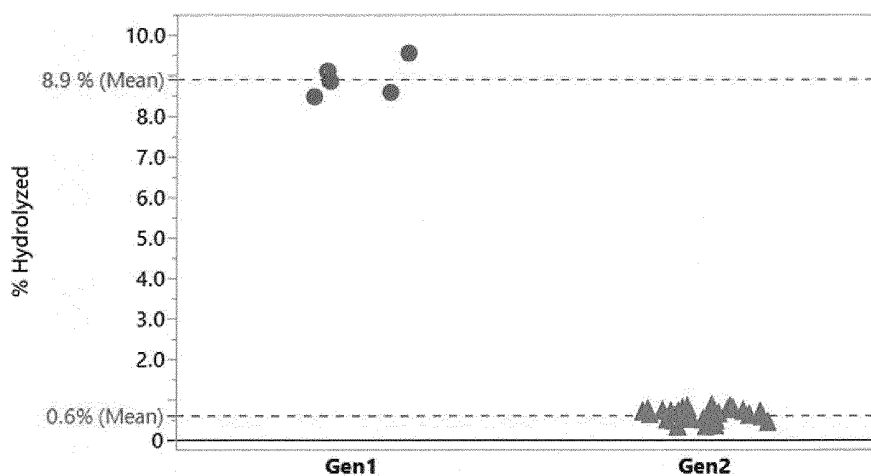


Figure 2 - Proportion of degraded (“hydrolyzed”) hyaluronidase product in “Gen1” (red, circles) vs “Gen2” batches (green, triangles)

(26) While there is naturally some batch-to-batch variation, it is clear from these data that not a single “Gen1” batch exhibited the low levels of “hydrolyzed” species that are consistently exhibited by “Gen2” batches of hyaluronidase. More specifically, the % degraded “hydrolyzed” species for “Gen1” hyaluronidase batches varied **between approximately 8% and 10% (average 8.9%)**, whereas the % degraded “hydrolyzed” species for “Gen2” hyaluronidase batches **was consistently ≤ 1% (average 0.1%)**.

(27) Thus, the “Gen2” hyaluronidase production process produces hyaluronidase batches with significantly lower hydrolyzation at the 311-312 position than the “Gen1” hyaluronidase production process. Moreover, these data from many different batches also demonstrate that this improved structural quality attribute of lower hydrolyzation is reproducibly achieved.

(28) Importantly, lower hydrolyzation in the final product reduces the risk of causing structural disruptions that may have a negative impact on enzyme activity. Thus, lower degradation levels as measured by these “hydrolyzed species” are a measure of improved quality of the final hyaluronidase product.

Functional quality attributes

The “Gen2” process results in a higher enzyme activity per ml of unclarified culture fluid

(29) The improved structural quality attributes discussed above are reflected in functional quality attributes.

(30) One functional quality attribute that is important as an indicator of a high-quality hyaluronidase culture batch is enzyme activity per ml of unclarified culture fluid.

(31) The higher the enzyme activity per ml of unclarified culture fluid, the more cells have been generated in the process and the higher the integrity and quality of the hyaluronidase that they produce. Ultimately, more active hyaluronidase has been produced per unit volume of cell culture. Measurements of enzyme activity in samples of unclarified culture fluid, prior to any further processing, provide a direct comparison of how much enzymatically active hyaluronidase is produced by different culture processes. Such measurements are not influenced by any downstream processing, such as filtration, concentration or purification.

(32) While there is of course a certain extent of batch-to-batch variation when producing recombinant proteins, the amounts of enzymatically active hyaluronidase (titer) produced by the “Gen1” and “Gen2” processes were significantly and reproducibly different.

