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Datasheet for the decision of 26 October 2009

Case Number: T 1437/07 - 3.3.04

Application Number: 99203735.8

Publication Number: 1010431

IPC: A61K 38/16

Language of the proceedings: EN

Title of invention:
Botulinum toxins A or B for treating pain associated with smooth muscle spasms

Patentee:
Allergan, Inc.

Opponents:
Solstice Neurosciences, Inc.
Ipsen Pharma S.A.S.

Headword:
Botulinum toxin for treating smooth muscle spasm/ALLERGAN

Relevant legal provisions:
EPC Art. 54, 56, 76(1), 83, 84, 123(2)(3)

Relevant legal provisions (EPC 1973):
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Keyword:
"Main request - novelty (no)"
"Auxiliary request - added matter, extension of scope (no); sufficiency of disclosure, novelty, inventive step (yes)"

Decisions cited:
T 0246/86, T 0158/96, T 0609/02, T 0715/03, T 0630/04

Catchword:
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Case Number: T 1437/07 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 26 October 2009

Appellant: (Patent Proprietor)	Allergan, Inc. 2525 Dupont Drive Irvine CA 92612 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte Arabellastraße 4 D-81925 München (DE)
Respondent I: (Opponent 02)	Solstice Neurosciences, Inc. 5 Great Valley Parkway, Suite 257 Malvern PA 19355 (US)
Representative:	Wachenfeld, Joachim Vossius & Partner Siebertstraße 4 D-81675 München (DE)
Respondent II: (Opponent 03)	Ipsen Pharma S.A.S. 65, Quai Georges Gorse F-91200 Boulogne-Billancourt (FR)
Representative:	Morf, Jan Stefan Abitz & Partner Patentanwälte Postfach 86 01 09 D-81628 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 23 July 2007 revoking European patent No. 1010431 pursuant to Article 102(1) EPC 1973.**

Composition of the Board:

Chairman: U. Kinkeldey
Members: G. Alt
F. Blumer

Summary of Facts and Submissions

I. European patent No. 1 010 431 entitled "Botulinum toxins A or B for treating pain associated with muscle spasms" is based on European patent application EP 99203735.8. This application was filed as a divisional application of European application EP 95906674.7 which was published as WO 95/17904 (hereafter "the parent application").

II. The patent had been granted with one independent and ten dependent claims.

Claim 1 read:

"1. The use of Botulinum toxin type A or type B for the manufacture of a medicament for relieving pain associated with muscle spasms in smooth muscle disorders."

III. Three notices of opposition were filed. Revocation of the patent was requested based on Article 100(a) EPC on the grounds of lack of novelty, lack of inventive step and exception to patentability, Article 100(b) EPC and Article 100(c) EPC on the ground of added matter, both vis-à-vis the parent application and the application as filed.

IV. By an interlocutory decision the opposition division came to the conclusion that none of the four requests before it was allowable and that therefore the patent had to be revoked.

In particular, the opposition division found that claim 1 of the main request (corresponding to claim 1 as granted) did not fulfil the requirements of Articles 76(1) and 123(2) EPC. Claim 1 of the first auxiliary request was considered not to be novel in view of any of documents R1, R2 and R10 (bibliographical data see below). The opposition division moreover found that Claim 1 of the second auxiliary request lacked an inventive step in the light of documents R1 or R2 in combination with document R14.

Claim 1 of the third auxiliary request read:

"1. The use of a Botulinum toxin type A for the manufacture of a medicament for relieving cramps and pain associated with spastic colon."

The opposition division found that this claim lacked an inventive step in view of document R14 in combination with document R1 or R2.

V. The patent proprietor (hereinafter "appellant") lodged an appeal against the decision of the opposition division.

VI. Opponent 01 withdrew its opposition.

VII. Oral proceedings before the board took place on 26 October 2009. The appellant filed a new auxiliary request and withdrew all the seven auxiliary requests he had filed before in writing.

VIII. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis

of the main request as filed on 28 September 2009 (claims 1-8),or, subsidiarily, on the basis of the auxiliary request (claims 1-4 and amended description pages 2-4) as filed during the oral proceedings before the board.

Claim 1 of the main request read:

"1. The use of a Botulinum toxin type A for the manufacture of a medicament for relieving pain associated with muscle spasms in smooth muscle disorders."

Claim 1 of the auxiliary request read:

"1. The use of a Botulinum toxin type A for the manufacture of a medicament for relieving pain associated with muscle spasms in smooth muscle disorders, wherein the medicament is for relieving cramps and pain associated with spastic colon."

IX. Respondents I and II (opponents 02 and 03) requested that the appeal be dismissed.

X. The following documents are referred to in the present decision:

R1: The Lancet, vol. 341, January 1993, pages 244-245, Pasricha, P.J. et al.

R2: Internist, vol. 34, 1993, pages 1122-1132, Allescher, H.-D.

R4: Current practice in surgery, vol. 5, 1993, pages 228-232, O'Donnell, L.J.D. and Heaton, K.W.

R5: Gastroenterology, vol. 104, no. 4, part 2, 1993, page A168, Pasricha, P.J. et al.

R6: Gastroenterology, vol. 105, 1993, pages 1045-1049, Pasricha, P.J. et al.

R10: WO-A-94/28923

R11: The American Journal of Gastroenterology, vol. 87, no. 9, 1992, page 1255, abstract 52, Pasricha, P.J. et al.

R13: Journal of the Royal Society of Medicine, 1992, pages 524-529, Anderson et al.

R14: The New England Journal of Medicine, April 1991, pages 1186-1194, Jancovic, J. and Brin, M.F.

R19: Dorland's illustrated medical dictionary; 26th edition, 1985, page 287

R21: Gastrointestinal Endoscopy, vol. 39, no. 2, March/ April 1993, page 320, Abstract 287, Pasricha, P.J. et al.

