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Datasheet for the decision of 17 September 2020

Case Number: T 1913/16 - 3.3.01

Application Number: 10709360.1

Publication Number: 2406629

IPC: G01N33/50, C12Q1/37

Language of the proceedings: EN

Title of invention:
IMMUNO-BASED RETARGETED ENDOPEPTIDASE ACTIVITY ASSAYS

Patent Proprietor:
ALLERGAN, INC.

Opponent:
Merz Pharma GmbH & Co. KGaA

Headword:
Retargeted endopeptidase assays/ALLERGAN

Relevant legal provisions:
EPC R. 76(2)(c)
EPC Art. 56

Keyword:
Admissibility of opposition - legal framework of the opposition
Inventive step - (no)

Decisions cited:
T 0067/11

Catchword:

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Beschwerdekammern

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Case Number: T 1913/16 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 17 September 2020

Appellant: (Patent Proprietor)	ALLERGAN, INC. 2525 Dupont Drive Irvine, CA 92612 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
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Representative:	Altmann Stößel Dick Patentanwälte PartG mbB Dudenstrasse 46 68167 Mannheim (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 10 June 2016 revoking European patent No. 2406629 pursuant to Article 101(2) and Article 101(3)(b) EPC**

Composition of the Board:

Chairman	A. Lindner
Members:	T. Sommerfeld
	M. Blasi

Summary of Facts and Submissions

I. European patent 2406629 is based on application 10709360.1, which was filed as an international application published as WO 2010/105236. The patent is entitled "Immuno-based retargeted endopeptidase activity assays" and was granted with 11 claims.

Granted claim 1 reads as follows:

"1. A method of detecting retargeted endopeptidase activity, the method comprising the steps of:
a. treating a cell from an established cell line with a sample comprising a retargeted endopeptidase, wherein the cell from an established cell line is susceptible to retargeted endopeptidase activity by a retargeted endopeptidase;
b. isolating from the treated cell a SNAP-25 (synaptosomal-associated protein 25) component comprising a SNAP-25 cleavage product having a carboxyl-terminus at the P_1 residue of the BoNT/A (botulinum toxin serotype A) cleavage site scissile bond;
c. contacting the SNAP-25 component with an α-SNAP-25 antibody linked to a solid phase support,
wherein the α-SNAP-25 antibody binds an epitope comprising a carboxyl-terminus at the P_1 residue of the BoNT/A (botulinum toxin serotype A) cleavage site scissile bond from a SNAP-25 cleavage product; and
d. detecting the presence of an antibody-antigen complex comprising the α-SNAP-25 antibody and the SNAP-25 cleavage product;
wherein detection by the antibody-antigen complex is indicative of retargeted endopeptidase activity;

wherein the α-SNAP-25 antibody binds an epitope comprising a carboxyl-terminus at the P_1 residue from the BoNT/A cleavage site scissile bond from a SNAP-25 cleavage product;
wherein the α-SNAP-25 antibody has a heavy chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, or SEQ ID NO: 81, or a nucleic acid sequence that is at least 90% identical to SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, or SEQ ID NO: 81;
and wherein the α-SNAP-25 antibody has a light chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 83, SEQ ID NO: 87, SEQ ID NO: 89, or SEQ ID NO: 91, or a nucleic acid sequence that is at least 90% identical to SEQ ID NO: 83, SEQ ID NO: 87, SEQ ID NO: 89, or SEQ ID NO: 91."

Independent claim 5 as granted reads:

"5. An α-SNAP-25 antibody which binds an epitope comprising a carboxyl-terminus at the P_1 residue from the BoNT/A cleavage site scissile bond from a SNAP-25 cleavage product;
wherein the α-SNAP-25 antibody has a heavy chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, or SEQ ID NO: 81, or a nucleic acid sequence that is at least 90% identical to SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, or SEQ ID NO: 81;
and wherein the α-SNAP-25 antibody has a light chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 83, SEQ ID NO: 87, SEQ ID NO: 89, or SEQ ID NO: 91, or a

nucleic acid sequence that is at least 90% identical to SEQ ID NO: 83, SEQ ID NO: 87, SEQ ID NO: 89, or SEQ ID NO: 91."

II. Opposition was filed against the granted patent, the opponent requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step (Articles 54(2) and 56 EPC and Article 100(a) EPC), lack of sufficiency of disclosure (Article 100(b) EPC) and added subject-matter (Article 100(c) EPC).

III. By its decision announced at the oral proceedings, the opposition division revoked the patent under Article 101(2) and 101(3)(b) EPC.