(33) The following graph shows the units of enzyme activity per ml of cell culture fluid detected in 5 exemplary acceptable batches of “Gen1” hyaluronidase (red, circles) in comparison to 33 exemplary acceptable batches of “Gen2” hyaluronidase (green, triangles). Each marker represents an individual batch:

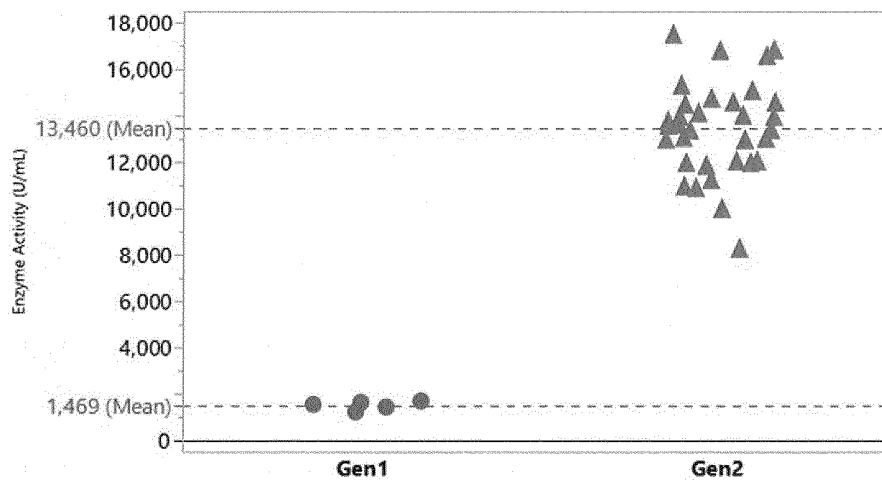


Figure 3 – Units of enzyme activity detected per ml in the unprocessed, harvested cell culture fluid of “Gen1” (red, circle) vs “Gen2” batches (green, triangles) of hyaluronidase

(34) It is clear from these data that not a single “Gen1” batch exhibited the high levels of enzyme activity per ml of culture fluid that are consistently achieved by “Gen2” batches of hyaluronidase. More specifically, the enzyme activity for “Gen1” hyaluronidase batches varied between approximately 1,180 – 1,650 U/mL (average = 1,469 U/mL), whereas the enzyme activity for “Gen2” hyaluronidase batches was consistently >8,200 U/mL (average = 13,460 U/mL).

(35) Thus, the “Gen2” hyaluronidase production process produces hyaluronidase batches with significantly higher content of active enzyme per ml than the “Gen1” process. Moreover, these data from many different batches demonstrate that the improved content of active enzyme per ml is reproducibly achieved.

(36) The improvement is attributable to the “Gen2” hyaluronidase production process.

Conclusions on improvements of Halozyme's "Gen1" versus "Gen2" hyaluronidase

(37) The data discussed herein demonstrate that Halozyme's "Gen2" hyaluronidase production process enables production of a structurally distinct and functionally superior hyaluronidase product compared to Halozyme's earlier "Gen1" hyaluronidase production process.

(38) As discussed above, the hyaluronidase batches produced by each of these processes are, effectively, mixtures of polypeptides having hyaluronidase sequences. An important factor explaining the improvement in the "Gen2" hyaluronidase product compared to that of "Gen1" in my opinion is that, within these mixtures that are ultimately produced from the recombinant cell cultures, the altered "Gen2" production process minimizes the proportion of inactive product-related variants such as aggregates and hydrolyzed species and maximizes the proportion of hyaluronidase species that are structurally intact and thus active.

Measuring activity of hyaluronidase with the microtiter plate-based assay

(39) The patent attorneys at Hoffmann Eitle informed me that the opponents attempt to draw conclusions on the activity of individual polypeptide species based on data in the table in paragraph [0564] of D3. Given my detailed insights into the development and improvement of Halozyme's hyaluronidase production and testing platform, including the monitoring of quality attributes such as enzyme activity, I can provide technical explanations in this regard.

(40) I strongly disagree with both opponents' interpretation of the data in this table of D3. Both opponents draw conclusions on the activities of certain polypeptide species in this table and extrapolate them to SEQ ID NOs: 4-8 as claimed in EP'578. These analyses misconstrue what is shown in the D3 table, for at least the following reasons.

(41) The assay used to measure the enzyme activity in D3 is the microtiter plate-based hyaluronidase assay using a biotinylated hyaluronic acid substrate set out in Example 1 of D3. Over the years, Halozyme has used different assays to measure hyaluronidase activity for different purposes. In some experiments (e.g., immediately before product release for commercial purposes), it is important to obtain highly accurate activity measurements with low error. In other instances, a rough indication of activity with higher error margins is sufficient to obtain the relevant information. The data shown in the table in paragraph [0564] of D3 is the result of an assay that only provides a rough indication of activity and has high error margins.