R23: Harrison's Principles of Internal Medicine, 11th edition, 1987, pages 96, 179, 1294, 1295, 1367

R27: Gut, 1994, pages 1319-1322, Pasricha, P.J. et al.

R36: Handbook of botulinum toxin treatment, 2nd edition, 2003, page 5, ed. Moore, P. et al.

XI. The appellant's arguments insofar as they are relevant for the present decision may be summarised as follows:

Main request

Articles 76(1) and 123(2)(3)

All claims of the main request had a basis in the parent application and the application as filed. In particular, there was no reason to disregard a disclosure only because it was contained in a heading. Neither was there any reason to interpret the disclosure in the heading of Example 9 as being restricted to the specific disclosure that followed.

The cases underlying decisions T 158/96, T 715/03 and T 630/04 related to situations different from the present one.

The term "and" between the expressions in the heading to example 9 - "muscle spasms" and "control of pain associated with muscle spasms" - did not indicate that the two applications were inseparably linked, i.e. one of the two could be claimed without infringing Article 76(1) or 123(2) EPC.

The intention according to the patent in the treatment of pain was clearly unidirectional, i.e. it was always aimed at reducing pain. Therefore, in this context "control" and "relief" meant the same.

The use of the term "urinary bladder" instead of "urinary system" in claim 2 was an allowable amendment.

Novelty

None of documents R1, R10 and R21 was relevant to the novelty of the subject-matter of claim 1.

In particular with regard to document R21, it could be seen from the definitions in documents R19 and R23 that the disclosure of an increased pressure of the sphincter of Oddi would not be considered as a "spasm". Moreover, a causal link between pain and spasm was not derivable from document R21. Finally, the document did not provide an enabling disclosure because the therapeutic effect - removal of pain - was not repeatable, as could be seen from the post-published document R27.

Auxiliary Request

Article 83 EPC

The patent provided all the necessary information to enable the skilled person to carry out the claimed invention and also made it credible that the therapeutic effect had been achieved.

Inventive step

The skilled person would not be motivated by the disclosure in any of documents R2, R13 or R14 to apply botulinum toxin for relieving cramps and pain in patients with a spastic colon in particular, because

he/she would not expect that peristaltic motility could be restored by that treatment.

Moreover, the expression "spasms of any cause could be temporarily relieved" in document R14 did not mean that spasms of any type could be relieved, as inferred by the respondents.

XII. The respondents' arguments insofar as they are relevant for the present decision may be summarised as follows:

Main Request

Articles 76(1) and 123(2)(3) EPC

The purpose of a heading was to structure a text. Therefore, headings could not be taken to "disclose" anything and therefore could not serve as the basis for a claim. The special character of a heading could be deduced from the fact that, according to the Guidelines, A-III, 7.2, the ultimate responsibility for the title of a patent rested with the EPO.

Moreover, even if the heading in Example 9 was regarded as a disclosure on which an amendment could be based, then this was only to the extent of the contents of the following example. This could be seen from the fact that a title such as "Material and Methods" as found in publications on natural science would not be understood to introduce any material and any method, but only those which are disclosed in the text following the title.

Thus, for that reason the title of Example 9 could not support amended claim 1 of the main request.

Moreover, Example 9 was an hypothetical example, i.e. it had never been carried out and neither had the subject-matter referred to in the title of this example. Case law from the field of novelty had established that hypothetical disclosures did not take away the novelty of corresponding claimed subject-matter (T 158/96, T 715/03, T 630/04). By analogy, a hypothetical disclosure in an application could not serve as a basis for a claim.

The title of Example 9 related to the use of botulinum toxin "in the treatment of muscle spasms and control of pain associated with muscle spasms", i.e. two symptoms are treated at a time. In contrast, this mandatory connection was not required according to claim 1.

Finally, the meaning of the term "relief" of pain recited in claim 1 was different from the meaning of "control" of pain according to the heading in Example 9. Relief always meant "reduction", whereas, "control" could mean "reduction or "no further increase" in pain.

Claim 2 inter alia related to the use of botulinum toxin A for the treatment of spasms of the sphincter of the urinary bladder. There was no basis for the term "urinary bladder" in either the parent application or the application as filed.

Moreover, claim 2 also contravened the requirements of Article 123(3) EPC since in claim 2 as granted reference was made to the "urinary system".

For all these reasons the requirements of Articles 76(1) and 123(2)(3) EPC were not fulfilled.

Novelty

The disclosure in all of documents R1, R10 and R21 anticipated the subject-matter of claim 1.

It was not permissible to use the post-published document R27 for the determination of the disclosure content of document R21.

Auxiliary Request

Article 83 EPC

Terms in the claim such as "smooth muscle disorder" or "pain" were not defined in the patent. Their unclarity resulted in a lack of sufficiency of disclosure.

From the way it was presented it was clear that Example 9 had never been carried out. Therefore, it was not credible that the therapeutic effect had been achieved.

Inventive step

Document R2 disclosed that one of the abnormalities in achalasia was an aperistaltic lower oesophagus. Since both the oesophagus and the colon were tubular organs,

document R2 could be considered as the closest prior art. The skilled person would derive from the disclosure in document R2 that the blocking of the release of acetylcholine at the neuro-muscular junction by botulinum toxin was used in the therapy of spastic neurologic disorders as a suggestion to use botulinum toxin to relax a spastic colon.

Document R14 disclosed the injection of botulinum toxin into the abnormally contracted detrusor muscle of the urinary bladder. Since the detrusor muscle was composed of smooth muscle fibres, this document was also suited as the closest prior art document. This disclosure, in particular in combination with the statement in document R14 that botulinum toxin could be used to relieve spasms of any cause, would motivate the skilled person to apply botulinum toxin as claimed.