The opposition division decided that the subject-matter of the claims according to the main request (patent as granted) and to auxiliary request I lacked novelty, and that the subject-matter of the claims according to auxiliary requests II to VI lacked inventive step.

IV. The patent proprietor (appellant) lodged an appeal against that decision. With the statement of grounds of appeal, the appellant requested that the patent be maintained as granted (main request) or, alternatively, according to the claims of auxiliary request I or II, both filed with a letter of 22 January 2016, or according to the claims of auxiliary request III, filed at the oral proceedings on 3 May 2016, or according to the claims of one of auxiliary requests IV to VI, filed with the letter of 22 January 2016, or according to the claims of auxiliary request VII or VIII, both filed with the grounds of appeal. It also requested that novelty be excluded as a ground for opposition from the appeal proceedings.

The claims according to the **main request** consist of the claims as granted.

Claim 1 of **auxiliary request I** is essentially identical to claim 1 of the main request, while claim 5 has been amended as follows:

"5. Use of an ~~An~~ α-SNAP-25 antibody which binds an epitope ...
...
..., or SEQ ID NO: 91,
in a cell-based assay for determining the activity of a re-targeted endopeptidase."

In addition, a new claim 11 was added, which reads:

"11. An α-SNAP-25 antibody which binds an epitope comprising a carboxyl-terminus at the P_1 residue from the BoNT/A cleavage site scissile bond from a SNAP-25 cleavage product;
wherein the α-SNAP-25 antibody has a heavy chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 75 or a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 75 and has a light chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 87 or a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 87;
or wherein the α-SNAP-25 antibody has a heavy chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 77 or a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 77 and has a light chain variable region comprising an amino acid sequence encoded by the

nucleic acid sequence SEQ ID NO: 89 or a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 89;
or wherein the α-SNAP-25 antibody has a heavy chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 79 or SEQ ID NO: 81 or a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 79 or SEQ ID NO: 81 and has a light chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 91 or a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 91."

In **auxiliary request II**, claims 1 and 5 are identical to claims 1 and 5, respectively of auxiliary request I while in claim 11 the required sequence identity has been changed from 95% to 98%.

In **auxiliary request III**, claim 1 has been amended as follows:

"1. A method of detecting retargeted endopeptidase activity, ...:
a. ...;
b. ...;
c. contacting the SNAP-25 component with ~~a~~ monoclonal α-SNAP-25 antibody ...; and
d. ...;
wherein ...;
wherein ...;
~~wherein the α-SNAP-25 antibody has a heavy chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, or SEQ ID NO: 81, or a nucleic acid sequence that is at least 90%~~

~~identical to SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 77, SEQ ID NO: 79, or SEQ ID NO: 81;~~
~~and wherein the α-SNAP-25 antibody has a light chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 83, SEQ ID NO: 87, SEQ ID NO: 89, or SEQ ID NO: 91, or a nucleic acid sequence that is at least 90% identical to SEQ ID NO: 83, SEQ ID NO: 87, SEQ ID NO: 89, or SEQ ID NO: 91~~
wherein the α-SNAP-25 antibody has a heavy chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 75 and has a light chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 87;
or wherein the α-SNAP-25 antibody has a heavy chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 77 and has a light chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 89."

The same amendments have been made to claims 5 and 9, which correspond, respectively, to claims 5 and 11 of auxiliary request II.

Auxiliary request IV differs from auxiliary request II in that claim 11 has been deleted.

Auxiliary request V differs from auxiliary request IV essentially in that claim 1 has been amended by combining it with granted claim 2 (with the deletion of the reference to SEQ ID NO: 78), as follows:

"1. A method of detecting retargeted endopeptidase activity, ...:

a. ...;
b. ...;
c. ...;
wherein ... and
d. ...;
wherein ...;
wherein ...;
wherein ...;
and wherein ... or SEQ ID NO: 91;
and wherein the α-SNAP-25 antibody has a heavy chain variable region comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 72, SEQ ID NO: 76, SEQ ID NO: 80, and SEQ ID NO: 82; and a light chain variable region comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 84, SEQ ID NO: 88, SEQ ID NO: 90, and SEQ ID NO: 92."

Claim 1 of **auxiliary request VI** differs from claim 1 of auxiliary request V in that the α-SNAP-25 antibody is characterised as being an isolated monoclonal antibody and as having a heavy chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 79 or SEQ ID NO: 81, and a light chain variable region comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 83, SEQ ID NO: 87, SEQ ID NO: 89 or SEQ ID NO: 91.