(42) The reason this assay was chosen is also clear from the context of paragraph [0564] of D3, which is part of Example 4. Example 4 describes how the gene encoding hyaluronidase was isolated from human PH20 cDNA, and truncation mutants were individually produced and separately assessed for activity with the microtiter plate-based hyaluronidase assay, with the aim of determining the minimally active domain of human hyaluronidase. More specifically, in D3, this assay was used to determine (i) how many amino acids need to be removed from the C-terminus to give rise to a soluble hyaluronidase lacking the GPI anchor and (ii) if there is a point when too many amino acids have been removed from the C-terminus and activity drops to zero.

(43) In other words, the assay used to generate the data shown in [0564] of D3 was used to provide a “yes or no” answer to the – essentially qualitative – question: “Is the truncated enzyme construct active?”. The assay is not accurate enough to resolve small differences in activity, nor was it used for this purpose in D3. In reality, our internal analyses show that the variability of data generated by this assay around the time the data in D3 was generated was up to +/- 50%. Thus, in practice, this assay was only useful to distinguish between enzymes with high activity and enzymes with little to no activity, as illustrated by the below color coded and annotated version of the table in [0564] of D3:

Amino acid 1 to:	Enzyme activity (U/ml/24 h)	Conclusion
347	0.000	Inactive
372	0.000	Inactive
394	0.000	Inactive
413	0.000	Inactive
430	0.000	Inactive
447	0.000	Inactive
467	0.089	Inactive/low activity
477	0.567	Active
478	0.692	Active
479	0.750	Active
480	0.575	Active
481	0.740	Active
482	0.392	Active
483	0.800	Active
509	0.044	Inactive/low activity

(44) The graph below is a plot of these same data from D3, with measured enzyme activity on the y-axis plotted versus length of the polypeptide on the x-axis, and further illustrates this distinction:

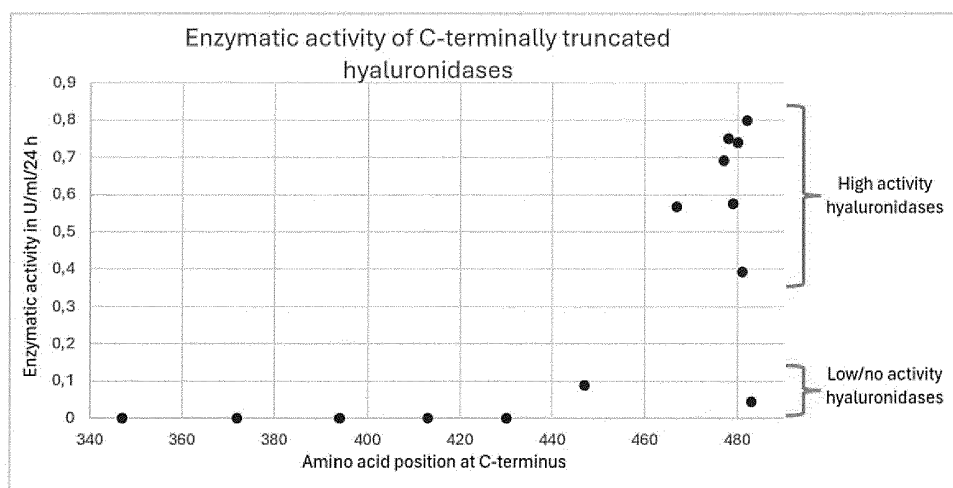


Figure 1 - Data from [0564] of D3, plotted

(45) As can be seen from both the Table and Figure 4 above, the only meaningful conclusion that can be drawn from the data in [0564] of D3 is of a qualitative nature, i.e., whether a given hyaluronidase construct is active or not.

(46) For the purpose of the experiment in Example 4 of D3, this was entirely sufficient: the assay allowed us to conclude that a construct having the GPI anchor that terminates at position 509 has little to no enzyme activity, constructs that terminate between positions 483 and 477 have much higher enzyme activity, and constructs that terminate at position 467 or even shorter constructs again have little to no enzyme activity.