Moreover, the subject-matter of claim 1 was obvious in view of the disclosure in document R13 that botulinum toxin relieved pain and spasms in patients with spasmodic torticollis.

Reasons for the Decision

Main request

Articles 76(1) and 123(2) EPC

Claim 1

1. The issue is whether or not the skilled person would clearly and unambiguously derive the subject-matter of

claim 1 from the disclosure in the parent application or the application as filed, in particular, from the heading of example 9.

2. The description of the parent application and the application as filed are identical. Thus, Example 9 (i.e. the first of two examples each entitled "Example 9") of both applications reads:

"Example 9

The Use of Botulinum toxin Types A-G in the Treatment of Muscle Spasms and Control of Pain Associated with Muscle Spasms in Smooth Muscle Disorders Such as Gastrointestinal Muscles

[0061] A female, age 35, with spastic colitis, is treated with 1-100 units of Botulinum toxin divided into several areas, enema (1-5 units) delivered in the standard enema volume, titrate dose, starting with the lowest dose. Injection is to the rectum or lower colon or a low dose enema may be employed. Cramps and pain associated with spastic colon are relieved in 1-10 days."

3. The respondents argue that a heading could not provide a basis for a claim because the purpose of a heading is merely to structure a text and therefore it could not be considered as "disclosing" anything. It is submitted that the special character of a heading becomes evident when considering that the title of a patent could be amended by the EPO without informing the applicant or patent proprietor.

3.1 However, the only titles that may be amended by the EPO are those printed on the cover sheet of a patent application (for the amendment procedures, see the Notice dated 13 March 1991 concerning the amendment of the title of the invention in European patent applications, OJ EPO 1991, 224; Guidelines, A-III, 7.2). This "title of the invention" is also part of the abstract (Rule 47(1) EPC). Both the abstract and the title of the invention serve for information and documentation purposes. In decision T 246/86 (OJ EPO 1989, 199, point 2.2), the board found that the abstract does not form part of the disclosure for the purposes of Article 123(2) EPC. Consequently, the title of the invention may not be used as a basis for any amendments of a claim as well.

3.2 In contrast, amended claim 1 is based on a heading which is not on the cover sheet, but which is within the description of the application as filed. According to Article 76(1) EPC and Article 123(2) EPC the allowability of an amendment is judged on the "content" of the application. The term "content" relates to the parts of a European patent application which determine the disclosure of the invention, namely the description, claims and drawings (Case Law of the Boards of Appeal, 5th edition 2006, III.A.1.1, first paragraph). Thus, headings that are situated within any of these parts form part of the disclosure content of an application and therefore amendments may be based on them.

4. The respondents further maintain that, even if the heading of Example 9 was regarded as a "disclosure", the skilled person would have considered it to be

limited to the content of the specific disclosure which follows.

4.1 However, the disclosure content of a document is to be determined on the basis of the document as a whole. In the present case, in the paragraph bridging pages 4 and 5 the invention is described in general terms: "The present invention provides a method for relieving pain, associated with muscle contractions, [...], and a method for treating smooth muscle disorders, including, but not limited to, spasms in the sphincter of ...". On page 9, lines 18 to 19 it is stated that the invention "will now be illustrated by reference to the following nonlimiting examples". In the board's view, these passages convey to the skilled person that the invention is not limited to the specific examples. This is also what the skilled person would derive from the Examples part of the description. Each of the twelve examples has a title disclosing in a "claim-like" manner a particular concept of use which is followed by a specific disclosure which illustrates it.

5. Furthermore, the respondents rely on decisions T 158/96 of 28 October 1998, T 715/03 of 16 January 2006 and T 630/04 of 13 December 2006 and put forward the following argument: In the three above-cited decisions the boards have ruled that "speculative" or "hypothetical" disclosures do not anticipate claimed subject-matter. Therefore, in analogy to the rationale of these decisions, Example 9 of the patent cannot be used as a basis for an amendment because it is "speculative" or "hypothetical" as well, since it has not actually been carried out.

5.1 In decisions T 158/96 and T 715/03 the boards regarded it as "speculative" to infer from the information that a medicament is undergoing clinical phase evaluation that a particular therapeutic effect has been achieved (see points 3.6 to 3.6.2 and point 2.2, respectively). In T 630/04 a statement in a document was denoted as a "hypothetical speculation" in the sense that it could not be interpreted as disclosing the claimed subject-matter (see points 2.2.1 to 2.3). Thus, in the three cited decisions the teaching in a document was considered as "speculative" or "hypothetical" because it was not clearly and unambiguously derivable from the document. Hence, in contrast to what is implied by the respondents' argument, the boards' reason for accepting novelty in the cited decisions was not that the subject-matter in the prior art documents was not disclosed in an enabling manner. Consequently, decisions T 158/96, T 715/03 and T 630/04 do not help the respondents' case.

5.2 With regard to the respondent's view that a "hypothetical" example cannot be used as the basis for an amendment, the board considers that the question of whether or not the disclosure in an application is sufficient to enable a skilled person to carry out the claimed invention is not relevant for the assessment of whether or not the requirements of Article 123(2) EPC are fulfilled. This is so, because the basis for amendments is the "content" of the application, i.e. what the skilled person would have clearly and unambiguously derived from the written disclosure as a whole. For the determination of the mere information

content of a document it is not relevant whether or not what is disclosed has in fact been carried out.

6. Turning now to the question of whether or not amended claim 1 has a basis in the parent application or the application as filed, it is the board's view, firstly, that the skilled person would have considered that the reference in the heading of Example 9 to the "use of botulinum toxin types A-G" means that all botulinum toxins embraced by the term "A-G" are equally suited for the use. Therefore, the skilled person would derive the claimed use of botulinum toxin type A from the heading of example 9.

7. Secondly, in the paragraph bridging pages 4 and 5 it is disclosed that "the present invention provides **a method for relieving pain**, associated with muscle contractions, [...] and **a method for treating smooth muscle disorders including, but not limited to, spasms** in the sphincter of the cardiovascular arteriole, gastrointestinal system, urinary, gall bladder and rectum, [...]" (emphasis added). Page 17, lines 10 to 15, discloses the treatment of muscle spasms in smooth muscle disorders. Thus, in the context of the description, the skilled person would have understood that the disclosure in the title of Example 9 of the "treatment of muscle spasms and control of pain associated with muscle spasms in smooth muscle disorders" relates to two alternative treatment options which may be carried out separately. He/she would not have considered that, as has been argued by the respondents, the disclosure related to the mandatory simultaneous treatment of muscle spasms and the control of pain. Thus, the

treatment indicated in claim 1 is derivable from the title of Example 9.

8. Finally, the respondents submit that the expression "for relieving pain" used in claim 1 has a different meaning than the expression "control of pain" recited in the heading of Example 9 since "control" could not only mean "reduction", but could also mean that pain is kept constant. However, the skilled person would have gathered from the application as a whole, and specifically, for example, from pages 4 and 5 (see first sentence of point 7 above), that the only objective of botulinum toxin treatment is the reduction of pain. Thus, when interpreted in a contextual manner, "control" can only mean "relief". Hence, the feature in claim 1 "for relieving pain" is derivable from the heading of Example 9.

9. Thus, the board concludes that the skilled person would clearly and unambiguously derive the subject-matter of claim 1 from the parent application and the application as filed, respectively.

10. Claim 2, in particular the term "urinary bladder", is based on a combination of the teachings in the headings of example 6, reciting "urinary or gall bladder", and example 9.

11. Claims 3 and 4 have a basis in claims 12 and 13 of the parent application. For the basis of claims 5 to 8 in the parent application, see points 30 and 32 below.

The basis for claims 3 and 4 in the application as filed is found in claims 6 and 7. For the basis of

claims 5 to 8 in the application as filed, see also points 30 and 32 below.

12. The requirements of Articles 76(1) and 123(2) are fulfilled.

Article 123(3) EPC

13. Claim 1 is a combination of claims 1 and 3 as granted. Claims 2 to 8 are based on claims 4 and 6 to 11 as granted with the exception that present claim 2 refers to "urinary bladder" instead of "urinary system". Since the urinary bladder is a part of the urinary system, no extension results from this amendment.

The requirements of Article 123(3) are fulfilled.

Article 84 EPC

14. The parties did not raise objections under Article 84 EPC and also the board had none.

Novelty

15. The respondents cited documents R1, R10 and R21 against the novelty of the claimed subject-matter.

16. Document R21 is an abstract summarising the contents of a poster shown at a conference of the American Society for Gastrointestinal Endoscopy. The abstract discloses the treatment of a patient with sphincter of Oddi dysfunction (SO) with botulinum toxin.

17. The sphincter of Oddi is a ring of smooth muscle fibres located at the end of the bile duct. Its role is to close the bile duct by a tonic contraction in order to avoid reflux of the duodenal contents into the pancreatic and into the bile duct.

18. The following is inter alia stated in the abstract:

"Case report: "A 43 year old woman who had a cholecystectomy 8 years previously presented with biliary type pain. Her past history was significant for cirrhosis of the liver with associated portal hypertension and coagulopathy. ERCP [note by the board: "Endoscopic Retrograde Cholangiopancreatography"] with SO manometry [note by the board: determination of the sphincter of Oddi pressure] (performed using standard station pull-through technique) revealed a dilated biliary tree without other abnormalities and elevated SO pressures to 57mm/Hg. In view of her coagulopathy the patient was felt to be at an increased risk of complications from ES [note by the board: endoscopic sphincterotomy - endoscopic cutting of the sphincter muscle] and was treated using local injection of BoTx into the SO. 20 units (2cc) of BoTx was injected with a 5mm sclerotherapy needle in 0.5cc increments in a longitudinal axis from the superior border of the bile duct orifice to the horizontal fold of the papilla. Within 24 hours the patient's biliary type pain had resolved completely. Follow-up ERCP with SO manometry was performed 1 week later. The manometric results were read by an interpreter blinded to the intervention and the baseline pressure measured to be 26mm/Hg, a reduction of 50% of pretreatment levels. The patient

has remained asymptomatic to present with a follow-up of 4 weeks."

19. The board considers that the skilled person would derive all features of claim 1 from the above passage in document R21, either explicitly or implicitly.

20. It is disclosed that botulinumn toxin is used - it is locally injected. It is used for the manufacture of a medicament - the patient is treated. Moreover, the pain was relieved - the 43 year old woman had biliary type pain which after injection had resolved completely. Since the sphincter of Oddi is a ring of smooth muscle fibres, the relief of pain occurs in connection with a smooth muscle disorder.

21. The term "spasm" is not used in document R21. Instead the abnormal tonus of the sphincter of Oddi is denoted as a "dysfunction". With reference to documents R19 and R23, both excerpts from medical dictionaries, the appellant argues that the skilled person would not consider the abnormally high tonus of the sphincter of Oddi disclosed in document R21 as a "spasm". In this respect document R23 discloses that "in clinical terminology, spasm refers to a brief unsustained contraction of a single or multiple muscles. Cramp is a paroxysmal, spontaneous, prolonged, and painful contraction of one or more muscles." Document D19 defines a spasm as a "sudden, violent, involuntary contraction of a muscle or a group of muscles" or a "sudden but transitory constriction of a passage or canal or orifice".

21.1 However, the board draws attention to the two sentences before the sentence cited from document D23 above, where it is stated that "the terms pain, spasm, and cramp are often used interchangeably by patients to describe symptoms referable to muscles". Moreover, with regard to the sphincter of Oddi it is stated on page 1367, second column, third full paragraph of document R23: "Criteria for diagnosing dyskinesia of the sphincter of Oddi are even more controversial than those of papillary stenosis. Proposed mechanisms include **spasm** of the sphincter, ..." (emphasis added).

21.2 Thus, the board comes to the conclusion that the skilled person would consider the increased tone of the sphincter of Oddi disclosed in document D21 as a "spasm" within the meaning of claim 1 of the main request.

22. Moreover, the skilled person would have derived from document R21 that pain and spasm are associated given the close connection in the document of the disclosures of the injection of botulinum toxin, the relief of pain, the lowered sphincter pressure and the lack of symptoms.

22.1 The appellant referred to document R27 to support his argument that the spasm of the sphincter of Oddi was not the cause for the pain in the patient disclosed in document R21. Document R27 is a scientific publication of the authors of document R21 and is published after the priority date of the patent. Thus, the document cannot be used for the interpretation of what the skilled person would have understood from the disclosure content of document R21 at the priority date of the patent.

23. Finally, it is argued that document R21 refers to "Botulinum toxin" or "BoTx", but not to "Botulinum toxin type A" as claimed.

23.1 However, at the priority date of the patent in December 1993, the use of botulinum toxin type A was predominant, in particular in a clinical context. See, for example, document R13 disclosing a clinical study of botulinum toxin treatment of spasmodic torticollis (page 525, "Injection") or document R14 reviewing the therapeutic uses of botulinum toxin (first paragraph). This may be so because at that time only botulinum toxin type A was commercially available (see document R36). Before the publication of document R21, Pasricha et al. had already utilised botulinum toxin type A for their studies (see document R6, page 1046, first column). It is also noted that Pasricha et al. never indicate the type of botulinum toxin utilized when information is presented in the form of an abstract (R1, R5, R11).

23.2 Thus, in the boards view, the skilled person would infer therefore that the term "Botulinum toxin" or "BoTx" used in document R21 refers to botulinum toxin type A. In fact, since the use of other types of botulinum toxin was rare, the skilled person would have expected that it would have been expressly stated in the abstract, if anything other than type A had been used. Thus, the board concludes that document R21 implicitly discloses the use of botulinum toxin type A.

23.3 The view that botulinum toxin type A was the type most frequently used at the priority date is confirmed in

the patent in paragraph [0012]: "Botulinum toxin type A, the toxin generally utilized in treating neuromuscular conditions, is currently available (...)".

24. Hence, document R21 discloses subject-matter which has all the features of claim 1.

Enabling disclosure in document R21

25. A disclosure in a prior art document is novelty-destroying only if the teaching it contains is reproducible. This need for an enabling disclosure is in conformity with the principle expressed in Article 83 EPC. Thus, the requirements of sufficiency of disclosure are identical for a prior art document and a patent.

26. In accordance with the principles developed by the case law in the framework of the evaluation of the requirements of Article 83 EPC in the case of a medical use, the skilled person should not only be able to carry out the teaching of document R21, but it should also be credible that the effect at issue - here relief of pain - has been achieved. It is stated, for example, in decision T 609/02 of 27 October 2004, point 9 of the Reasons: "Where a therapeutic application is claimed in the form allowed by the Enlarged Board of Appeal in its decision G 5/83 (OJ EPO 1985, 64), ie in the form of the use of a substance or composition for the manufacture of a medicament for a defined therapeutic application, attaining the claimed therapeutic effect is a functional technical feature of the claim (see G 2/88 and G 6/88, OJ EPO 1993, 93 and 114, Headnote III. and point 9 of the reasons; for non-

medical applications, see also T 158/96 of 28 October 1998, point 3.1 of the reasons). **As a consequence, under Article 83 EPC, unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application.**" (emphasis added).

26.1 Evidence that the requirements are indeed fulfilled may come in different forms. If, as in document R21, data from a particular patient are reported, the later identical repetition of the teaching is of course not an option.

26.2 In the present case it is argued neither that the skilled person did not have botulinum toxin type A at its disposal, nor that he/she did not know how to apply it. In fact, the instructions in document R21 are detailed: "20 units (2cc) of BoTx was injected with a 5mm sclerotherapy needle in 0.5cc increments in a longitudinal axis from the superior border of the bile duct orifice to the horizontal fold of the papilla."

As to the therapeutic effect, the board has prima facie no reason to doubt in view of the disclosure in document R21 that the treatment results in a relief of pain in response to a lowering of the sphincter pressure.

26.3 Document D27 reports on the same patient as document R21, followed up for a longer period. It is disclosed that after four weeks with no pain (four weeks is the follow-up period disclosed in document R21), pain restarted and returned to baseline level, although the

sphincter of Oddi pressure had remained at a low level, i.e. at 27mm/Hg (Figure 1). It is further reported that a second botulinum toxin injection resulted in a further decrease of the sphincter pressure, yet with no pain relief at all. The respondents argue that these data were evidence that the pain relief disclosed in document R21 was not reproducible.

26.4 However, these further pain-related data reported in document R27 with regard to the patient also disclosed in document R21, namely that pain re-occurred and could not be removed by further botulinum toxin injections are not relevant for the question of whether the teaching in document R21 is reproducible because document R21 only discloses a period of four weeks after injection. In fact, the positive results within the first four weeks after botulinum toxin injection are confirmed by Figure 1 of document R27.

26.5 Document R27 discloses a second case report with a different patient. The patient is a 45-year-old woman with sphincter Oddi dysfunction and an 18-month history of right upper quadrant pain. While injection into the sphincter of Oddi improved bile duct emptying, there was no clinical improvement, i.e. the pain did not disappear.

26.6 However, a sphincter of Oddi-dysfunction is not the only reason for chest pain (see for example document R30, first sentence disclosing chest pain as a symptom of achalasia). Moreover, different human beings may respond differently to the same treatment. Therefore, the data obtained from the second patient are not

appropriate to demonstrate lack of reproducibility of the teaching of document R21 either.

27. Thus, the board concludes that no case of lack of enabling disclosure in document R21 has been made out.

28. The subject-matter of claim 1 is thus not novel in view of document R21. The requirements of Article 54 EPC are not fulfilled.

29. In view of this finding the question of whether or not the subject-matter of the claims of this request is novel over the disclosure in either of documents R1 and R10 is not dealt with.

Auxiliary request

Admission

30. The appellant submitted the auxiliary request at the oral proceedings before the board. Claim 1 of the request corresponds to a combination of claims 1 and 5 and claims 2 to 4 correspond to a combination of claim 1 and claims 6 to 8 of the main request. Moreover, the auxiliary request is identical to the third auxiliary request before the opposition division. None of the parties objected to the admission of this request. Hence the auxiliary request was admitted into the proceedings.

Rule 80 EPC

31. The request was filed in response to the board's finding that the main request lacked novelty over document D21. The parties did not raise an objection. The requirements of Rule 80 are fulfilled.

Articles 76(1), 84, 123(2)(3) EPC

32. The basis for claim 1 in the parent application and in the application as filed is the complete Example 9 (recited in point 2 above). Additionally, claims 1 and 8 support amended claim 1 in the application as filed.

Claims 2 to 4 rely on page 7, first full paragraph of the parent application.

The wording of claims 2 to 4 of the auxiliary request is identical to that of claims 9 to 11 as filed.

33. Since the only independent claim among the claims as granted related to "The use of a Botulinum toxin type A or type B for the manufacture of a medicament for relieving pain associated with muscle spasms in smooth muscle disorders", the amendment does not extend the scope of the present claims over that of the claims as granted.

The respondents did not raise any objections.

34. The respondents did not raise any objections pursuant to Article 84 EPC either, and nor did the board.

35. The requirements of Articles 76(1), 84, 123(2)(3) EPC are fulfilled.

Article 83 EPC

36. The parties did not make any submissions at the oral proceedings with respect to Article 83 EPC, but referred to their written submissions, all made in opposition proceedings.

37. As has already been noted in points 25 and 26 above in the context of the evaluation of the enabling character of the disclosure in the prior art document R21, the requirement of sufficiency of disclosure is considered as fulfilled with respect to a claim to a second medical use if the disclosure in the patent or the common general knowledge enables the skilled person to obtain the compound to be applied and to apply it, and if there is evidence that the intended therapeutic effect can be achieved.

37.1 Botulinum toxin type A is a known compound. Paragraph [0012] of the patent discloses the commercial availability of botulinum A from different sources. Paragraphs [0024] to [0029] give general instructions as to its application, such as dosage, the method of application or that anaesthesia may be necessary. Spastic colon is a known disease (see below).

Example 9 discloses which patients may for example be treated ("A female, age 35"). Possible ways of application and dosage of botulinum toxin are stated, i.e. (a) injection into several areas of the colon, in particular rectum or lower colon, of between 1 and 100

units or (b) by way of enema with 1 to 5 units, whereby the dose has to be titrated, starting with the lowest dose. The therapeutic effect is indicated and when it is expected to occur, i.e. cramps and pain will disappear within a period of 1-10 days.

37.2 The board considers that the instructions in the patent are sufficient to enable the skilled person to carry out the claimed use.

38. The respondents argue that it was not credible that the therapeutic effect could be achieved because the treatment disclosed in Example 9 had not actually been carried out.

38.1 However, Article 83 EPC stipulates that an invention must be disclosed "in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art" (emphasis added by the board). Thus, Article 83 EPC does not stipulate that a claimed invention must have actually been carried out by the applicant or the inventor. Moreover, according to Rule 42(1)(e) EPC, even the presence of an example is not mandatory. Therefore, just because a patent discloses an effect which has not in reality been achieved, there is no reason - in the absence of convincing evidence that the effect cannot be achieved - for the board to doubt that the effect can be achieved. Thus, the respondents' argument does not convince the board.

39. It is further argued that the patent does not disclose precisely what was meant by particular terms in the claim, i.e. "smooth muscle disorder", "muscle spasm"

and "pain", leading to a lack of sufficiency of disclosure.

There may be situations where claimed subject-matter is unclear due to lack of proper information in the patent or from the common general knowledge and that for these same reasons the invention defined in the claims cannot be carried out. However, this is not the situation here (see above). Therefore, the argument rather gives rise to an objection under Article 84 EPC, which may not be raised with regard to the terms above, since they were already contained in the claims as granted.

40. The requirements of Article 83 EPC are fulfilled.

Novelty

41. The respondents did not object to the claims for lack of novelty. It is also the position of the board that none of the documents on file anticipates the claimed subject-matter.

Inventive step

42. Claim 1 relates to the use of botulinum toxin type A for "relieving pain", wherein "the medicament is for relieving cramps and pain". Thus, the medicament which is used removes both pain and cramps. Hence, the board interprets claim 1 such as to relate to the use of botulinum toxin type A for the manufacture of a medicament for relieving cramps and pain.

43. Documents R2 and R14 were considered as the closest prior art documents by the respondents. However,

neither of them deals with the relief of cramps and pain associated with a spastic colon. Yet, according to established case law the primary criterion for determining the closest prior art document for assessing inventive step is that it discloses subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention. The commonality of structural features is a secondary consideration. Thus, a known treatment for the relief of cramps and pain associated with spastic colon would be the appropriate closest prior art.

44. It was not disputed at the priority date that spastic colon was a known disease and that treatments existed. Spastic colon is also called "irritable bowel syndrome" (see document R19, page 287, keyword "colitis", under "mucous c." or document R23, page 179, second column under "Irritable bowel").

45. Document R23 discloses on page 1294, second column that irritable bowel syndrome is "the most common gastrointestinal disease in clinical practice, and although not a life-threatening illness, it causes great distress to those afflicted and a feeling of helplessness and frustration for the physician attempting to treat it". The document also discloses on page 179, second column, last paragraph that "[a] variety of therapeutic approaches, including the avoidance of foods which tend to upset the patient, addition of bulk-forming agents, judicious use of antispasmodics and tranquilizers, and psychotherapy may provide some degree of relief. If the patient's life goals can be shifted away from the quixotic search for the perfect stool, much can be accomplished." It

transpires also from page 1295, second column, second paragraph that no satisfactory treatment for irritable bowel syndrome existed.

46. Thus, the problem to be solved by the patent vis-à-vis any of the known treatments of spastic colon is the provision of an alternative treatment for relieving cramps and pain in patients with spastic colon.

The solution provided by the patent is the use of botulinum toxin A.

47. The respondents submit that this solution is obvious in view of any of documents R2, R13 and R14.

Document R2

48. Document R2 reviews the swallowing disorder achalasia. The two main abnormalities in achalasia are, on the one hand, a raised lower oesophagal sphincter tone and the failure to relax with swallowing and, on the other hand, the lack of peristaltic motility in the lower half of the oesophagus. Therapy relies mainly on reducing the pressure of sphincter (page 1125, second column), but also on restoring the motility of the oesophagus.

49. The respondents argue that the oesophagus and colon are similar in that they are tubular organs. Moreover, their dysfunction is the same in achalasia and spastic colon, namely lack of peristalsis. Thus it would be obvious to apply a treatment suggested for restoring peristalsis in achalasia to patients suffering from spastic colon.

In the respondents' view, the following sentence (bold below, emphasis added by the board) in a passage on page 1129 of document R2 suggests the use of botulinum toxin A for restoring peristalsis of the oesophagus:

"Mögliche neue Therapieverfahren

Lokale Injektionen mit
Botulinustoxin

Botulinustoxin A stellt ein hochselektives Neurotoxin dar, das die Azetylcholinfreisetzung aus den präsynaptischen Nervenendigungen blockiert. **Dieser therapeutische Effekt wird unter anderem bei der Therapie von spastischen neurologischen Störungen eingesetzt.** Da die Achalasie theoretisch ebenfalls durch ein Ungleichgewicht zwischen reduzierter inhibitorischer (NO, VIP) und exzitatorischer Innervation erklärt wird, wurde die lokale Injektion von Botulinustoxin in den unteren ösophagealen Sphinkter als mögliche Therapieform vorgestellt [37]."

49.1 However, in the board's view, when read in context and given the use of the present tense ("wird"), the skilled person would have understood the phrase as referring to the already known uses of botulinum toxin for alleviating spastic disorders of striated muscles, such as disclosed in document R14. This view is supported by the fact that when document R2 specifically refers to the treatment of achalasia, only the injection of Botulinum toxin into the sphincter is mentioned (see last sentence of citation above). A similar distinction is also derivable from document R4, where botulinum toxin treatment is reported to relax

the contracted oesophageal sphincter, while nifedipine is mentioned in the context of the relief of the oesophageal spasm (page 230, first column, first paragraph).

49.2 Hence, the board concludes that the skilled person would not derive from document R2 the suggestion to treat the aperistalsis of the lower oesophagus with botulinum toxin A and would for that reason also not be motivated by the disclosure in document R2 to treat spastic colon with botulinum toxin A.

Document R14

50. Document R14 reviews, on the one hand, the clinical applications of botulinum toxin known in 1991, such as disorders of ocular motility, dystonias such as blepharospasm, spasmodic torticollis or hemifacial spasm. On the other hand, under the heading "Other Potential Indications" on page 1191, future applications for botulinum toxin are suggested (emphasis added):

"The therapy may also be useful in patients with other forms of dystonia and in those with certain focal repetitive involuntary movements such as tremor [...]. Motor dysfunction due to abnormally increased muscle tone, such as spasticity, may also be ameliorated [...]. The effects of botulinum toxin on spasticity in children with cerebral palsy are also being studied. **Injections of botulinum toxin into the detrusor and sphincter muscles have been found to improve bladder function in patients with spinal cord injury.**[113,114]

Anismus [...] has been reported to respond favourably to local injections of botulinum toxin."

In the following paragraph it is stated that "[f]urther studies are needed to establish the efficacy and safety", that "[t]here are no absolute contraindications to injections of botulinum toxin except a history of hypersensitivity" and that "no teratogenicity has been attributed to botulinum toxin". It is then said that "[b]ecause botulinum toxin acts on the final common pathway, **spasms of any cause could be temporarily relieved by this treatment.**"

51. The respondents argue that the disclosure of injection of botulinum toxin into the detrusor muscle and the statement that spasms of "any cause" could be relieved would motivate the skilled person to treat cramps and pain due to spastic colon with botulinum toxin.

"any cause"

52. On page 1187 of document R14 under the heading "Dystonias" - dystonias are involuntary muscle contractions frequently causing twisting, flexing or extending and squeezing movements or abnormal postures - the causes for dystonias are enumerated. They may be caused by a damage to the brain or they may be genetically determined. Moreover, there are "many secondary dystonias due to specific causes such as Wilson's disease, metabolic and neurodegenerative disorders...". Finally it is said that "[b]esides primarily central causes, which presumably account for the vast majority of dystonias, there is convincing evidence that they can be caused or triggered by injury

to a peripheral nerve or root" and that "[i]f no specifically treatable causes of dystonia can be identified, then patients can be offered only symptomatic relief."

Thus, in this passage the term "cause" is used to describe the reason for the occurrence of the spasm, i.e. genetic, damage of the brain, ganglia or peripheral nerves.

53. In the board's view, the skilled person would infer that the term "cause" has the same meaning in the context of the passage relied on by the respondents cited above in point 50. This is so, firstly, due to the use of the identical word and secondly, due to the fact that it is emphasised that botulinum toxin acts at the nerve ending. In the context, the skilled person would understand this to mean that, whatever failure may have caused the spasm - damage to the brain or the nerve somewhere on its way to the muscle, or even genetic reasons - spasms occurring due to all of these causes could be treated with botulinum toxin because it interferes at the very end of the pathway. Thus, the passage puts emphasis on the **reason** for the spasm and not on the muscle type or organ concerned.

54. Thus, the skilled person would not derive from the statement that spasms of any cause could be temporarily relieved by treatment with botulinum toxin a suggestion to treat any other type of spasm, and in particular spastic colon, with botulinum toxin.

"detrusor"

55. At the oral proceedings the question of whether or not the detrusor muscle is truly a smooth muscle could not be answered by the parties to the board's satisfaction. For the sake of the argument the board will assume that the detrusor is composed of smooth muscle fibres.

56. The detrusor muscle of the urinary bladder contracts when urinating to squeeze out urine. Otherwise, it remains relaxed to allow the bladder to fill. The patients referred to in the cited passage in document R14 had - as can be seen from the titles of references 113 and 114, i.e. "Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients" and "Treatment of detrusor-sphincter dyssynergia with botulinum A toxin: a double-blind study" - suffered from a detrusor-sphincter dyssynergia, i.e. both the detrusor muscle and sphincter are abnormally contracted resulting in obstruction of normal urinary outflow and in a rise in bladder pressure.

57. However, even if both detrusor and colon were smooth muscles their shapes are completely different. Compared with the long tubular structure of the colon, the detrusor is a compact muscle. Therefore, the skilled person seeking a treatment for spastic colon and seeing the disclosure in document R14 would firstly wonder how, in practice, botulinum toxin should be applied in order to lower tension in such a big area. Secondly, the skilled person would understand that injection of botulinum toxin into the detrusor results in a "simple" relaxation of that muscle. This would not however

suffice for the treatment of a spastic colon; rather, in this case the relaxation must be such that the peristaltic contractions of the colon are restored so that defecation can occur. Thus, the skilled person would also have doubts whether peristalsis could be restored by botulinum toxin injection. The board considers that, due to these uncertainties, the skilled person would not be motivated to treat cramps and pain due to spastic colon with botulinum toxin by the disclosure of the use of botulinum toxin for relaxation of the urinary bladder detrusor muscle.

58. Thus, in summary, the subject-matter of claim 1 is not obvious in view of the disclosure in document R14.

59. In addition, the board considers it remarkable in view of the known need for satisfactory treatment of the widespread problem of spastic colon (see above point 45) that the first disclosures of the relaxation of a smooth muscle with botulinum toxin after the disclosure of detrusor relaxation in document R14 concern sphincter muscles (R1, R21), i.e. small muscle groups where local injection can relatively easily be achieved, and relate to - compared with spastic colon - the rather rare disorders achalasia and sphincter of Oddi dysfunction.

Document R13

60. The respondents maintain that the claimed method for relieving pain and cramps due to spastic colon is obvious in view of document R13. The document reviews the efficacy and adverse effects of repeated botulinum toxin injections into the hyperactive neck muscles of

patients with spasmodic torticollis. In the discussion section it is stated that, where pain was present, there was a considerable improvement after botulinum toxin injection. Pain even disappeared permanently after the first treatment. Therefore it is suggested that "this prominent relief of pain, common to all studies, raises the possibility of a direct or indirect analgesic property of botulinum toxin even though sensory changes are not a feature of systemic botulism" (page 528, first paragraph under "Discussion").

61. Spasmodic torticollis affects the neck muscles, causing spasmodic head movements or abnormal postures of the head as a result of twisting, tilting toward one shoulder, flexing or extending the neck. The board considers that for the same reasons given in point 57 above in relation to the relaxation of the urinary bladder detrusor muscle - the colon is a long tubular organ and there is a need for restoring peristalsis - the disclosure in document R13 would not have motivated the skilled person to treat spastic colon with botulinum toxin A. Thus, the subject-matter of claim 1 is not obvious in view of document R13.

62. The board notes that it is even questionable whether or not the disclosure of the treatment of cramps and pain for a striated muscles disorder would have suggested to the skilled person to treat the same symptoms in the context of a smooth muscle disorder such as spastic colon. The first clinical trials with botulinum toxin for the treatment of muscle spasms were published in 1980 (strabismus) and 1982 (nystagmus, hemifacial spams, lid retraction, torticollis and spacicity; see document R36), whereas the first documentations of the

clinical use of botulinum toxin for relaxation of a smooth muscle date from 1988 (or 1990 1991 - detrusor; see above points 50 and 56) and 1993 (achalasia, sphincter of Oddi; see above points 16 and 48).

63. Thus, the board concludes that the subject-matter of claim 1 and of dependent claims 2 to 4 involves an inventive step.

The requirements of Article 56 EPC are fulfilled.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of the auxiliary request as filed during the oral proceedings before the board (claims 1-4 and pages 2-4 of a description adapted thereto).

The Registrar: The Chair:

P. Cremona U. Kinkeldey