Auxiliary request VII comprises two claims, claim 1 differing from claim 1 of auxiliary request VI in that it is restricted to an antibody wherein the heavy chain variable region and the light chain variable region comprise an amino acid sequence encoded, respectively, by the nucleic acid sequences SEQ ID NO: 71 and SEQ ID NO: 83.

Auxiliary request VIII comprises a sole claim, which is identical to claim 1 of auxiliary request VII.

V. With its reply to the grounds of appeal, the opponent (respondent) requested that the appeal be dismissed. It moreover requested that auxiliary requests VII and VIII not be admitted into the proceedings and submitted a new document, labelled Exhibit A.

VI. A summons to oral proceedings before the board, as requested by the parties, was issued and followed by a communication pursuant to Article 15(1) RPBA 2020 providing the board's preliminary opinion on some issues.

VII. The oral proceedings before the board took place as scheduled. At the end of oral proceedings, the chairman announced the decision of the board.

VIII. The following documents are cited in this decision:

D1 WO 2009/114748
D2 WO 96/33273
D3 WO 95/33850

IX. The appellant's submissions, in so far as relevant for this decision, may be summarised as follows:

Novelty as ground for opposition

The respondent's novelty objections had not been sufficiently substantiated in the notice of opposition or within the opposition period, and therefore this ground for opposition should be excluded from the appeal proceedings. The sequence comparisons between

the sequences of document D1 and the claimed sequences had been filed not with the notice of opposition but only with a later letter outside the opposition period. Moreover, the respondent had not even substantiated that the sequences of D1 were at all citable against the patent, which would require that either the effective date of the cited subject-matter of D1 was the priority date of D1 or that the priority of the patent was invalid.

Auxiliary requests II and IV: inventive step

The patent was directed to the detection of retargeted endopeptidases and it was apparent from paragraph [0005] that this was not straightforward, because the test which was normally used for detection of clostridial toxins was not applicable to retargeted endopeptidases due to the differences in the upstream mechanisms of action. Document D2 was the closest prior art and the difference from claim 1 was that different antibodies were used. D2 did not disclose any antibody sequences, and a different assay format was used: while isolated monoclonal antibodies that were immobilised were used in the patent, D2 used polyclonal antibodies that were not immobilised, the protein to be detected being immobilised instead. The method in the patent had a much higher sensitivity than the one in D2, as was evidenced by Figure 3 and paragraph [0286] of the patent. Therefore, the technical problem was to be formulated as the provision of means to improve sensitivity of an assay to detect activity of retargeted endopeptidase. The solution as claimed was not obvious, because the skilled person starting from D2, which did not provide any incentive to improve the detection, would have had a large number of alternative paths. Even if the skilled person considered changing

antibodies, they would not have turned to document D1, which was not even referenced in D2, but rather to D3, which was specifically referenced in D2. Since D3 also disclosed antibodies that bound to the same epitope as the antibodies specified in the patent, the skilled person willing to improve the antibodies would have looked for other possible antibodies, such as those disclosed on page 19 of D3, directed to other epitopes. Moreover the skilled person would have feared that replacing a polyclonal antibody, which comprised a mixture of antibodies, each possibly directed to different sites of the protein to be detected, with a monoclonal antibody could result in decreased sensitivity. As to D1, it did not teach that the antibodies it disclosed could be used to detect activity of retargeted endopeptidases. Hence, even if the skilled person would have turned to D1, they would have had doubts as to whether the antibodies of D1 could be used in assays as claimed. The respondent's arguments that the antibodies of D1 had the same properties as the antibodies of the patent were based on hindsight. While there were no experiments comparing the antibodies of the patent with those of D2 and D1, there were in fact plenty of experiments in the patent that also used other antibodies for comparative purposes, such as those disclosed in paragraph [0251] on page 70, thus rendering it plausible that the antibodies contributed to the solution of the problem. That the assay worked and had more sensitivity was made plausible in the patent in Table 22 on page 70 (relating to Example VII, starting on page 65), and in paragraphs [0285] and [0286] (showing that the antibodies of Example VII were used); this information was not present in D1.

