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# Datasheet for the decision of 18 September 2012

**Case Number:** T 0109/09 - 3.3.02

**Application Number:** 00964006.1

**Publication Number:** 1210090

**IPC:** A61K 31/724, A61K 31/194, A61P 39/04

**Language of the proceedings:** EN

**Title of invention:**
Use of chemical chelators as reversal agents for drug-induced neuromuscular block

**Applicant:**
MSD Oss B.V.

**Headword:**
Use of chemical chelators as reversal agents for NMBAs/MSD OSS B.V.

**Relevant legal provisions:**
EPC Art. 83, 84, 123(2), 56

**Keyword:**
"New main request filed in appeal proceedings: allowable (yes)"

**Decisions cited:**
-

**Catchword:**
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0109/09 - 3.3.02

# D E C I S I O N
**of the Technical Board of Appeal 3.3.02**
**of 18 September 2012**

**Appellant**: (Applicant)
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**Representative**:
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**Decision under appeal:**
**Decision of the Examining Division of the European Patent Office posted 21 July 2008 refusing European patent application No. 00964006.1 pursuant to Article 97(2) EPC.**

**Composition of the Board:**

**Chairman:** U. Oswald
**Members:** M. C. Ortega Plaza
R. Cramer

## Summary of Facts and Submissions

I. European patent application No. 00964006.1, based on international application PCT/EP00/07694, published as WO 01/12202, was filed with 11 claims.

II. The present appeal lies from a decision of the examining division refusing the application (Article 97(2) EPC).

III. The following documents were cited in the examination and appeal proceedings:

D1 B. Désiré, Experentia, vol. 43(4), 395-397, 1987

D2 B. Désiré, Fundamental and Applied Toxicology, vol. 7(4), 647-657, 1986

D3 C. May, Australian Veterinary Journal, vol. 76(11), 752-756, 1998

D4 AU 36626 95 A

D5 G. M. Escandar, Analyst, vol. 124(4), 587-591, 1999

D6 P. K. Zarzycki, Journal of Pharmaceutical and Biomedical Analysis, vol. 18(1-2), 165-170, 1998

D7 J. M. Adam, J. Med. Chem., vol. 45(9), 1806-1816, 2002

D8 R. D. Miller, Anesthesia and Analgesia, vol. 104(3), 477-478, 2007

D9 L. Fielding, Tetrahedron, 56, 6151-6170, 2000.

IV. The examining division's decision was based on the main request filed with the letter of 7 November 2007.

Claim 1 of the main request filed with the letter of 7 November 2007 read as follows:

1. Use of a water-soluble chemical chelator which can engage in host-guest complex formation in aqueous solution with a clinically used neuromuscular blocking agent for the manufacture of a medicament for the reversal of neuromuscular block induced by the clinically used neuromuscular blocking agent.

The examining division considered that the main request did not meet the requirements of Articles 84 and 83 EPC.

The examining division considered that the expression "which can engage in host-guest complex formation" did not meet the requirements of Article 84 EPC. It stressed *inter alia* that the formation of a complex depends on the conditions to which the two compounds are subjected and cited documents D5 and D6. Moreover, the examining division considered that there was insufficiency of disclosure (Article 83 EPC) in relation to the formation of the complexes and the testing conditions and that in order to reproduce the claimed "invention" a full research programme was required. It further considered that claim 1 did not contain any structural limitation in relation to the compounds intended to form a complex, and thus the application put an undue burden on the skilled person when trying to reproduce the claimed invention. The examining division pointed *inter alia* to the fact that the tested compound 21 showed no "reversal effect".

As regards the post-published document D7, which had been filed by the applicant during the examination proceedings, the examining division considered that it did not show that the methods described in examples 5 and 6 of the application as filed could be used as a

standard method for identifying which chemical chelators should be used according to the claims.

The examining division's decision also contained as *obiter dictum* some comments in relation to Article 56 EPC.

V. The applicant (appellant) filed an appeal and filed grounds thereto. With the grounds of appeal the appellant filed two sets of claims: "Claims for the main request" (Annex 1) and "Auxiliary request 1" (Annex 2). It also filed a further document, namely D9.

VI. The board sent a communication under Rule 100(2) EPC and Article 12(1)(c) RPBA on 22 December 2011. With said communication the board sent a copy of the documents D5 and D6 in their entirety since the file contained only their abstracts.

In said communication the board explained the reasons why the main request and auxiliary request 1, both filed with the grounds of appeal, were not admissible. Moreover, the board expressed its preliminary opinion in relation to Articles 84 and 83 EPC.

VII. The appellant filed a letter dated 24 April 2012 as a reply to the board's communication. With said letter it filed a new main request.