(47) However, this microtiter plate-based hyaluronidase activity assay in D3 was not accurate enough to support the conclusions drawn by the opponents on supposed differences in activity of the polypeptides ending in amino acids 477-482 shown in the table in [0564] of D3.

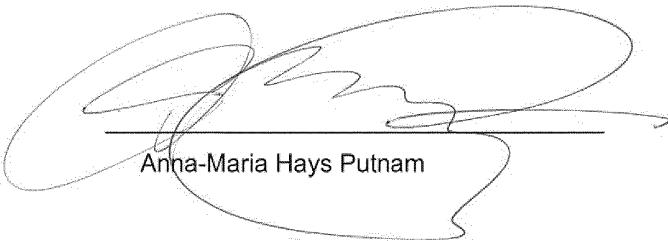
Conclusion

(48) Based on the foregoing data, Halozyme has generated an improved hyaluronidase product using the "Gen2" production process that can be distinguished from hyaluronidase

product generated by the “Gen1” production process by a unique structural fingerprint and improved functional quality attributes, as described herein.

(49) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

16 July 2025
Date


Anna-Maria Hays Putnam

DECLARATION PURSUANT TO 37 C.F.R. §1.132

Our Ref.: 225 788 m10/ann

Opposition proceedings concerning

European Patent: 3 760 715 B1

Granted: August 4, 2021

Inventors: Baker, David; Bookbinder, Louis

Title: LARGE-SCALE PRODUCTION OF SOLUBLE HYALURONIDASE

Sir:

I, MICHAEL LABARRE, declare as follows:

1) I am familiar with the subject matter of the above-captioned patent, which granted August 4, 2021.

2) I have reviewed the Opposition filed May 4, 2022, in connection with the above-captioned application. I have also reviewed Decision T 1471/16 of Board of Appeal 3.3.08 concerning the parent application to the present case.

3) I currently am Senior Vice President and the Chief Technical Officer at Halozyne Therapeutics, Inc. ("Halozyne"). I have held this position since January 2020. Previously, I was employed at Halozyne as Vice President of Product Development from September 2017 to December 2019, Vice President of Product Development and Chief Scientific Officer from August 2015 to August 2017, Vice President of Product Development and Alliances from January 2012 to July 2015, and Vice President of Product Development from June 2008 to December 2011.

4) From April 2006 to June 2008, I was employed as Vice President of Product Development at Paramount Biosciences. From December 2003 to April 2006, I was employed as Director of Analytical and Formulation Sciences at Biogen Idec. From November 1995 to December 2003, I was employed as Director of Analytical and Formulation Sciences at IDEC Pharmaceuticals. From September 1993 to December 1999, I was employed as adjunct faculty in the Department of Chemistry at San Diego Mesa College. From January 1994 to November 1995, I also was employed as a Scientist at Vical. From September 1992 to December 1993, I was employed as a Scientist at Hybritech. I received a Ph.D. in Chemistry from the University of Arizona, in 1992, and a Bachelor of Science in Chemistry from Long Island University, Southampton Campus, in 1985.

Inventors : Baker et al.
Patent No. : EP 3 760 715 B1
Granted : August 4, 2021

Declaration under 37 C.F.R. § 1.132

5) The above-captioned patent describes methods for large-scale production of recombinant human PH20 (rHuPH20) and a harvested cell culture fluid, comprising soluble rHuPH20. The patent further describes methods for the production and purification of soluble hyaluronidases. In particular, described are methods for the production and purification of soluble rHuPH20. Also described are cell culture medium and harvested cell culture fluid that contain soluble rHuPH20 with an enzymatic activity of 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.

6) Between 2010 and 2022, Halozyme manufactured over one-hundred clinical (GMP) and commercial batches, or homogeneous pools, of soluble rHuPH20 according to the methods described in European Patent 3 760 715 B1. Table 1 (below) provides a listing of the batches, including date of manufacture, that were used to provide the subsequent yields and accompanying statistical analysis provided in this declaration. In particular, one harvested cell culture fluid sample for each batch, produced per the methods described in European Patent 3 760 715 B1 and containing the nucleic acid encoding soluble recombinant human PH20 (rHuPH20), were tested for enzymatic activity. The Chinese hamster ovary (CHO) cell line DG44, designated 2B2, was used for these batches.