Auxiliary requests III, V and VI: inventive step

D2 disclosed polyclonal antibodies and there was no teaching that monoclonal antibodies could be used to get a higher sensitivity. Moreover, antibodies with the sequence pairs defined in claim 1 (SEQ ID NOs: 75 and 87 and SEQ ID NOs: 77 and 89) were not disclosed anywhere in the prior art, not even in D1. Therefore, even when combining D2 with D1, the skilled person would not arrive at the claimed solution; a further modification was needed. However, there was no motivation for modifying further. Hence, the skilled person was taught away from the claimed sequences. Specific antibody sequences, even if differing from those of the prior art in just minor modifications in the framework region, could be inventive if there was no pointer to them (T 67/11), which was the case here. The sequences with SEQ ID NOS: 81 and 87 were quite different from any of the sequences of D1 and, in any case, D1 did not teach using any of its antibodies for detecting retargeted endopeptidase.

Auxiliary requests VII and VIII: inventive step

Since the priority was valid for these requests, document D1 was not citable, and the claimed subject-matter was inventive over the disclosure of D2 in combination with D3.

X. The respondent's arguments may be summarised as follows:

Novelty as ground for opposition

Novelty had been effectively raised as a ground for opposition with the notice of opposition and had been sufficiently substantiated. The notice of opposition

contained sufficient facts, evidence and arguments that made it possible to understand this ground for opposition and analyse it as to its merits. Even if the sequence alignments had only been filed subsequently, there was no requirement in the EPC according to which copies of the written evidence cited in the notice of opposition had to be filed within the opposition period.

Auxiliary requests II and IV: inventive step

The closest prior art D2 disclosed an assay like the one of claim 1, with the only differences that specific antibodies, defined by specific sequences in claim 1, and a different assay format were used: D2 used Western blot, while claim 1 required that an antibody be coupled to a support. These differences were not linked, however, to any technical effect: the different antibodies still recognised the same epitope. And, even if an effect were linked to the different assay format, the skilled person would routinely know how to choose different assay formats depending on the needs. There were no comparative examples on file, so there was no evidence of any improvement. The results of Figure 3 and paragraph [0286] of the patent could not be compared to the disclosure of D2 on page 20, first paragraph, and in Figure 3: the assays used different cell lines and different binding domains for example. Since Western blots were known to be less quantitative and were therefore not accepted by the drug regulatory authorities - which would require ELISAs (D1, paragraph [0004]) instead - the technical problem could be formulated as the provision of an assay for the detection of retargeted endopeptidase activity which would be accepted by the regulatory authorities. The solution would be obvious from D2 in combination with

D1. D1 did not use polyclonal antibodies but monoclonal antibodies, which were directed to the same epitope as the claimed antibodies. They also had exactly the same properties (e.g. affinity values) as the claimed antibodies, as was evident when comparing Tables 8 and 9 (and paragraph [0176]) of D1 with Tables 21 and 22 of the patent. The two table pairs related to exactly the same experiment, as was evident from the same title of Example III (and paragraph [0176]) of D1 and Example VII of the patent, and showed exactly the same results. The hybridoma names were also the same. Moreover, D1 also used ELISA (Example VI), as did D3, which was apparent from page 11; D3's Example 4 also used an ELISA although with the peptide coupled to the solid support. It was essential for the activity assays that the antibodies were specific for the cleaved SNAP-25 and not for the full length SNAP-25. This was already acknowledged by D1; even if D1 did not refer specifically to assessing the activity of targeted endopeptidase but rather to detecting cleaved SNAP-25, the principle of the assay was the same. Accordingly, the skilled person would just have to modify the assay of D2 by using the antibodies and the assay format of D1 in order to arrive at the claimed subject-matter.

Auxiliary requests III, V and VI: inventive step

The same arguments as for auxiliary request II also applied. The antibodies of D1 were different from those claimed, but had the same properties and were structurally closely related, as was apparent from the submitted sequence comparisons. Structural non-obviousness was not a standard for inventive step in the EPC.

Auxiliary requests VII and VIII: inventive step

The subject-matter was not inventive over D2, which disclosed the assay for detecting retargeted endopeptidase, in combination with D3, which disclosed the use of ELISA and antibodies specific to cleaved SNAP-25 (D3, page 9, last paragraph). Although both D2 and D3 used a polyclonal antibody, it was clear from D3 that specificity and sensitivity were important.

XI. The appellant requested that the decision of the opposition division be set aside and the patent be maintained as granted (main request), implying that the opposition be rejected, or, alternatively, that the patent be maintained in amended form according to one of the sets of claims of auxiliary request I or II, both filed with the letter of 22 January 2016, or according to the claims of auxiliary request III, filed at the oral proceedings on 3 May 2016, or according to one of the sets of claims of auxiliary requests IV to VI, filed with the letter of 22 January 2016, or of auxiliary request VII or VIII, both filed with the grounds of appeal. It moreover requested that novelty be excluded from the appeal proceedings as ground for opposition.