Claim 1 of the main request filed with the letter of 24 April 2012 read as follows:

1. Use of a water-soluble chemical chelator, selected from the group consisting of cyclic oligosaccharides, cyclophanes and calixarenes, for the manufacture of a medicament for the reversal of neuromuscular block induced by a clinically used neuromuscular blocking agent which is selected from rocuronium, vecuronium, pancuronium, rapacuronium, mivacurium, (cis)atracurium, tubocurarine and suxamethonium.

VIII. The board sent a communication pursuant to Article 15(1) RPBA as an annex to the summons to oral proceedings.

The board informed the appellant that the new main request filed with the letter of 24 April 2012 was admitted into the proceedings.

In said communication, the board expressed a preliminary opinion in relation to the new main request.

IX. With a letter dated 24 August 2012, the appellant filed a reply to the communication sent as an annex to the summons to oral proceedings. The appellant filed with said letter a new main request containing three claims and requested the board to admit it into the proceedings.

Claim 1 of the main request filed with the letter of 24 August 2012 read as follows:

1. Use of a water-soluble chemical chelator, selected from the group consisting of: γ-cyclodextrin, γ-cyclodextrin-phosphate sodium salt (DS=3), carboxymethyl-γ-cyclodextrin (DS=3.2), carboxyethyl-γ-cyclodextrin (DS=3.8) and 2-hydroxypropyl-γ-cyclodextrin (DS=4),
for the manufacture of a medicament for the reversal of neuromuscular block induced by a clinically used neuromuscular blocking agent which is selected from rocuronium, vecuronium, pancuronium, rapacuronium, mivacurium, (cis)atracurium, tubocurarine and suxamethonium.

Claim 3 of the main request filed with the letter of 24 August 2012 read as follows:

3. Use of a water-soluble chemical chelator, selected from the group consisting of:

γ-cyclodextrin, γ-cyclodextrin-phosphate sodium salt (DS=3), γ-cyclodextrin-phosphate sodium salt (DS=7), carboxymethyl-γ-cyclodextrin (DS=3.2), carboxyethyl-γ-cyclodextrin (DS=3.8), 2-hydroxypropyl- γ-cyclodextrin (DS=4),

β-cyclodextrin, carboxymethyl-β-cyclodextrin (DS=3 – 3.5), per 2,6-dimethyl-β-cyclodextrin (DS=12.6), β-cyclodextrin-phosphate sodium salt (DS=3), β-cyclodextrin-phospha sodium salt (DS=8), carboxyethyl-β-cyclodextrin (DS=3), 2-hydroxypropyl-β-cyclodextrin,

cyclo-[(1-4)-α-L-rhamnopyranosyl-(1-4)-α-D-mannopyranosyl]tetraose,

N,N',N'',N'''-tetrakis(3-carboxypropionyl)-3,4,5,6,7,8,26,27,28,29,30,31-dodecahydro-1,10,24,33-tetraaza[2.2.1.2.2.1]paracyclophane,

4-sulfonic calix[6]arene and 4-sulfonic calix[8]arene,

for the manufacture of a medicament for the reversal of neuromuscular block induced by rocuronium.

X. Oral proceedings took place on 18 September 2012. During the oral proceedings the appellant confirmed that it was withdrawing the auxiliary request filed with the grounds of appeal.

XI. The appellant's arguments can be summarised as follows:

The set of claims filed with the letter of 24 August 2012 represented a direct reply to the board's communication sent as an annex to the summons to oral proceedings. It had been drafted with two independent second medical use claims directed to the use of particular chemical chelators in relation to specific neuromuscular blocking agents (NMBAs) in order to comply with the requirements of Article 123(2) EPC. The claims' wording remained as close as possible to the disclosure in the application as filed. It could be true that there was a certain overlap between the

subject-matter of the independent claims 1 and 3, but their subject-matter was different. Thinking of possible litigation proceedings after grant, neither the deletion nor the modification of any of the claims in the main request was justified at this stage of the proceedings.

The amended claims overcome all the objections raised by the board in relation to Articles 84 and 83 EPC to the sets of claims previously on file.

As regards the inventive step issue, the definition of the problem given in the description had to be followed and the test results disclosed in the application (*in vitro* and *in vivo* models) showed that the subject-matter now claimed solves the technical problem beyond doubt. The solution proposed in the amended claims for the reversal of neuromuscular block, induced by the particular NMBAs mentioned, concerned the specific chemical chelators and thus was completely different from the clinically used reversal agents at the filing date, which were acetylcholinesterase (AChE) inhibitors. None of the prior art documents pointed in the direction proposed by the claims. In some prior art documents such as D1 and D2 cyclodextrins were used for quite different purposes with very different chemical products, namely neurotoxic gases from the type of phosphonic acid derivatives such as sarin and soman. Moreover, the mechanism involved was different, since the cyclodextrins catalysed the deactivation of these toxic agents, instead of forming host-guest complexes for their elimination. The other prior art documents (D3 and D4) related to the use of cyclodextrins as protectors from dietary poisoning in animals. Thus,

these documents belonged to a different field of application and were not relevant for the skilled person when looking for reversal of neuromuscular block induced by NMBAs.

