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Opposition proceedings against

European Patent 3 530 670 B1 / 17 862 926.7

**METHOD FOR PRODUCING ENDOTOXIN DETECTING AGENT
COMPRISING RECOMBINANT LIMULUS FACTOR C AND USE THEREOF**

On behalf of the Proprietor

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Partnerschaftsregister Amtsgericht München | PR 1372

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**CRL Exhibit 1043
CRL v. Seikagaku
PGR2025-00023**

Table of contents

1	Requests.....	3
2	Documents filed by the Proprietor.....	3
3	Main Request	4
3.1	Amendments (Rule 80 EPC).....	4
3.2	Added matter (Articles 100(c) and 123(2) EPC)	4
3.2.1	Summary of the basis.....	4
3.2.2	Response to O1's objections	5
3.2.3	Claim 2.....	6
3.3	Sufficiency of disclosure (Article 100(b) and 83 EPC)	6
3.4	Inventive step (Articles 100(a) and 56 EPC)	7
3.4.1	Starting from recombinant TtFC (D1).....	9
3.4.2	Starting from recombinant CrFC (D5 or D6).....	13
4	Auxiliary Requests	15
4.1	Auxiliary Request 1	15
4.2	Auxiliary Request 2	16
4.3	Auxiliary Request 3	16
4.4	Auxiliary Requests 4-7.....	16
4.5	Auxiliary Requests 8-11.....	16

- 1 In response and with reference to the Opposition Division's (OD's) communication of December 10, 2024 and the communication under Rule 132 EPC of April 2, 2025 informing the proprietor of the grant of extension of time limit, we herewith provide the Proprietor's response to the notice of opposition filed by O1 as identified in the OD's communication of December 10, 2024. We thank the OD for granting an extension in the present case.

1 Requests

- 2 The Proprietor requests that the oppositions be rejected.
- 3 The Proprietor requests maintenance of the opposed patent (hereinafter: the Patent) on the basis of the attached Main Request.
- 4 Should the Opposition Division not allow the Proprietor's Main Request, it is requested that the Patent be maintained on the basis of one of Auxiliary Requests 1-11 as filed herewith.
- 5 For ease of reference, each of the claim requests submitted herewith indicate the differences to the claims as granted.
- 6 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.
- 7 In the interest of procedural efficiency, the opportunity is requested to be allowed to combine two or more of the Proprietor's present claim requests if that is expedient to the progress of the proceedings, and to be allowed to combine or delete claims in any of the Proprietor's present claim requests. The opportunity is also requested to adjust the order of the Proprietor's Auxiliary Requests.
- 8 Oral proceedings are requested prior to any decision by the Opposition Division that is adverse to the Proprietor.

2 Documents filed by the Proprietor

- 9 We file the following further documents:

D33 Experimental report signed by Dr. Hikaru Mizumura on April 25, 2025

D34 European Pharmacopoeia 5.0 (2005). Council of Europe, Strasbourg. pp. 161-168

D35 The United States Pharmacopoeial Convention (2011). USP 85.

3 Main Request

3.1 Amendments (Rule 80 EPC)

- 10 Claim 1 has been amended to remove subclaim (C). This amendment is occasioned by O1's objection under Article 123(2) EPC against subclaim (C) (see statement of grounds for opposition, paragraphs 24-27). Thus, the Main Request satisfies the requirements of Rule 80 EPC.

3.2 Added matter (Articles 100(c) and 123(2) EPC)

3.2.1 Summary of the basis

- 11 The application was originally filed in Japanese. We refer to the English translation filed on March 14, 2019 with entry into the EPO regional phase (hereinafter "A0").
- 12 Claim 1 finds direct and unambiguous basis in the following passages of A0:
- page 53, paragraph [0121];
 - page 59, paragraphs [0139] and [0141];
 - page 60, paragraph [0143]; and
 - page 27, paragraphs [0043] and [0044].
- 13 A0, paragraph [0121] is contained within the section entitled "<9> *First cDNA and Utilization Thereof*" (see A0, bottom of page 52). A0, paragraph [0121] discloses the subject matter of subclaims (A), (B) and (C).
- 14 A0, paragraph [0139] provides the start to a section entitled "<12> *Method for Producing Endotoxin Detecting Agent*" and discloses a method that involves expressing a protein using the first cDNA disclosed in section <9>. It is directly and unambiguously derivable from A0, paragraph [0141] that the term "*first cDNA*" refers to the first cDNA as disclosed in A0, section <9> (see paragraph [0121]).
- 15 A0, paragraph [0143] discloses that the expressed recombinant protein may be present in a culture solution or culture supernatant as described in section <1>.
- 16 A0, section <1> starts on the bottom of A0, page 16. A0, paragraphs [0043] and [0044] are contained within section <1> and disclose that:

- the expressed recombinant protein is collected as a solution fraction, and
- the solution fraction may be a culture solution or a culture supernatant.

17 Thus, claim 1 satisfies the requirements of Article 123(2) EPC.

3.2.2 Response to O1's objections

18 O1's allegation that the subject matter of claim 1 involves selections from independent lists of sizeable length is incorrect.

19 A0, paragraph [0121] refers to a group of cDNA molecules defined by a certain minimal sequence similarity to SEQ ID NO: 1 or 3. The sequence similarity is defined by:

- the ability of the variant sequence to hybridize to SEQ ID NO: 1 or 3 under "stringent conditions";
- 95% or more sequence identity to the recombinant polypeptide encoded by SEQ ID NO: 1 or 3 (i.e., SEQ ID NO: 2 or 4); or
- 95% or more sequence identity to SEQ ID NO: 1 or 3.

20 Each of embodiments (B) to (E) as disclosed in paragraph [0121] encompasses embodiment (A):

- a sequence that is 100% identical to SEQ ID NO: 1 or 3 can hybridize to SEQ ID NO: 1 or 3 under stringent conditions;
- SEQ ID NOs: 1 and 3 encode a recombinant polypeptide that is 100% identical to SEQ ID NOs: 2 and 4, respectively; and
- a sequence that is 100% identical to SEQ ID NO: 1 or 3 is encompassed by the expression "95% or more".

21 Thus, the removal of embodiment (A) does not result in a change in scope. Claim 1 as granted still encompasses embodiment (A) as described in paragraph [0121].

22 Claim 1 of the Main Request also still encompasses embodiment (B) as disclosed in A0, paragraph [0121]. Due to the degeneracy of the genetic code, the group of cDNA molecules provided in embodiment (E) as disclosed in paragraph [0121] entirely

encompasses and is broader than embodiment (B) because embodiment (E) (which corresponds to subclaim (B) of claim 1) allows for each amino acid to be encoded by any relevant codon. Thus, the removal of embodiment (B) also does not result in a change in scope.

23 The omission of embodiment (C) as disclosed in paragraph [0121] does not justify an objection under Article 123(2) EPC. Either embodiment (C) as disclosed in paragraph [0121] is encompassed by claim 1, subclaim (B) in which case there has not been a change in scope, or embodiment (C) as disclosed in paragraph [0121] defines a broader group of variants in which case the deletion merely shrinks the generic group without singling out a particular cDNA (see CLBA10¹: II-E, 1.6.3 and GL²: H-V, 3.3). This is in accordance with T 2134/10 (cited in CLBA10: II-E, 1.6.2(b)) where the Board stated that a specific degree of sequence identity is not a property that could single out a particular molecule (see point 11 of the reasons). Thus, there is no first selection as alleged by O1.

24 There is no second selection either. A0, paragraph [0044] discloses that the solution fraction can be a culture solution, a culture supernatant, a cell homogenate extract, a mixture thereof, or the like. The list of alternatives has been reduced to a method comprising collecting a culture solution or a culture supernatant. No single option has been singled out. It is allowable to delete part of the claimed subject matter if the limitations do not result in the singling out of a particular combination of specific features (see GL, H-V, 3.3).

3.2.3 Claim 2

25 O1 has not specifically objected to the subject matter of claim 2. Claim 2 also satisfies the requirements of Article 123(2) EPC.

3.3 Sufficiency of disclosure (Article 100(b) and 83 EPC)

26 O1's first objection under Article 83 EPC is a poorly disguised clarity objection. Article 84 EPC is, however, not a ground for opposition and, thus, O1's objection should be dismissed.

¹ Case Law of the Boards of Appeal, 10th ed.

² Guidelines for Examination

- 27 O1 is essentially alleging that there is an inconsistency between paragraph [0037] of the Patent and claim 1. Paragraph [0037] states that the recombinant protein can be produced using a cell-free protein synthesis system. At the same time, claim 1 requires the collection of a culture solution or a culture supernatant. According to O1, it is not possible for the expressed protein to be collected from a culture solution or culture supernatant if a cell-free protein synthesis system is used.
- 28 Any alleged inconsistencies between the claims and the description are only relevant under Article 84 EPC (GL: F-IV, 4.3). The skilled person would read claim 1 with a mind willing to understand and gather that the culture solution or supernatant means that the method must involve a cell culture system (see, for example, paragraph [0036] of the Patent). The Patent teaches how to put such cell culture systems into practice. Thus, O1's objection is unconvincing.
- 29 O1 also alleges that claim 1 is not enabled over the entire claim scope because there are serious doubts that the claimed Factor C could be produced using COS-1 cells. To substantiate its objection, O1 has referred to D31.
- 30 D31 relates to Factor C of *Carcinoscorpius rotundicauda* (hereinafter "CrFC"), which is simply outside of the claimed scope.
- 31 Even if there were evidence that the claimed Factor C could not be produced in certain cell lines, such evidence would not justify an objection under Article 83 EPC. The Patent contains sufficient information on the relevant criteria for finding appropriate alternatives over the claimed range with reasonable effort (see G 1/03, point 2.5.2 of the reasons).
- 32 The claims satisfy the requirements of Article 83 EPC.

3.4 Inventive step (Articles 100(a) and 56 EPC)

- 33 O1 alleges that the subject matter of claim 1 is obvious when starting from D1, D5 or D6. For the following reasons, we disagree with O1's assessment.
- 34 Regardless of the starting point, according to O1 the prior art does not disclose SEQ ID NO: 2 or 4, nor does the prior art disclose a sequence that is 95% identical to SEQ ID NO: 2 or 4 (see O1's statement of grounds for opposition, paragraphs 46, 110 and 132). Thus, D1, D5 or D6 do not disclose any method for producing the claimed protein

sequences. Nor do D1, D5 or D6 disclose that such methods would involve collecting a culture solution or supernatant comprising the claimed recombinant protein.

35 O1 essentially starts from two different concrete embodiments in section VI.5³ of its statement of grounds for opposition:

- recombinantly produced *Tachypleus tridentatus* Factor C (hereinafter “TtFC”) as disclosed in D1; or
- recombinantly produced CrFC as disclosed in D5 or D6.

36 O1 also attempts to start its analysis beginning from a general reference to *Limulus polyphemus* in each one of D1, D5 and D6 (D1: para [0151] | D5: col 3, lines 22-24 | D6: para [21]). This approach is, however, not in accordance with established case law. The problem-solution approach should start from a situation as close as possible in reality to that encountered by the inventor (CLBA10: I-D, 3.2). *Ex post facto* considerations should be avoided (see T 1533/19, point 2 of the reasons).

37 In reality, according to common EPO practice, the skilled person would start from the preferred embodiments, or the embodiments exemplified as specific working examples disclosed in D1, D5 or D6. D1 indicates that recombinant TtFC is preferred (see para [0151]) and the production of TtFC is exemplified as the working example. Similarly, in D5 the preferred Factor C is CrFC (D5: col 7, lines 48-63) and CrFC is exemplified as the working example. D6 indicates that, when the Factor C is recombinantly produced, TtFC or CrFC are preferred because these sequences were known (D6: para [23]).

38 For the purposes of the EPO’s problem-solution approach, it would not be realistic for the skilled person to start from one of the many non-preferred options in D1, D5 or D6. The skilled person, seeking to produce an endotoxin detecting agent, would realistically start from one the concrete preferred embodiments disclosed in D1, D5 or D6, i.e., TtFC or CrFC.

39 For the following reasons, the claimed subject matter is not obvious starting from D1, D5 or D6.

³ Beginning on page 30.