Table 1: Historical Batches Used for the Statistical Analysis

Batch Number	Date of Manufacture	Batch Number	Date of Manufacture
HUB1001C	07/01/2010	HUB1603M	04/01/2016
HUB1004C	09/10/2010	HUB1604M	04/20/2016
HUB1005C	10/12/2010	HUB1605M	05/12/2016
HUB1006C	11/03/2010	HUB1607M	06/19/2016
HUB1101C	02/23/2011	HUB1608M	07/12/2016
HUB1202C	06/08/2012	HUB1609M	07/30/2016
HUB1203C	06/29/2012	HUB1610M	08/19/2016
HUB1204C	07/20/2012	HUB1611M	09/10/2016
HUB1205C	08/10/2012	HUB1612M	09/27/2016
HUB1206C	09/07/2012	HUB1613M	10/15/2016
HUB1207C	09/28/2012	HUB1614M	12/20/2016
HUB1208C	10/19/2012	HUB1615M	01/13/2017
HUB1209C	12/21/2012	HUB1616M	01/31/2017

Inventors : Baker et al.
Patent No. : EP 3 760 715 B1
Granted : August 4, 2021

Declaration under 37 C.F.R. § 1.132

Batch Number	Date of Manufacture	Batch Number	Date of Manufacture
HUB1210C	01/16/2013	HUB1701M	03/03/2017
HUB1211C	02/06/2013	HUB1702M	03/22/2017
HUB1301C	02/26/2013	HUB1703M	04/09/2017
HUB1302C	03/21/2013	HUB1704M	05/08/2017
HUB1303C	04/10/2013	HUB1705M	05/31/2017
HUB1304C	05/01/2013	HUB1706M	06/16/2017
HUB1305C	05/22/2013	HUB1801M	05/02/2018
HUB1306C	06/11/2013	HUB1802M	08/26/2018
HUB1307C	07/05/2013	HUB1803M	11/10/2018
HUB1308C	07/25/2013	HUB1804M	12/02/2018
HUB1310C	09/05/2013	HUB1905M	11/14/2019
HUB1311C	09/24/2013	HUB1906M	11/03/2019
HUB1312M	10/11/2013	HUB2002M	06/07/2020
HUB1313M	11/27/2013	HUB2003M	06/24/2020
HUB1314M	12/17/2013	HUB2004M	07/12/2020
HUB1315M	01/14/2014	HUB2005M	08/3/2020
HUB1316M	01/24/2014	HUB2006M	09/20/2020
HUB1317M	02/14/2014	HUB2007M	10/10/2020
HUB1401M	03/04/2014	HUB2008M	10/29/2020
HUB1402M	03/21/2014	HUB2009M	11/18/2020
HUB1403M	04/09/2014	HUB2010M	12/09/2020
HUB1404M	04/29/2014	HUB2011M	12/31/2020
HUB1405M	05/16/2014	HUB2012M	01/22/2021
HUB1406M	06/06/2014	HUB2013M	02/11/2021
HUB1407M	06/26/2014	HUB2101M	03/02/2021
HUB1409M	08/02/2014	HUB2102M	03/21/2021
HUB1410M	08/19/2014	HUB2103M	04/21/2021
HUB1412M	10/15/2014	HUB2104M	04/30/2021
HUB1413M	10/31/2014	HUB2105M	05/18/2021
HUB1414M	11/18/2014	HUB2107M	06/25/2021
HUB1415M	12/16/2014	HUB2108M	07/15/2021
HUB1416M	12/31/2014	HUB2109M	08/05/2021