The respondent requested that the appeal be dismissed and that auxiliary requests VII and VIII not be admitted into the proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. Novelty as ground for opposition

2.1 The appellant argued that the ground for opposition concerning lack of novelty had not been sufficiently substantiated in the notice of opposition or otherwise within the opposition period and requested that this ground for opposition be excluded from the appeal proceedings for this reason.

2.2 As noted by the board in its communication pursuant to Article 15(1) RPBA 2020, the appellant's case was not directed to the inadmissibility of the opposition, but solely concerned the question of whether or not the ground for opposition of lack of novelty should be excluded from the appeal proceedings.

2.3 Even if the ground for opposition of lack of novelty had not been sufficiently substantiated during the opposition period, or not even raised at all by the respondent, the opposition division could have raised it *ex officio*, thereby making it part of the opposition proceedings. In the present case, the ground for opposition concerning lack of novelty was in fact examined during the opposition proceedings by the opposition division, and the assessment included the determination of the relevant state of the art and the relevant effective dates. It formed part of the opposition proceedings and was addressed and considered in the decision under appeal. Thus, whether or not the ground for opposition concerning lack of novelty had initially been sufficiently substantiated in the notice of opposition or during the opposition period is not relevant in the circumstances of the present case and cannot lead to its exclusion from the appeal proceedings. Moreover, the respondent, by relying on the objections of lack of novelty in its reply to the

grounds of appeal, has made those objections as part of its appeal case.

2.4 For the sake of completeness, the following is noted. None of the documents cited in the notice of opposition was actually filed with it. Instead, they were only filed with a letter received after the opposition period had expired. Pursuant to Rule 83 EPC, documents referred to by a party to opposition proceedings are to be filed with the notice of opposition or the written submissions. If such documents are neither enclosed nor filed in due time upon invitation by the opposition division, it may decide not to take into account any arguments based on them. In the present case, the documents had been filed in due time, even before an invitation pursuant to Rule 83 EPC was sent, and the opposition division did decide to take the arguments based on them into account, as specifically stated in the appealed decision (sections 2.2. and 2.3). As for the argument that the respondent failed to sufficiently substantiate that the allegedly novelty-destroying subject-matter of D1 was in fact citable, the board notes that the respondent did argue that the patent's priority was not valid (Article 87(4) EPC), which would automatically make D1 citable under Article 54(2) EPC.

2.5 Accordingly, the ground for opposition concerning lack of novelty and the novelty objections decided upon by the opposition division are part of the appeal proceedings.

3. Main request and auxiliary request I: novelty

3.1 The appellant contested the consideration of novelty as ground for opposition in the appeal proceedings but did not present any arguments, either in writing or at the

oral proceedings, to address the conclusions reached by the opposition division concerning invalidity of priority and lack of novelty of the subject-matter of claim 5 of the main request and of claim 11 of auxiliary request I.

3.2 Since the conclusions of the opposition division as regards novelty of the main request and of auxiliary request I were not contested on appeal, the board comes to the conclusion that they are still valid. Hence, the main request and auxiliary request I are not allowable due to lack of novelty over the disclosure of document D1.

4. Auxiliary request II: inventive step

4.1 The patent in dispute is directed to assays for determining the presence or absence of an active retargeted endopeptidase in a sample and for determining the activity/potency of a retargeted endopeptidase (patent, paragraph [0014]). As explained in paragraph [0005], one general difference between retargeted endopeptidases and clostridial toxins is that because retargeted endopeptidases typically do not target motor neurons, the lethality associated with overdosing a mammal with a retargeted endopeptidase is greatly minimised, if not avoided altogether. Although this non-lethal property is of great therapeutic benefit, it raises manufacturing problems because the standard activity assay which is used to manufacture clostridial toxin-based biologics, namely a mouse LD50 bioassay, is a lethality test, which, therefore, cannot be used to assess the potency of these molecules. Accordingly, the patent aims at providing "a simple, reliable, validated, and governmental agency acceptable

activity assay" (paragraph [0005] of the patent) for retargeted endopeptidases.