3.4.1 Starting from recombinant TtFC (D1)

3.4.1.1 The objective technical problem

- 40 It was made credible at the effective filing date of the Patent that the subject matter of claim 1 results in a Factor C having higher activity than the recombinantly produced TtFC of D1. Specifically, A0, paragraphs [0186] to [0191] (see, also, paragraphs [0187] to [0192] of the Patent) provides an experimental report describing how recombinantly produced Factor C according to claim 1 was compared to recombinantly produced TtFC. The results of the comparison are reported in paragraph [0191]. The Factor C produced according to claim 1 had a higher activity than recombinantly produced TtFC.
- 41 O1 alleges that paragraph [0192] of the Patent only provides a “*mere statement*” and that the Patent “*fails to provide any data which may be used to confirm the statement*” (see O1’s statement of grounds for opposition, paragraph 158). This is not true. The Patent presents its data in text-form instead of providing a graph or table. The data is, however, clearly provided in paragraph [0192] of the Patent. There is no formal requirement for data to be presented in a particular format.
- 42 O1 then criticizes the data by alleging that a comparison cannot be made because the 2C12 antibody would not allow for an accurate determination of the relative concentrations of TtFC and LpFC (see O1’s statement of grounds for opposition paragraphs 159 to 161). O1’s criticism relies on pure speculation. There is no evidence that 2C12 binds with different affinities to TtFC and LpFC. There is no evidence that the difference in affinity would affect the results of a western blot which generally involves the use of a significant excess of antibody.
- 43 In general, western blotting is performed under conditions that use an excess amount of primary antibody and the primary antibody is generally allowed to incubate with the membrane for a significantly long period. So, even if the 2C12 antibody should not have the same affinity to TtFC and LpFC, one would reasonably expect the amount of primary antibody to be saturating.
- 44 It is established EPO practice that each party bears the burden of proof for the facts it alleges (CLBA10: III-G, 5.1.1). The Patent discloses that it was possible to use the 2C12 antibody to quantify and compare the relative concentrations of TtFC and LpFC (see paragraph [0189] of the Patent). In contrast, O1 only speculates that the quantification may not have been entirely accurate. O1’s speculation should be dismissed.

- 45 O1's baseless speculation is, anyhow, shown to be incorrect in D33, an experimental report wherein it is demonstrated that 2C12 results in bands of lower intensity when the concentration of Factor C is lower regardless of whether TtFC, LpFC or CrFC is contained in the sample (D33: paragraphs 4, 5 and 9; Figures 1-3, 5 and 6). Further, the results of the Patent were confirmed using nonspecific Coomassie Brilliant Blue staining (D33: Figures 4 and 7). Thus, the results reported in the Patent are not due to an alleged difference in affinity of the 2C12 antibody. LpFC has a higher activity than TtFC.
- 46 O1 then continues to speculate, without any evidence to support its allegations, that other parameters such as the use of a different cascade system, expression system, and culture solution may affect the results of a comparison between TtFC and LpFC. At present, however, the Patent and D33 provide evidence that LpFC has a higher activity than TtFC and there is no evidence to the contrary.
- 47 Post-filing evidence further confirms the teaching of the Patent. As can be seen from D33, Table 1A and 1B, regardless of whether CHO cells or Sf9 cells are used, there were no tendencies that the activity of recombinant LpFC was more sensitive to the presence of ions in the test specimen than recombinant TtFC.
- 48 Thus, in view of the available evidence in the Patent and D33, it is credible that an improved endotoxin detecting agent is obtained. Thus, the objective technical problem should be the provision of a method for producing an improved endotoxin detecting agent.
- 49 O1's proposed objective technical problem cannot be correct. Not only does it ignore the presence of a technical effect, but it also contains a pointer to the claimed solution, i.e., "*the determination of the full-length Limulus Factor C sequence*" (see O1's statement of grounds for opposition, paragraph 58). An objective technical problem cannot contain a pointer to the technical solution. See GL, G-VII, 5.2:

"It is noted that the objective technical problem must be so formulated as not to contain pointers to the technical solution, since including part of a technical solution offered by an invention in the statement of the problem must, when the state of the art is assessed in terms of that problem, necessarily result in an ex post facto view being taken of inventive activity (see T 229/85)."

3.4.1.2 The claimed subject matter is not obvious

50 Because O1 has formulated the objective technical problem incorrectly, its assessment of obviousness is riddled with the sort of *ex post facto* analysis that should be avoided when assessing Article 56 EPC. There is no suggestion in the prior art that recombinant LpFC would have a higher activity than recombinant TtFC. Thus, the subject matter of claim 1 is not obvious.

51 O1 has provided a lengthy explanation as to all the experiments that the skilled person could have done prior to the effective filing date to determine the sequence of LpFC. However, this is not the correct standard. In the third stage of the problem-solution approach, the could-would approach should be applied and O1 has failed to demonstrate that there was any motivation to arrive at the claimed subject matter with the expectation of some advantage. See GL, G-VII, 5.3:

*“In other words, the point is not whether the skilled person could have arrived at the invention by adapting or modifying the closest prior art but whether the skilled person **would have done** so because the prior art provided motivation to do so in the expectation of some improvement or advantage (see T 2/83).”*

52 D1 discloses in paragraph [0151] that *Limulus polyphemus* is an example of a horseshoe crab. D1 then states in paragraph [0151] that CrFC and, particularly, TtFC are preferred. D1 also discloses that CrFC, a sequence with 97.7% sequence homology to TtFC (D24: abstract), can be complicated to express recombinantly (D1: para [0265]). It was inactive when expressed in S2 cells. Thus, there were no reasons to speculate that LpFC would behave better than TtFC in a recombinant system.

53 D3, including D3a-c, were not available at the effective filing date and, thus, cannot be relevant for the interpretation of D1 at the effective filing date. Regardless of their availability, the applicable standard at the USPTO for determining whether an Applicant is in possession of the full scope of the claims is not the same as required by the EPO’s could-would approach.

54 In D3, it was argued that the skilled person could put the invention in practice over the entire claim scope. But it was never argued that the skilled person would have been motivated to put every single embodiment encompassed by the claims into practice, in particular, to achieve some sort of improvement. It is a common occurrence to grant Patents directed to narrower embodiments encompassed by earlier broader claims

when, for example, there is an improvement associated with the narrower embodiments. O1's attempt at a "squeeze" is, thus, not convincing.

- 55 O1 has also attempted to mischaracterize D3a. In D3a, Dr. Mizumura stated on page 4, paragraph 2 that *"a person skilled in the art would readily recognize that the presently claimed invention could also work when Factor C is the Factor C of Limulus Polyphemus"* (emphasis added). There is no indication in D3a that Dr. Mizumura believed that the skilled person would have been motivated to employ LpFC for the purpose of obtaining the recombinant Factor C having a higher enzymatic activity than TtFC.
- 56 Dr. Mizumura then stated in D3a, paragraph bridging pages 4 and 5 *"the above-described evidence supports that the Factor C of Limulus polyphemus would also have unexpectedly superior property of being less susceptible to inhibition by ions, as exhibited by Factor C of Tachypleus tridentatus"* (emphasis added). The evidence that Dr. Mizumura referred to was an alignment of the sequence of LpFC with TtFC provided on pages 2-4 of D3a. The sequence of LpFC was not publicly disclosed prior to the effective filing date of the Patent. Thus, the alignment was also not part of the prior art.
- 57 We note that O1 has conveniently omitted *"the above-described evidence supports that"* when it misquoted D3a (see O1's statement of grounds for opposition, paragraph 54). It is not acceptable to misquote Dr. Mizumura and then allege that Dr. Mizumura believed it was obvious that recombinant LpFC would be associated with a superior property based solely on what was known prior to the effective filing date of the Patent. This is not the case. Dr. Mizumura based their conclusion on the *"above-described evidence"* provided in D3a. Said evidence included an alignment of a previously unknown sequence. The reality is that Dr. Mizumura acknowledges in D33 that the higher activity of LpFC was surprising (D33: paras 22 and 23) and the Proprietor maintains the position that the claimed subject matter involves an inventive step.
- 58 The claimed subject matter is also not obvious in view of D1 in combination with any one of D11, D13-D18, D20, D22, D23 and/or D24. D1 does not direct nor motivate the skilled person to prioritize the use of the sequence of LpFC over TtFC. Thus, the combination of D1 with any one of these documents can only involve hindsight. See GL, G-VII, 8 (emphasis added):