Batch Number	Date of Manufacture	Batch Number	Date of Manufacture
HUB1417M	01/21/2015	HUB2110M	09/25/2021
HUB1418M	02/05/2015	HUB2111M	10/13/2021
HUB1501M	02/24/2015	HUB2112M	11/01/2021
HUB1502M	03/13/2015	HUB2113M	11/22/2021
HUB1503M	04/01/2015	HUB2114M	12/10/2021
HUB1504M	04/21/2015	HUB2115M	12/31/2021
HUB1505M	05/08/2015	HUB2116M	01/18/2022
HUB1506M	06/04/2015	HUB2201M	02/27/2022
HUB1507M	06/19/2015	HUB2204M	04/26/2022
HUB1508M	07/07/2015	HUB2205M	05/12/2022
HUB1509M	07/24/2015	HUB2207M	06/05/2022
HUB1510M	08/13/2015		
HUB1511MA	09/01/2015		
HUB1512MA	09/18/2015		
HUB1513MA	11/12/2015		
HUB1514MA	12/02/2015		
HUB1516MA	01/15/2016		
HUB1517MA	02/01/2016		
HUB1601MA	02/19/2016		
HUB1602MA	03/10/2016		

7) The following sections provide a description of the test methods, statistical analysis and results related to the above-referenced batches.

I. TEST METHODS

The analytical procedure used to test the batch yield, in particular the enzyme activity, at the end of the bioreactor was the Microturbidity (Micro-T) Assay for Enzyme Activity (in-process test number TM-0134). According to this method, a unit of hyaluronidase activity is determined by incubating soluble rHuPH20 with sodium hyaluronate (hyaluronic acid) for a set period of time (10 minutes), precipitating the undigested sodium hyaluronate with the addition of acidified serum albumin, measuring the turbidity of the resulting sample at 640 nm after a 30-minute development period, and comparing the harvested cell culture fluid (as

clarified of cells, cell debris and aggregates) with a calibration curve generated with dilutions of a soluble rHuPH20 assay working reference standard.

II. STATISTICAL ANALYSIS

A. Yield Assessment Steps:

The following steps were performed for the yield assessment:

1. Perform univariate analysis on the continuous variables from the harvested cell culture fluid sample from each batch described in Table 1 for enzyme activity; from this analysis, use the best fit to model the population.
2. Calculate the K-sigma (3σ) interval(s) using the best determined model fit.

B. JMP® Software

Calculations for the statistical analysis were performed using JMP® 16.

C. Univariate Analysis

Using the enzyme activity release results from each batch listed in Table 1, univariate analysis on the continuous variables was performed. Using this data, the best model or curve fit was determined using both JMP statistical software and a comprehensive understanding of the variables and their constraints.

D. K-sigma Intervals

The K-sigma interval is similar to a tolerance interval (TI) except that the constant “K” does not correct for sample size, CI, nor proportion of the population as the sample size is greater than or equal to 30. At a sample size of 30 or more, there is a diminishing return on the precision of the TI to contain the specified distribution proportion with an incremental increase in sample size unless the increase in sample size is increased by a large factor. Therefore, a K-sigma interval approach was used as opposed to TI approach.

The K-sigma intervals were calculated using the constant “K” value of 3 which represents 3σ the population standard deviation (σ) and is roughly equivalent to 99% proportion of the population (future results) with a confidence level of 95%.

III. RESULTS

A. Harvest Cell Culture Fluid Dataset

Harvested cell culture fluid samples produced per the methods described in European Patent 3 760 715 B1 and containing the nucleic acid encoding soluble recombinant human PH20 (rHuPH20) were tested for enzyme activity following the above-referenced Microturbidity (Micro-T) Assay. Table 2 lists the resulting enzyme activity for each batch:

Table 2: Enzyme Activity of Harvested Cell Culture Fluid (HCCF) Samples

Batch	Enzyme Activity (U/mL)
HUB1001C	11910
HUB1004C	17210
HUB1005C	14380
HUB1006C	13480
HUB1101C	14280
HUB1202C	18320
HUB1203C	14210
HUB1204C	11410
HUB1205C	14260
HUB1206C	15680
HUB1207C	16190
HUB1208C	13380
HUB1209C	17210
HUB1210C	13830
HUB1211C	12840
HUB1301C	13560
HUB1302C	13550
HUB1303C	13030
HUB1304C	15020
HUB1305C	14130
HUB1306C	14150
HUB1307C	13840
HUB1308C	16330