XII. The following requests are on file:

The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed with the letter of 24 August 2012.

## Reasons for the Decision

1. The appeal is admissible.

1.1 The main request filed with the letter of 24 August 2012 is admitted into the proceedings since it represents a clear and direct response to the board's communication sent as an annex to the summons to oral proceedings.

2. *Main (sole) request*

2.1 The set of claims of the main request contains two independent second medical use claims in the Swiss-type form (claims 1 and 3) and a dependent claim (claim 2).

In both independent claims the chemical chelators and the NMBAs have been specified. Each and every combination encompassed and singled out in the amended claims has been specifically exemplified in the application as filed for the use claimed. Thus, the

present claims' wording finds its basis *inter alia* in examples 3, 4, 5, 6 and 7. Therefore, the requirements of Article 123(2) EPC are met.

Moreover, the amended claims are clear and supported by the description (Article 84 EPC). The broad functional definitions which were objected to under Article 84 EPC have been now replaced by specific chemical identities using standard nomenclature. There is a certain overlap between the two independent claims which address specific combinations. The application as filed does not disclose an allowable basis for an intermediate generalisation in one independent claim which could have been followed by dependent claims for preferred embodiments. However, this overlap does not cause any problem to the skilled person when reading and understanding which the subject-matter actually claimed.

2.2 As regards the requirements of sufficiency of disclosure (Article 83 EPC) the amended claims now encompass the use of specific chelators (compounds known *per se*), which has been specifically disclosed in the description (formation of the complexes and valid models *in vitro* and *in vivo* for the reversal of neuromuscular block induced by the specific NMBAs now defined in the claims). The reasoning in the examining division's decision no longer applies since the contested functional definitions have been replaced in the claims by the standard names of the specific chemical chelators and NMBAs. The chemical chelator compound 21, which according to the result in table II did not show reversal of neuromuscular block induced by rocuronium, is not encompassed by the claims of the main request. The claims are in fact directed to those

chelators for which a credible reversal has been shown in the application as filed.

Therefore, the requirements of Article 83 EPC are met.

2.3 None of the documents on file discloses the uses of the specific chelators claimed in claims 1 and 3. In fact, the examining division did not question the novelty of a much broader claim.

Therefore, the subject-matter claimed in the main request meets the requirements of novelty (Article 54 EPC).

2.4 It appertains to the general knowledge of the skilled person that neuromuscular blocking agents (NMBAs) are commonly used in modern clinical anesthesia to attain skeletal muscle relaxation. Moreover, at the time of the effective filing date of the application underlying the present appeal, it was also generally known to the skilled person that acetylcholinesterase (AChE) inhibitors were administered to the patient at the end of surgery or a period of intensive care in order to achieve reversal of neuromuscular block induced by NMBAs.

This general knowledge is acknowledged in the description of the application as filed.

Additionally, none of the prior art documents within the meaning of Article 54(2) EPC on file relates to reversal of neuromuscular block induced by NMBAs.

Thus, the objective starting point is the generally known use of AChE inhibitors (such as neostigmine, edrophonium and pyridostigmine) as reversal drugs of neuromuscular block induced by NMBAs.

The problem to be solved lies in the provision of an alternative for the reversal of neuromuscular block induced by specific NMBAs.

The solution lies in the uses of the specific chemical chelators named in claims 1 and 3.

The description discloses positive test results for the reversal of neuromuscular block *in vivo* and/or *in vitro* (examples 5 and 6) induced by the specific NMBAs mentioned in the claims for all the chemical chelators specified in the claims. Thus, the problem has been credibly solved.

None of the cited prior art documents within the meaning of Article 54(2) EPC gives any indication as to how to attain a reversal of neuromuscular block induced by NMBAs. The fact that some cyclodextrins are known as antidotes to some toxical chemicals (documents D1, D2) does not render the claimed subject-matter obvious, since in the case of the toxic gases sarin, soman and tabun (their chemical nature is quite different from the NMBAs specified in the claims) the cyclodextrins act as catalysts for their degradation, which is quite different to the mechanism behind the use claimed.

Additionally, the teaching that certain cyclodextrins are able to bind the sheep poison tunicamycin (document D3) or other toxins and contaminants known in animal

dietary intake (document D4) does not give any useful information to the skilled person when looking for a solution to the technical problem of reversing neuromuscular block induced by very specific chemical compounds of the class of NMBAs which are remote in their structure from the toxic compounds referred to in documents D3 and D4.

Therefore, the subject-matter claimed in the main request meets the requirements of Article 56 EPC.

## 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 grant a patent with claims 1-3 according to the main request filed with the letter of 24 August 2012, and a description to be adapted thereto.

The Registrar: The Chairman:

N. Maslin U. Oswald