“Once a new idea has been formulated, it can often be shown theoretically how it might be arrived at, starting from something known, by a series of apparently easy steps. The examiner must be wary of ex post facto analysis of this kind. When combining documents cited in the search report, it always has to be borne in mind that the documents produced in the search have, of necessity, been obtained with foreknowledge of what matter constitutes the alleged invention. In all cases the examiner must attempt to visualise the overall state of the art confronting the skilled person before the applicant's contribution, and must seek to make a "real-life" assessment of this and other relevant factors. The examiner has to take into account all that is known concerning the background of the invention and give fair weight to relevant arguments or evidence submitted by the applicant. If, for example, an invention is shown to be of considerable technical value, and particularly if it provides a technical advantage which is new and surprising and which is not merely achieved as a bonus effect in a "one-way street" situation (see G-VII, 10.2), and this technical advantage can convincingly be related to one or more of the features included in the claim defining the invention, the examiner has to be hesitant in pursuing an objection that such a claim lacks inventive step.”

- 59 Prior to the effective filing date, it was known that native LpFC was “indistinguishable” from native TtFC (D22: p 151, left col, para 1 | D33: paras 22 and 23). Both amoebocyte lysates from *Tachypleus tridentatus* and *Limulus polyphemus*, which contain native Factor C, Factor B and proclotting enzyme, were authorized for the detection and quantification of endotoxins (D34: p 161, section 2.6.14, first paragraph | D35: p 1, left col, para 5). There was no suggestion that recombinantly produced LpFC might have a higher enzymatic activity than recombinantly produced TtFC or may be associated with any sort of advantage or improvement. Thus, the skilled person was not motivated to produce LpFC recombinantly to improve the endotoxin detecting agents of the prior art. There is no evidence that the skilled person would have done so in the expectation of some improvement or advantage (see GL, G-VII, 5.3).

3.4.2 Starting from recombinant CrFC (D5 or D6)

- 60 For the purposes of the EPO’s problem-solution approach, recombinant CrFC was a less promising starting point than recombinant TtFC (D1: paras [0265] and [0266]). According to D31, CrFC is a membrane bound Factor C. It was membrane bound when

expressed in COS-1 (D31: p 360, right col, para 2) and *Pichia pastoris* (D31: p 357, right col, para 1).

- 61 D5 confirms that a possible explanation as to why CrFC was found in the supernatant in Example 1 was due to the lysis of the infected Sf9 cells (D5: col 10, lines 50-53). However, even though some of the CrFC was released into the culture solution following cell lysis, a substantial level of CrFC remained in the cell lysate (D5: col 10, lines 46-50). In contrast, it was known that TtFC could be secreted by Sf9 cells (D1: paras [0235]-[0239]).
- 62 Nevertheless, even if recombinant CrFC were selected as the starting point, the subject matter of claim 1 would not be obvious.

3.4.2.1 The objective technical problem

- 63 As already mentioned in paragraph 40 above, A0 and the Patent provide an experimental report describing how recombinantly produced Factor C according to claim 1 has an especially high enzymatic activity. An improved enzymatic activity is, thus, derivable from A0 and the Patent.
- 64 Post-filing evidence demonstrating an improved activity of LpFC when compared to CrFC should be taken into account in the present case because high activity is an effect derivable from A0. This is supported by the case law of the Enlarged Board of Appeal and the Technical Boards of Appeal.
- 65 In T 31/18, Reason 2.5.2 *“the board of appeal held that the technical effect relied upon for inventive step according to the problem-solution approach must either be explicitly mentioned in the application as filed or at least be derivable therefrom, but not necessarily originally supported by experimental evidence. It could not be expected from a patent applicant to include an extensive amount of experimental evidence corresponding to all technical features which could possibly be claimed in the application as filed and which could possibly constitute a future distinguishing feature over the closest prior art, since said closest prior art and its technical disclosure may not be known to the applicant at the filing date of the application”* (G 2/21, Reason 65). T 31/18 is one of the decisions endorsed by the Enlarged Board in G 2/21 (see T 116/18, Reason 11.12.4) and is further supported by more recent decisions, such as T 2465/19. See Reason 5.3:

“The Board notes that the technical effect of an invention over the closest prior art need not be explicitly stated in the application, as long as it is derivable from the original application, in particular since the closest prior art may not have been known to the applicant when drafting it (see also decision G 2/21, Headnote II.).”

- 66 D33 demonstrates that the activity of LpFC is also higher than the activity of CrFC (D33: Figures 4 and 7). It is credible that the technical effect associated with the distinguishing feature is an improved endotoxin detecting agent with higher enzymatic activity. Thus, the objective technical problem should be the provision of a method for producing an improved endotoxin detecting agent.

3.4.2.2 The claimed subject matter is not obvious

- 67 The claimed subject matter is not obvious in view of D5/D6 in combination with any one of D11, D13-D18, D20, D22, D23 and/or D24 for essentially the same reasons provided in section 3.4.1.2 above. D5/D6 does not direct nor motivate the skilled person to prioritize the use of the sequence of LpFC over CrFC or TtFC. Instead, the skilled person would have been motivated to replace CrFC with TtFC in view of the teaching of D1 (see, e.g., D1, paragraphs [0265] and [0266]). Thus, the combination of D5/D6 with any one of D11, D13-D18, D20, D22, D23 and/or D24 can only involve hindsight (see GL, G-VII, 8).

4 Auxiliary Requests

4.1 Auxiliary Request 1

- 68 Auxiliary Request (AR) 1 corresponds to the Main Request (MR) except that claim 1 has been amended to recite that the cDNA is contained in a mammalian cell with basis in A0, paragraphs [0037], [0039] and [0129]. The Examples of the application as filed provide a pointer towards the use of mammalian cells. In the Examples, the cDNA was exclusively contained in a mammalian cell (A0: paragraph [0178]).
- 69 The amendment is occasioned by O1's objections under Article 56 EPC. The methods of D5 and D6 involve the use of insect cells and D5 suggests that it would be preferable to use insect cells because insects and horseshoe crabs are in the same phylum (D5: col 2, lines 11-22). Thus, D5/D6 is even less of a promising starting point for the EPO's problem-solution approach than D1.

4.2 Auxiliary Request 2

- 70 AR 2 corresponds to the MR except that claim 1 has been amended to remove the “*culture solution*” alternative. The amendment is occasioned by O1’s objections under Article 123(2) EPC. It is derivable from A0, paragraphs [0114] and [0143] that the culture supernatant option is preferred because it is the only option that is singled out in the exemplary embodiment. A pointer is further provided by the Examples. A0, paragraph [0178] discloses that the recombinant protein was obtained as culture supernatant fractions.

4.3 Auxiliary Request 3

- 71 AR 3 corresponds to a combination of the amendments introduced into ARs 1 and 2. A mammalian cell was used in the Examples. Further, the protein was collected as a culture supernatant (A0: para [0178]). Thus, there is a pointer to the combination of features provided in claim 1.

4.4 Auxiliary Requests 4-7

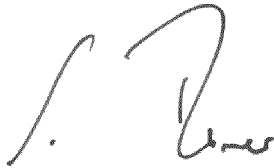
- 72 ARs 4-7 correspond to the MR and ARs 1-3, respectively, except that claim 1 has been amended to recite that the sequence identity is 99% or more with basis in, for example, A0, paragraph [0124]. 99% or more is the most preferred option in paragraph [0124]. Further, a specific degree of sequence identity is, anyhow, not a property that could single out a particular molecule (see T 2134/10, point 11 of the reasons). Thus, amended claim 1 satisfies the requirements of Article 123(2) EPC.
- 73 The amendment is occasioned by O1’s unsupported allegation that “*there does not appear to be any effect attributable to the sequences in claim 1, least of all one that is achieved over the whole scope of the claim*” (see O1’s statement of grounds for opposition, paragraph 172).

4.5 Auxiliary Requests 8-11

- 74 ARs 8-13 correspond to ARs 1, 3, 5 and 7 except that claim 1 has been amended to recite that the cDNA is contained in a HEK or CHO cell with basis in A0, paragraphs [0037], [0039] and [0129].
- 75 The amendment is occasioned by O1’s objections under Article 56 EPC. The methods of D5 and D6 involve the use of insect cells and D5 suggests that it would be preferable to use insect cells because insects and horseshoe crabs are in the same phylum (D5:

col 2, lines 11-22). Thus, D5/D6 is even less of a promising starting point for the EPO's problem-solution approach than D1.

- 76 Further, D33, Figures 4 and 7 show that a higher enzymatic activity is achieved when LpFC is expressed in a CHO or HEK cell.



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Enclosures:

D33-D35

Main Request

Auxiliary Requests 1-11