Inventors : Baker et al.
Patent No. : EP 3 760 715 B1
Granted : August 4, 2021

Declaration under 37 C.F.R. § 1.132

Batch	Enzyme Activity (U/mL)
HUB1310C	16780
HUB1311C	16350
HUB1312M	12710
HUB1313M	14890
HUB1314M	15240
HUB1315M	14040
HUB1316M	14190
HUB1317M	13900
HUB1401M	13790
HUB1402M	14040
HUB1403M	15300
HUB1404M	14550
HUB1405M	12910
HUB1406M	12400
HUB1407M	15030
HUB1409M	13050
HUB1410M	12880
HUB1412M	14570
HUB1413M	11680
HUB1414M	12390
HUB1415M	14370
HUB1416M	12060
HUB1417M	12770
HUB1418M	12520
HUB1501M	10500
HUB1502M	9920
HUB1503M	14710
HUB1504M	15600
HUB1505M	12460
HUB1506M	14190
HUB1507M	11560
HUB1508M	11510

Inventors : Baker et al.
Patent No. : EP 3 760 715 B1
Granted : August 4, 2021

Declaration under 37 C.F.R. § 1.132

Batch	Enzyme Activity (U/mL)
HUB1509M	12760
HUB1510M	15700
HUB1511M	15030
HUB1512M	20880
HUB1513M	12070
HUB1514M	14880
HUB1516M	14680
HUB1517M	12700
HUB1601M	13160
HUB1602M	13240
HUB1603M	14700
HUB1604M	11710
HUB1605M	11930
HUB1607M	13950
HUB1608M	18690
HUB1609M	15080
HUB1610M	14670
HUB1611M	13220
HUB1612M	14780
HUB1613M	14910
HUB1614M	12440
HUB1615M	16070
HUB1616M	12400
HUB1701M	13120
HUB1702M	10490
HUB1703M	15409
HUB1704M	13860
HUB1705M	15360
HUB1706M	13040
HUB1801M	15090
HUB1802M	16920
HUB1803M	15750

Inventors : Baker et al.
Patent No. : EP 3 760 715 B1
Granted : August 4, 2021

Declaration under 37 C.F.R. § 1.132

Batch	Enzyme Activity (U/mL)
HUB1804M	15060
HUB1905M	12930
HUB1906M	12840
HUB2002M	13530
HUB2003M	13660
HUB2004M	13890
HUB2005M	14010
HUB2006M	12830
HUB2007M	11660
HUB2008M	12450
HUB2009M	13190
HUB2010M	15210
HUB2011M	11690
HUB2012M	10960
HUB2013M	10640
HUB2101M	8810
HUB2102M	11420
HUB2103M	10630
HUB2104M	10050
HUB2105M	11950
HUB2107M	11250
HUB2108M	12180
HUB2109M	11520
HUB2110M	10770
HUB2111M	11180
HUB2112M	11860
HUB2113M	11780
HUB2114M	12180
HUB2115M	10490
HUB2116M	12840
HUB2201M	11170
HUB2204M	11120

Inventors : Baker et al.
 Patent No. : EP 3 760 715 B1
 Granted : August 4, 2021

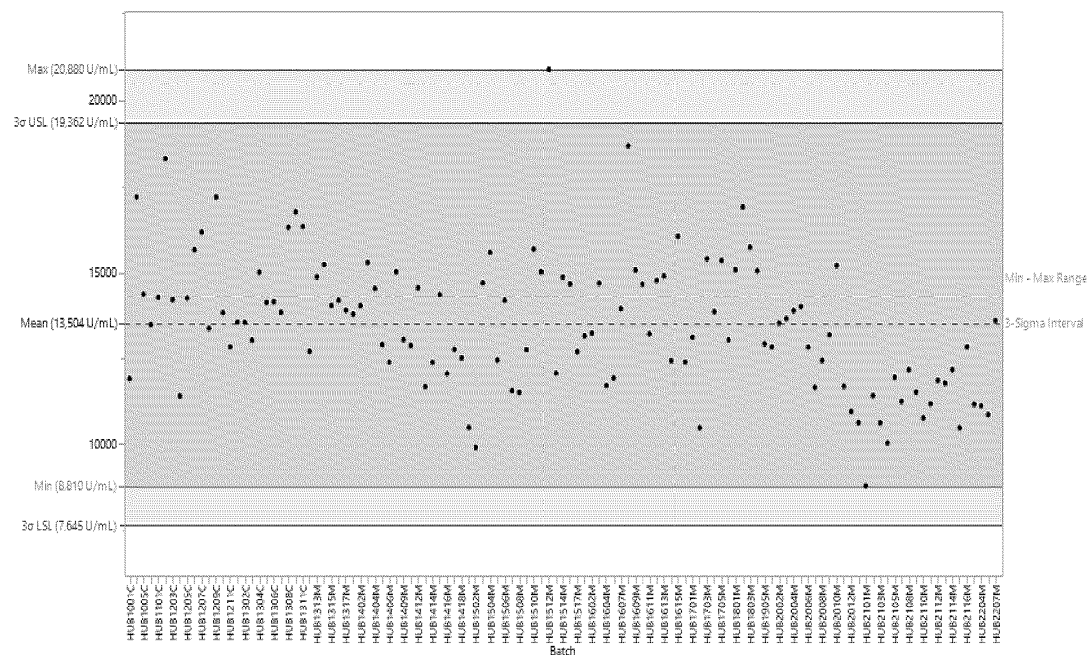
Declaration under 37 C.F.R. § 1.132

Batch	Enzyme Activity (U/mL)
HUB2205M	10870
HUB2207M	13600

B. Summary of Statistics

Sample data were analyzed using a Shapiro-Wilk W test, having a normal distribution ($p > 0.05$, 0.07). As shown in Figure 1 (below), the data 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. The 3σ interval range was calculated as 7,645 U/mL for the lower limit (LSL) and 19,362 U/mL for the upper limit (USL).

Figure 1: Enzyme Activity for Harvested Cell Culture Fluid



8) During this time, additional cells lines were generated and CHO DG44-derived clones and CHO-GS clones were produced. Pools of these clones were cultured and culture fluid from the pooled clones was tested for PH20 activity.

a. **DG 44 Derived Cell Line Non-Homogeneous Pools.** Ten (10) non-homogeneous pools before and without any cell selection, comprising mixtures of variable producing cells, were generated using the DG-44 derived cell line. The results of the enzyme

activity of the harvested cell culture fluid can be found in Table 3. Since the pools include a mixture of high-producing and low-producing cells, the enzyme activity listed in Table 3 is the resultant enzyme activity from the mixture of enzyme producing cells. As such, Pool 3, for example, includes populations of cells producing less than 23,840 (U/mL) and populations of cells producing greater than 23,840 (U/mL).

Table 3: Enzyme Activity at Harvest for DG44 Derived Cell Line

Pool	Pool 1	Pool 2	Pool 3	Pool 4	Pool 5	Pool 6	Pool 7	Pool 8	Pool 9	Pool 10
Enzyme Activity (U/mL)	13,600	8320	23,840	11,850	16,320	17,550	7655	14,950	6955	16,920

b. **CHO-GS Cell Line Non-Homogeneous Pools.** Four (4) non-homogeneous pools before and without any cell selection, comprising mixtures of variable producing cells, were generated using the CHO-GS cell line. The results of the enzyme activity of the harvested cell culture fluid can be found in Table 4. Since the pools include a mixture of high-producing and low-producing cells, the enzyme activity listed in Table 4 is the resultant enzyme activity from the mixture of enzyme producing cells. As such, Pool 2, for example, includes populations of cells producing less than 18,895 (U/mL) and populations of cells producing greater than 18,895 (U/mL).

Table 4: Enzyme Activity at Harvest for CHO-GS Cell Line

Pool	Pool 1	Pool 2	Pool 3	Pool 4
Enzyme Activity (U/mL)	13,790	18,895	17,790	12,930

9) **Conclusion.** Based on the foregoing data, Halozyme has generated a harvested cell culture fluid, comprising soluble recombinant human PH20 (rHuPH20), with an enzymatic activity that is greater than 5000 and, in some instances, greater than 24,000 units of hyaluronidase activity/mL of cell culture fluid as harvested, using at least three (3) different cell lines.

Inventors : Baker et al.
Patent No. : EP 3 760 715 B1
Granted : August 4, 2021

Declaration under 37 C.F.R. § 1.132

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

28 Sep 2022
Date

Michael LaBarre
Michael LaBarre