4.2 Claim 1 of auxiliary request II is identical to claim 1 as granted. It is directed to a method of detecting retargeted endopeptidase activity, the method making use of an α-SNAP-25 antibody which binds an epitope comprising a carboxyl-terminus at the P_1 residue from the BoNT/A cleavage site scissile bond from a SNAP-25 cleavage product, wherein the α-SNAP-25 antibody has a heavy chain variable region comprising an amino acid sequence encoded by a nucleic acid sequence which is identical or at least 90% identical to a nucleic acid sequence from a given group, and a light chain variable region comprising an amino acid sequence encoded by a nucleic acid sequence which is identical or at least 90% identical to a nucleic acid sequence from another group.

4.3 As concluded by the opposition division, and not disputed by the parties, document D2 can be taken as the closest prior art for the subject-matter of claim 1 of auxiliary request II. It was also agreed by the parties that the difference between the method in claim 1 and the assay disclosed in Example 2 of D2 resides in the use of a different α-SNAP-25 antibody, defined by specific heavy and light chain sequences in the present claims, and another assay format (namely using an antibody linked to a solid phase support in the patent, rather than using a Western blot as in D2).

4.4 There is no evidence on file for a technical effect linked to the above-mentioned distinguishing features, because there are no experiments which make it possible to compare the assay as claimed with an assay as disclosed in D2. Hence, the board considers that the

objective technical problem has to be formulated as the provision of a further assay for detecting retargeted endopeptidase activity. In view of the evidence provided in the patent, and in Table 22 in particular, the board concludes that the claimed subject-matter plausibly solves the technical problem.

4.5 The claimed solution, however, does not involve an inventive step.

4.6 It was not disputed that D2 teaches "botulinum toxin derivatives" (title) which correspond to the definition of retargeted endopeptidase of the patent (compare page 13 and Example 1 of D2 with the definition of retargeted endopeptidase in paragraph [0004]) of the patent. The construction of one of those botulinum derivatives is disclosed in Example 1 of D2, namely a conjugate of NGF and the LH_N fragment (which contains the L-chain or a functional fragment of it; see page 9, lines 13 to 15) of BoNT/A. As explained in D2 on page 12, lines 12 to 19, the clostridial neurotoxins possess a highly specific zinc-dependent endopeptidase activity, residing in the L-chain, that hydrolyses a specific peptide bond in at least one of three proteins: synaptobrevin, syntaxin or SNAP-25. D2 then discloses in Example 2 a method to detect the activity of that conjugate by assessing the proteolysis of SNAP-25 using an antibody "that recognises the newly revealed carboxy-terminus of the cleaved SNAP-25" (page 20, lines 4 to 5). In this context, D2 specifically states that the antibody used "is described in Patent Application PCT/GB95/01279". The referenced patent application, which has been published as WO 96/33273, is document D3 in the present proceedings. From D3, page 8 and Example 4 on page 19, it is apparent that D2's antibody is specific to the sequence RIDEANQ, i.e.

the carboxyl end of the cleaved SNAP-25, which is exactly the same epitope that was targeted in the patent (paragraph [0238]).

4.7 The skilled person would thus know from D2 that the activity of retargeted endopeptidases, just like the activity of unmodified clostridial neurotoxins such as BoNT/A, could be measured by assessing their proteolytic activity on their substrate SNAP-25, and that this could be made by using antibodies specifically directed to the cleaved SNAP-25, i.e. antibodies that recognise the cleaved SNAP-25 but not the full length SNAP-25, since they are directed to the "newly revealed carboxy-terminus of the cleaved SNAP-25" (see point 4.6 above). Faced with the problem of providing further assays for the detection of retargeted endopeptidase activity, the skilled person would thus have looked for further antibodies directed to the same epitope and/or for different known assay formats, and would have arrived at the claimed antibodies, or at equally suitable antibodies, as well as at the claimed assay format or any other suitable assay format. In this context, it is noted that the provision of further antibodies or of monoclonal antibodies against a known epitope is considered to be routine for the skilled person, as it merely involves the use of well-known techniques.

4.8 Hence, on the basis of D2 alone, the board cannot acknowledge an inventive step for the claimed subject-matter. In addition, in the present case, antibodies like those claimed were even already available in the prior art and were used in the same type of assays, namely in D1, which discloses monoclonal antibodies against the peptides comprising the same epitope (paragraph [0171]), including those that have variable

light chain and variable heavy chain regions falling within the definition of present claim 1, and methods of detecting BoNT/A activity comprising the same steps as in present claim 1 (see e.g. claim 8 of D1). Accordingly, the skilled person would not even have had to produce new antibodies, but rather would just have had to modify the assays of D2 by using the antibodies and the assay formats of D1.

4.9 The board thus comes to the conclusion that the claimed subject-matter does not involve an inventive step.

4.10 The appellant disagreed with the formulation of the technical problem, arguing that, since the method in the patent had a much higher sensitivity than the one in D2, the technical problem was to be formulated as the provision of means to improve sensitivity of an assay to detect activity of retargeted endopeptidase. While there were no experiments comparing the antibodies of the patent with those of D2, the patent showed that the chosen antibodies contributed to the solution of the problem, and this had never been disputed. It was plausible from the experiments disclosed in the patent that the assay worked and that it had a greater sensitivity, and such information was not present in D1.

4.11 The board notes that, for a technical problem to be formulated as an improvement over the closest prior art, it must have been shown or at least made plausible in the patent that the features distinguishing the claimed invention from the closest prior art do in fact result in a technical effect. This is not the case here. It is not disputed that the assays of the invention work and that they have good sensitivity. However, there are no data that make it possible to

conclude that the use of the claimed antibodies and/or of the claimed assay format result in any effect over the assays of D2. It is true that Figure 3 of the patent teaches that retargeted endopeptidase can already be detected at concentrations as low as 100 pM, and that paragraph [0286] also discloses detection of concentrations in the low nanomolar range whereas D2 uses higher concentrations of the BoNT/A construct (page 20, first paragraph; Figure 3). However, Figure 3 and paragraph [0286] of the patent refer to very specific assay embodiments which differ from the assay of D2 not only in the above-mentioned two distinguishing features. D2 is not at all concerned with determining the lowest concentration of the BoNT/A construct that could still be detected using the assay disclosed there. In fact, this would not be easily assessed using Western blots, as used in D2, which are suitable for detection but not for quantification. As to the experiments of the patent which make use of other, commercially available, antibodies for comparative purposes, such as those disclosed in paragraph [0251] and Table 22 on page 70, it is noted that none of the comparative antibodies is the antibody of D2, and it is not even known to which epitope of SNAP-25 they are directed. In fact, it appears that at least one of these commercially available antibodies must be directed to a different epitope, since it is said to detect both the uncleaved and the cleaved SNAP-25 product (page 68, lines 27 to 29).

4.12 Finally, as regards the appellant's argument that document D1 did not provide any teaching that would have allowed the skilled person to expect that the antibodies disclosed there could be used to detect retargeted endopeptidase, let alone with a higher sensitivity than in D2, the following is noted. First,

as set out above, even without combining D2 with the disclosure of D1, the board already comes to the conclusion that the claimed subject-matter is not inventive. Second, without teaching that its antibodies are to be used in assays for detecting retargeted endopeptidases, document D1 nevertheless teaches exactly the same properties for its antibodies as are shown for the patent's antibodies, and teaches their use for detecting BoNT/A (i.e. the unmodified neurotoxin) with the same assays as claimed. That such antibodies, directed to the cleaved SNAP-25 product, could be used in assays for detecting retargeted endopeptidases had already been made plausible in D2 and so there would have been no reason for the skilled person to doubt that the antibodies of D1 too could be used for exactly the same purpose.

4.13 Auxiliary request II is thus not allowable due to lack of compliance with Article 56 EPC.

5. Auxiliary request III: inventive step

5.1 Claim 1 of this request differs from claim 1 of auxiliary request II in that it has been amended to specify that the α-SNAP-25 antibody used in the assay is monoclonal and that it is to be selected from two groups of antibodies further defined by the amino acid sequences of their variable regions, namely an antibody that has a heavy chain variable region and a light chain variable region comprising an amino acid sequence encoded, respectively, by the nucleic acid sequences SEQ ID NO: 75 and SEQ ID NO: 87; or an antibody that has a heavy chain variable region and a light chain variable region comprising an amino acid sequence encoded, respectively, by the nucleic acid sequences SEQ ID NO: 77 and SEQ ID NO: 89.

5.2 Since there are no data in the patent or elsewhere on file providing evidence that assays using these particular antibodies have any advantages over the assay of the closest prior art D2, the board considers that the technical problem is still to be formulated as the provision of a further assay for the detection of retargeted endopeptidase activity and, for the same reasons as set out above, the board comes to the conclusion that the skilled person, faced with the formulated problem, would have routinely arrived at the claimed solution on the basis of D2 alone.

5.3 The appellant's arguments were essentially that there was no teaching in D2 that monoclonal antibodies could be used to obtain a higher sensitivity and that antibodies with the defined sequence pairs for the variable regions (SEQ ID NOs: 75 and 87 and SEQ ID NOs: 77 and 89) were not disclosed anywhere in the prior art, not even in D1. The board agrees but notes that, since the technical problem is not formulated as an improvement, it is irrelevant whether or not there was any teaching in the prior art as regards using monoclonal antibodies to improve sensitivity. Moreover, the now specifically claimed antibodies are simply two more antibodies for use against the same epitope as the antibody disclosed in D2 and D3. As already stated above, it is routine to produce antibodies against a known epitope. Hence, despite the fact that the claimed antibodies were not known from the prior art, it would still have been routine for the skilled person to arrive at them or any other equally suitable antibodies. The present situation is different from the situation underlying decision T 67/11, mentioned by the appellant in this context, because, in the case at issue there, specific mutations had been introduced to

obtain a specific effect, namely reduced immunogenicity in humans. In the present case, by contrast, there is no evidence on file to support any particular effect associated with the specific sequences of the antibodies as claimed over the antibodies of the prior art.

5.4 Auxiliary request III is thus not allowable due to lack of compliance with Article 56 EPC.

6. Auxiliary request IV: inventive step

6.1 Claim 1 of auxiliary request IV is identical to claim 1 of auxiliary request II. Accordingly, for the same reasons as given above for auxiliary request II, auxiliary request IV is not allowable due to lack of compliance with Article 56 EPC.

7. Auxiliary requests V and VI: inventive step

7.1 Claim 1 of these requests differs from claim 1 of auxiliary request II in that the α-SNAP-25 antibody to be used in the assay is defined as having a heavy chain variable region comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 72, SEQ ID NO: 76, SEQ ID NO: 80 and SEQ ID NO: 82; and a light chain variable region comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 84, SEQ ID NO: 88, SEQ ID NO: 90 and SEQ ID NO: 92. Claim 1 of auxiliary request VI further differs from claim 1 of auxiliary request II in that the antibody is characterised as being isolated and in that the nucleic acid sequences encoding the amino acid sequences of the light and heavy chain variable regions were further restricted.

7.2 For the same reasons as given above for auxiliary request III, the board considers that the restriction to antibodies with given amino acid sequences does not lead to a reformulation of the technical problem as an improvement, since no data are available for any of these claimed antibodies which make it possible to conclude that they result in assays having advantages over the assay of D2. Hence, for the same reasons given above as regards auxiliary request III, the use of these specific antibodies cannot contribute towards inventive step. As for the added feature "isolated" (present in auxiliary request VI), the board, in the absence of any reasoning provided by the appellant, does not see how it could contribute towards inventive step either.

7.3 Auxiliary requests V and VI are thus not allowable due to lack of compliance with Article 56 EPC.

8. Auxiliary requests VII and VIII:

Admission

8.1 The respondent objected to the admission of these requests, both filed with the statement of grounds of appeal, into the appeal proceedings. In its communication pursuant to Article 15(1) RPBA 2020, the board indicated that it was inclined not to exclude these requests from the appeal proceedings under Article 12(4) RPBA 2007 and gave reasons for this. After hearing the parties again on this issue at the oral proceedings, the board decided that these requests were to be admitted into the proceedings. However, in view of the conclusions reached below under inventive step, the board does not consider it necessary to provide reasons for this point of the decision.

Priority

8.2 In the statement of grounds of appeal, the appellant argued that priority was valid for the subject-matter of these requests and therefore document D1 was not citable in the context of inventive step. At the oral proceedings, the respondent disagreed and provided arguments as to why priority was not valid for the claimed subject-matter. After hearing the parties on this issue, the board came to the conclusion that priority was validly claimed for the subject-matter of auxiliary requests VII and VIII. However, in view of the board's conclusions below under inventive step, for which document D1 was not relevant, the board does not consider it necessary to provide reasons for this point of the decision.

Inventive step

8.3 Claim 1 of each of auxiliary requests VII and VIII differs from claim 1 of auxiliary request VI in that the antibody to be used has been restricted to an antibody wherein the heavy chain variable region and the light chain variable region comprise, respectively, SEQ ID NO: 71 and SEQ ID NO: 83.

8.4 For the same reasons as given above for auxiliary request III, the board considers that the restriction to antibodies with given amino acid sequences does not lead to a reformulation of the technical problem as an improvement, since no data are available for any of these claimed antibodies which make it possible to conclude that they result in assays having advantages over the assay of D2. Hence, also for the same reasons given above as regards auxiliary request III, the use

of these specific antibodies cannot contribute towards inventive step.

8.5 Auxiliary requests VII and VIII are thus not allowable due to lack of compliance with Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated