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# Datasheet for the decision of 12 December 2017

**Case Number:** T 1089/11 - 3.3.08

**Application Number:** 03766057.8

**Publication Number:** 1434858

**IPC:** C12N5/0735

**Language of the proceedings:** EN

**Title of invention:**
METHOD FOR THE AMPLIFICATION OF A POXVIRUS UNDER SERUM FREE CONDITIONS

**Patent Proprietor:**
Bavarian Nordic A/S

**Opponents:**
Emergent Product Development UK Limited
Sanofi Pasteur
Transgene S.A.

**Headword:**
Serum-free medium/BAVARIAN NORDIC

**Relevant legal provisions:**
EPC 1973 Art. 54(3), 54(4)
EPC Art. 56, 83, 84, 87, 113(1), 123(2), 123(3)
RPBA Art. 12(4)

**Keyword:**

Admission of documents (68) and (69) - (no)
Added matter - (no)
Clarity - (yes)
Sufficiency of disclosure - (yes)
Priority - (yes)
Novelty - (yes)
Inventive step - (yes)

**Decisions cited:**

T 0023/86, T 0939/92, T 0006/01, T 0235/04, T 1599/06, T 0824/07

**Catchword:**

Europäisches Patentamt
European Patent Office
Office européen des brevets

**Beschwerdekammern**

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**Case Number: T 1089/11 - 3.3.08**

# D E C I S I O N
## of Technical Board of Appeal 3.3.08
## of 12 December 2017

| | |
|---|---|
| **Appellant I:** (Opponent 3) | Emergent Product Development UK Limited<br>540-545 Eskdale Road<br>Winnersh Triangle<br>Wokingham, Berkshire RG41 5TU (GB) |
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| **Respondent:** (Patent Proprietor) | Bavarian Nordic A/S<br>Boegeskovvej 9<br>3490 Kvistgaard (DK) |
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**Decision under appeal:** **Interlocutory decision of the Opposition Division of the European Patent Office posted on 18 April 2011 concerning maintenance of the European Patent No. 1434858 in amended form.**

**Composition of the Board:**

**Chairman** B. Stolz
**Members:** M. R. Vega Laso
D. Rogers

## Summary of Facts and Submissions

I. European patent No. 1 434 858 with the title "Method for the amplification of a poxvirus under serum free conditions" was granted on the European patent application No. 03766057.8 filed under the Patent Cooperation Treaty and published as WO 2004/022729 (in the following "the application as filed") claiming the priority of an earlier Danish application filed on 5 September 2002.

II. Five oppositions based on the grounds for opposition of Article 100(a) in conjunction with Articles 54 and 56, Article 100(b) and (c) EPC were filed. Opponent 01 withdrew its opposition during opposition proceedings.

III. In an interlocutory decision under Article 101(3)(a) and 106(2) EPC posted on 18 April 2011, an opposition division found that, account being taken of the amendments introduced into claims 1 to 17 according to the main request and the description adapted thereto, both filed during the oral proceedings, the patent and the invention to which it relates met the requirements of the EPC.

IV. Amended claims 1, 3 and 5 of the main request read as follows:

"1. Method for the amplification of a poxvirus comprising the following steps:

(a) cultivation of primary avian cells in a serum free medium;

(b) infection of the primary avian cells with the poxvirus; and

(c) cultivation of the infected cells in serum free medium until progeny poxvirus is produced,

wherein the primary avian cells are cells allowing the productive replication of the poxvirus, and wherein the serum free medium of steps (a) to (c) comprises epidermal growth factor (EGF).

3. Method according to anyone of claims 1 to 2, wherein the EGF is recombinant-human EGF.

5. Method according to anyone of claims 1 to 4, wherein said serum free medium of steps (a) to (c) further comprises an attachment factor, preferably fibronectin."

Dependent claims 2, 4 and 6 to 17 are identical to claims 2, 4, 6 to 16 and 18 of the patent as granted, except that claim 7 refers to claim 1 or 5 (instead of claim 1 or 2).

V. Opponents 03 and 05 (appellants I and II, respectively) lodged an appeal against the decision of the opposition division. Together with their respective statement of grounds of appeal, the appellants filed new evidence and requested oral proceedings if the board did not intend to set aside the decision under appeal and revoke the patent.

VI. The patent proprietor (respondent) replied to the statements of grounds of appeal. Together with its reply, the respondent re-filed the set of claims according to the main request underlying the decision under appeal, and submitted six sets of claims as auxiliary requests I to VI, as well as additional evidence. As a subsidiary request, the respondent requested oral proceedings.

VII. Appellant II submitted comments on the respondent's reply and the new auxiliary requests. Opponent 04 (party as of right) did not make any substantive submissions. Opponent 02 withdrew its opposition.

VIII. The board summoned the parties to oral proceedings. In a communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) attached to the summons, the board made observations on procedural and substantive issues, in particular on the admission of the new evidence into the proceedings and various issues under Articles 123(2), 84, 83, 87, 54 and 56 EPC.

IX. The oral proceedings were postponed twice, upon a reasoned request of the respondent and appellant II.

X. The respondent replied to the board's communication. The appellants and the other party informed the board that they would not be represented at the oral proceedings. Moreover, appellant I withdrew its request for oral proceedings. Neither appellant made any substantive submissions.

XI. At the oral proceedings held on 12 December 2017 only the respondent was represented.

XII. In the present decision the following documents are referred to:

(1): WO 03/008533 A2, published on 30 January 2003;

(4): US 4,072,565, published on 7 February 1978;

(5): WO 98/15614, published on 16 April 1998;

(7): Z. Pietrzkowski et al., 1988, Folia Histochemica et Cytobiologica, vol. 26, no. 3, pages 123 to 132;

(10): Product sheet for VP-SFM (Gibco), not dated;

(15): WO 95/22978, published on 31 August 1995;

(D21):K.D. Nakamura et al., March 1983, Molecular and Cellular Biology, Vol. 3, No. 3, pages 380 to 390;

(22): US 5,405,772, published on 11 April 1995;

(25): S.D. Balk et al., February 1982, Proc. Natl. Acad. Sci. USA, vol. 79, pages 1154 to 1157;

(28): Product sheet for VP-SFM (Gibco), May 1999;

(31): Product sheet for BMS Serum Alternative (Biochrom AG), not dated;

(36): "Serum-free media for cell culture", August 2006, ed. Focus on Alternatives;

(37): A. Lingnau et al., 1993, Parasitol. Res., vol. 79, pages 378 to 384;

(44): P.J. Price et al., 1997, Focus, vol. 19, no. 3, pages 67 and 68, and Figure 3;

(48): D. Gospodarowicz and J.S. Moran, 1976, Annu. Rev. Biochem., Vol. 45, pages 531 to 558;

(55): Bundesanzeiger, 28 July 1977, no. 138, pages 4 and 5;

(58): http://www.sigmaaldrich.com/life-science/cell-culture/cell-culture-products.htlm2Tabl, dated 13 December 2010;

(62): S.J. Froud, 1999, Dev. Biol. Stand, vol. 99, pages 157 to 166;

(63): S.E. Broedel et al., February 2003, BioProcess International, pages 56 to 58;

(64): The Biomedical Scientist, September 2003, pages 941 and 942;

(65): E. Mariani et al., 1991, Journal of Immunological Methods, vol. 145, pages 175 to 183;

(66): H. Graf et al., 1991, Journal of Immunological Methods, vol. 139, pages 135 to 144;

(67): K. Wunderlich et al., 1994, Graefe's Arch Clin Exp Ophthalmol, vol. 232, pages 355 to 360;

(68): Ch.L. Lau, 1993, Tissue and Cell, Vol. 25, No. 5, pages 681 to 693;

(69): "Growth factor" in http://www.everythingbio.com/glos/definition.php?word=Growth+factor, and http://www.thefreedictionary.com/p/growth%20factor, both dated 15 August 2011;

(71): A. Mayr et al., 1974, Virologische Arbeitsmethoden, Band I, Gustav Fischer Verlag, pages 231 to 282;

(72): Wikipedia entry "Chemically defined medium", http://en.wikipedia.org/wiki/Chemically_defined_medium, dated 12 January 2012;

(73): M. Schwenecker et al., 14 December 2011, J. Virol., doi:10.1128/JVI.06166-11.

XIII. The submissions made by appellant I concerning issues relevant to this decision, were essentially as follows:

*Article 123(2)(3) EPC*

The subject-matter of the amended claims according to the main request extended beyond the content of the application as filed. A method for amplifying poxviruses using **the** same serum free medium comprising EGF in steps (a) to (c) was not clearly disclosed in the application as filed. In fact, in opposition proceedings, the patent proprietor had admitted that EGF and fibronectin were only required in step (a). Since the amendments introduced into claim 1 resulted in the skilled person being confronted with new information which was not derivable from the application as filed, Article 123(2) EPC was contravened.

*Article 84 EPC*

The feature "*wherein the serum free medium of steps (a) to (c) comprises epidermal growth factor (EGF)*" introduced into claim 1 was not only unclear, in particular when read in connection with step (b) of the method, but also had no support in the patent as granted. It was stated in paragraphs [0042] and [0068] of the patent that, during infection an appropriate infection medium without serum could be added, and that

the medium might or might not comprise a factor selected from growth factors and fibronectin, depending on the cell type. However, neither claim 1 nor claim 5 specified a "cell type", and it was unclear whether "infection medium" was necessarily the same as "growth medium". Moreover, the wording "***the*** *serum free medium of steps (a) to (c)*" was ambiguous because it could mean that exactly the same serum free medium formulation was used in all steps of the method, or that different formulations were used, but each formulation comprised EGF. Hence, amended claim 1 did not meet the requirements of Article 84 EPC.

The feature "attachment factor" in claim 5 was not defined in the patent. Document (58) described a variety of completely different, structurally unrelated proteins, solutions and other compositions that seemed to be encompassed by the term "attachment factor". It was unclear which of these many attachment factors might work in the claimed method. Thus, also claim 5 (and dependent claim 6) did not meet the requirements of Article 84 EPC.

*Article 83 EPC*

The invention was not enabled over the whole scope of the claims. Claim 1 covered all primary avian cell types in combination with all poxvirus strains. However, certain poxviruses could only grow on particular cells, e.g. for the productive replication of MVA ("Modified Vaccinia Ankara") only CEF ("Chick Embryo Fibroblasts") cells could be used. Moreover, adherent cells would not form a suitable monolayer without the addition of an attachment factor, which was not specified in claim 1. While claim 1 related to

poxviruses in general, only one viral strain (MVA-BN) was tested in the examples.

A person skilled in the art could not carry out the claimed invention without applying inventive skills. As apparent from the patent itself, each cell type required not only a different concentration of EGF and fibronectin, but also further additives. The patent did not provide any technical information in this respect. There were also hundreds of serum free media on the market. Finding a suitable medium and determining suitable parameters for EGF and further compounds required for cell growth was a laborious endeavour amounting to an undue burden.

The method of claim 9 (and dependent claims 10 to 12) was not sufficiently disclosed, because it was not apparent from the patent how the "extracts" recited in the claim participated in the solution of the technical problem, or how they would be put into practice. Moreover, while the method of claims 13 to 15 could only be carried out using CEF cells, neither these claims nor claim 1, on which they depended, specified CEF cells.

*Article 87 EPC*

The patent claimed the priority of an earlier application filed in September 2002. Document (1), an international application filed by the same applicant in July 2002, disclosed a method of producing poxviruses in which primary avian cells were seeded and grown in VP-SFM, a serum free medium containing EGF. For infection with the MVA-BN poxvirus and subsequent incubation, the VP-SFM medium was replaced by serum free RPMI medium. However, since the cells were not

washed, at least a low amount of EGF was present also in the medium used for infection and cultivation of the infected cells. Hence, document (1) disclosed the same invention defined in claim 1 and the Danish application from which the priority was claimed could not be regarded as the first application within the meaning of Article 87 EPC. Consequently, the priority rights could not be claimed.

*Article 54(3)(4) EPC 1973*

Claim 1 lacked novelty in view of document (1). It could not be derived from Example 1 of that document that the EGF-containing VP-SFM medium used for cultivation of the CEF cells was actually removed prior to infecting the cells. Even if it were considered that in the method described in document (1) the VP-SFM medium was replaced by serum free RPMI medium, a washing step between the initial cell cultivation and the viral infection was not described. Hence, the inevitable outcome of the literal disclosure in Example 1 was that the serum free RPMI medium used for infection and production of viral progeny contained at least low levels of EGF.

*Article 56 EPC*

The method of claim 1 was obvious in view of document (15) combined with document (28). Document (15) described the propagation of MVA viruses in a totally synthetic medium comprising 10% of serum substitute BMS ("Basal Medium Supplement") which contained growth factors. Medium comprising BMS was used for cell cultivation and also for the subsequent infection of the cells with the virus and the propagation of the virus. As defined in document (36),

a serum free medium did not contain whole serum as an ingredient, but it was not necessarily entirely free of serum-derived products. Although BMS contained some serum proteins, such as growth factors, it was clearly a serum free medium. Incidentally, also the EGF and fibronectin used in the claimed method were serum proteins.

The feature distinguishing the method of claim 1 from the method described in document (15) was the presence of EGF in all three steps (a) to (c). However, there was no technical effect associated with the use of serum free medium comprising EGF in steps (b) and (c). Example 3, to which it was referred in the decision under appeal, did not actually relate to virus production, but only to cell cultivation.

At the relevant date, there was a general desire to improve methods for the amplification of viruses involving the use of serum free medium. A skilled person would have naturally considered seeking advice from publications in the field of cultivation of primary cells in serum free media. Hence, he/she would have considered document (28), which was a product information sheet describing VP-SFM, a serum-free medium containing 10 ng/ml EGF which was described as particularly suitable for growing viruses. VP-SFM was said to be formulated without any animal origin components and have a reduced risk of viral contamination.

Starting from document (15), the claimed method was obvious also in view of any of documents (5), (22) and (25), which described media meeting the "serum free" requirement and being suitable for propagating viruses.

As an alternative to document (15), document (55), which related to the amplification of vaccinia poxvirus in primary avian cells, could be considered to be the closest state of the art. It was obvious to combine the teachings of documents (55) and (28), thus arriving at the method of claim 1. Hence, the claimed subject-matter did not involve an inventive step.

XIV. The submissions made by appellant II were essentially as follows:

*Admission of documents (62) to (68) into the proceedings*

Filing new evidence had become necessary in view of the erroneous interpretation of the term "serum free medium" in the decision under appeal, and the amendments introduced into the claims during the oral proceedings in opposition proceedings.

*Article 123(2)(3) EPC*

Claim 7 and the passage on page 10, lines 8 to 10 of the application as filed described the combination of at least two factors selected from growth factors and attachment factors. However, the specific combination of at least a growth factor with at least an attachment factor as specified in amended claim 5, had no basis in the application as filed. Moreover, although EGF was disclosed in the application as a preferred growth factor, a combination of EGF with any attachment factor was not. Therefore, the amendment to claim 5 offended against Article 123(2) EPC.

*Article 84 EPC*

Claim 1 was unclear because step (b) did not specify the use of serum free medium. The feature introduced into claim 1 was ambiguous as to whether a medium with the same composition was used in all three steps of the method.

*Article 56 EPC*

Document (15), which represented the closest state of the art, described a method for the propagation of poxviruses that comprised the cultivation of primary avian cells in a serum free medium. As derivable from documents (36), (37) and (62) to (67), a serum free medium was not necessarily entirely free of serum-derived products. At the relevant date, it was well known from, e.g., documents (4), (7) and (55) that primary avian cells could be cultivated in serum free medium and formed a confluent monolayer.

The presence of EGF in steps (b) and (c) of the claimed method was an arbitrary feature without any technical effect. The alleged high virus yield obtained by the claimed method was not supported by any evidence. The experimental conditions in Example 8 of the patent and in document (15) were not the same and, therefore, the results obtained could not be compared. Document (73) did not support any advantageous effect on the virus yield linked to the presence of EGF in steps (b) and (c), as the inhibition of the signal pathway via EGFR was shown to have only a very limited effect on the size of the plaques produced by the virus. This was not sufficient to make plausible that a stimulation by the addition of EGF had a positive effect. Moreover, the experimental results in document (73) did not show

a correlation between the size of the plaques and the global viral yield. In any case, an improved yield was not apparent from the patent and, therefore, according to the jurisprudence of the Boards of Appeal (e.g. T 939/92, OJ EPO 1996, 309; T 235/04 of 29 June 2006, and T 824/07 of 5 October 2007) it could not be acknowledged as a technical effect when formulating the problem to be solved by the alleged invention.

Starting from document (15), the problem to be solved was to provide an alternative method for the amplification of poxviruses in a serum free medium. Looking for a solution to that problem, the skilled person would turn to documents describing the propagation of viruses in serum free conditions, e.g., document (10), (28), (44) or (5). The skilled person had a motivation to try serum free media comprising compounds with a mitogenic effect on the cells. Since it was known from, e.g., documents (21) and (68) that EGF had a mitogenic effect, it was obvious to add EGF to the serum free medium. Thus, in view of document (15) combined with either document (28) or document (5), the method of claim 1 lacked an inventive step.

XV. The respondent's submissions, insofar as they were relevant to the present decision, may be summarised as follows:

*Article 123(2)(3) EPC*

The amendments introduced into claim 1 had a basis on page 12, lines 17 to 22 of the application as filed. From claim 13 as originally filed, which referred to claim 3, a skilled person would derive that EGF could be used as a growth factor in the method of the

invention. Further, having in mind the disclosure at page 9, second paragraph, the skilled person would derive from the passage on page 10, second paragraph of the application as filed that the serum free medium used in the method of the invention could comprise both a growth factor, such as EGF, and an attachment factor. Hence, the subject-matter of claim 5 did not extend beyond the content of the application as filed.

*Article 84 EPC*

What mattered in regard to clarity under Article 84 EPC was whether a skilled person was able to determine whether or not a given method fell under the scope of claim 1. A skilled person would understand that the infection step (b) and the cultivation step (c) had to be carried out with the serum free medium comprising EGF as used in the cultivation step (a). The technical support was provided by Example 8 of the application as filed.

Also claim 5 complied with Article 84 EPC. It was immediately clear to a skilled person that the term "attachment factor" defined a group of chemically diverse compounds having the same function, namely to promote adhesion of cells to a solid support.

*Article 83 EPC*

The requirement of Article 83 EPC was fulfilled. There were no serious doubts, substantiated by verifiable facts that a method falling under the claims was reproducible without the need of undue experimentation or inventive skills.

*Article 87 EPC*

The priority claimed in the patent was valid because document (1) did not disclose the same invention as claimed in the patent. The allegation that, since no washing step was performed after removal of VP-SFM, some EGF remained in the culture, was mere speculation without any basis on facts. As apparent from document (71), it was common practice in the prior art to wash infected cells before they were transferred to a maintenance medium.

*Article 54(3)(4) EPC 1973*

The method described in Example 1 of document (1) did not fall under the scope of claim 1. Thus, the claimed method was novel.

*Article 56 EPC*

The subject-matter of claim 1 involved an inventive step. Starting from document (15) as the closest state of art, the problem to be solved was to provide a method for the amplification of poxvirus that was on the one hand reliable and safe, and on the other hand provided yields that were at least comparable to those obtained by methods using serum-containing media. The problem was solved by the method of the invention. In view of document (73), it was plausible that the presence of EGF in the infection medium had a positive effect on virus growth. This stood against the allegation that the use of EGF in steps (b) and (c) did not contribute to the technical effect underlying the invention. None of the documents cited by the appellants gave the skilled person a clear incentive to use a serum free medium containing EGF in steps (b)

and (c). A skilled person would not have arrived at the claimed invention by combining the teachings of documents (55) and (28).

XVI. Appellants I and II (opponents 03 and 05, respectively) requested in writing that the decision under appeal be set aside and that the patent be revoked.

XVII. The respondent (patent proprietor) requested, as main request, that the appeals be dismissed, or alternatively that the decision under appeal be set aside and the patent be maintained upon the basis of one of auxiliary requests I to VI, all filed under cover of a letter received on 16 January 2012.

## Reasons for the Decision

*Admission of the new evidence into the proceedings*

1. Pursuant to Article 12(4) of the Rules of Procedure of the Boards of Appeal (RPBA), it is a matter of discretion of the board whether or not evidence filed for the first time in appeal proceedings, but which could have been presented in the previous proceedings, is admitted and considered.

2. Both the appellants and the respondent filed additional evidence in appeal proceedings. Appellant II submitted documents (62) to (67) as support for its line of argument concerning the interpretation of the term "serum-free medium" used in claim 1. The construction of this term is relevant to the question whether or not a medium containing BMS as described in document (15) is to be considered a "serum-free medium". These pieces of evidence have been filed as an attempt to refute the

adverse findings in this respect in the decision under appeal (see page 14, lines 24 and 25 of the decision "*...BMS does not fall into the scope of a "serum-free medium*""). Hence, documents (62) to (67) have been filed at the earliest possible point of time and are to be admitted into the proceedings.

3. Document (68) was submitted by appellant II to support an objection of lack of inventive step, in particular as evidence that the use of the growth factor EGF in serum-free medium for the cultivation of primary avian cells was known in the art at the relevant date. Since claim 3 of the patent as granted was directed to a method using serum-free medium comprising EGF, document (68), if considered to be relevant evidence for the use of such a medium, should have been submitted either together with the notice of opposition or, at the latest, during the opposition proceedings. Despite the board indicating in its communication in preparation of the oral proceedings that it might become necessary to discuss the admission of document (68), any circumstances that may eventually have prevented appellant II from filing this document in opposition proceedings were not put forward. Nor are any apparent from the file.

4. Document (69) was submitted by appellant I as evidence that growth factors like EGF are normal components of serum. In its communication in preparation of the oral proceedings, the board observed that the same evidence had already been provided by document (48) filed in opposition proceedings. If appellant I considered that the probative value of document (48) differed from that of document (69), the question arose why the latter could not have been filed during opposition proceedings. Appellant I did not reply to the board's

communication. Hence, the board sees no reason why document (69) should be admitted and considered in appeal proceedings.

5. Consequently, exercising its discretion under Article 12(4) RPBA, the board decides not to admit documents (68) and (69) into the proceedings.

6. The appellants did not oppose the admission into the proceedings of documents (70) to (73) submitted by the respondent to address issues raised in the statements of grounds of appeal. Thus, these documents are admitted into the proceedings.

*Article 123(2)(3) EPC*

*Claim 1*

7. Appellant I's argument that there is no basis in the application as filed for the subject-matter of amended claim 1, in particular as regards the feature "... *wherein the serum free medium of steps (a) to (c) comprises epidermal growth factor (EGF)*", cannot be accepted. The subject-matter of claim 1 according to the main request (see section V above) can be derived, directly and unambiguously, from claim 13 and the passage of the description starting on page 11, line 8, in particular page 12, lines 18 to 22 of the application as filed. Claim 13 of the application as filed is directed to a method for the amplification of a virus comprising three steps: (i) cultivation of primary avian cells, (ii) infection of the cells with a virus, and (iii) cultivation of the infected cells to produce the virus. Step (i) of the method is defined by reference to, *inter alia*, the method for the cultivation of primary avian cells of claim 3,

according to which the growth factor comprised in the serum free medium is an epidermal growth factor (EGF). See also the passage on page 11, lines 13 to 17 of the application as filed in which it is stated that the conditions, definitions and preferred embodiments disclosed for the method of cultivation of primary cells apply equally for the definition of the first step of the method for the amplification of a virus.

8. The passage on page 12, lines 18 to 22 of the application as filed reads:

> "*The serum free medium that is used in the second and third step of the method for the amplification of a virus may be the same medium that has already been used before, i.e. a serum free medium comprising a factor selected from growth factors and attachment factors, depending on the cell type.*"

The wording "*the same medium that has already been used before*" in this passage can only be interpreted to refer to a medium as used for cultivating the primary cells in the first step of the method, i.e. "*... a serum free medium comprising a factor selected from the group consisting of growth factors and attachment factors, depending on cell type*" (see the identical wording used on page 11, lines 11 to 13 of the application as filed to describe the medium used in step (i)). Since according to the application as filed the medium used for cultivating the primary avian cells in step (i) may comprise epidermal growth factor (EGF), so does the medium used in steps (ii) and (iii) (steps (a) to (c) in claim 1 as presently on file). Hence, the subject-matter of amended claim 1 does not extend beyond the content of the application as filed.

*Claim 5*

9. The board does not share appellant II's view that the passage on page 10, lines 8 to 10 of the application as filed does not disclose directly and unambiguously the subject-matter of present claim 5. A person skilled in the art reading the passage in question ("*..., it is also possible to add two or more factors selected from growth factors and attachment factors to the medium*.") in connection with the next sentence disclosing a specific embodiment (page 10, lines 10 to 12; "*The medium may preferably comprise EGF and fibronectin, ...*"), understands that the passage on lines 8 to 10 discloses the addition of (at least) one growth factor (e.g. EGF) and (at least) one attachment factor (e.g. fibronectin). Hence, contrary to appellant II's contention the subject-matter of amended claim 5 does not extend beyond the content of the application as filed.

10. In view of the above, the board concludes that Article 123(2) EPC is not contravened. No objections under Article 123(3) EPC were raised by the appellants in appeal proceedings.

*Article 84 EPC*

*Claim 1*

11. The findings in the decision under appeal concerning claim 1 were contested by appellant I arguing that the feature "*... wherein the serum free medium of steps (a) to (c) comprises epidermal growth factor (EGF)*" introduced into claim 1 is ambiguous because it can be construed as meaning that the same serum free medium is

used in steps (a) to (c), or that different serum free media are used in the different steps, each medium comprising EGF.

12. The board cannot accept this argument. If, as in the present case, a feature can be read to cover two different embodiments of the claimed subject-matter, this does not necessarily mean that the feature is ambiguous, and that a claim including it lacks clarity within the meaning of Article 84 EPC. As a rule, a claim is considered to lack clarity if the exact distinctions which delimit the scope of protection conferred by the claim cannot be learnt from it (see decision T 6/01 of 2 December 2003, paragraph 14). In the board's view, the scope of protection of claim 1 is clearly delimited: the claim encompasses two alternative embodiments of the method of the invention, an embodiment in which the same serum free medium comprising EGF is used in all three steps of the method, and a different embodiment in which, as illustrated by Example 7 of the application as filed, the composition of the serum free medium used in the different steps varies, but each medium comprises EGF.

13. Appellant II's argument that claim 1 lacks clarity because there is no reference in step (b) to a serum free medium, cannot be accepted either. It is undisputed that, although not expressly specified in step (b), the infection of the primary avian cells with a poxvirus (step (b) of the claimed method) takes place in a medium. This medium can be either the serum free medium used for the cultivation of the cells, as specified in step (a), or a fresh medium which, as required by the feature introduced into claim 1 ("*... wherein the serum free medium of steps (a) to (c)*

*comprises epidermal growth factor (EGF) ...*"), must also be a serum free medium comprising EGF.

14. In connection with its objection that the amended claims lack support in the description, appellant I pointed to paragraphs [0042] and [0068] of the patent as granted. However, the board observes that, for the assessment whether or not the amended claims fulfil the requirements of Article 84 EPC, what has to be considered is the amended specification adapted to the claims as filed by the respondent during the oral proceedings before the opposition division, rather than the patent as granted.

15. It is stated in paragraph [0042] of the amended specification that the serum free medium used in the second and third step of the method "*... is the same medium that has already been used before, i.e. a serum free medium comprising EGF and optionally attachment factors, depending on the cell type*". It is clear from this passage that the serum free medium used in the three steps of the method according to the invention comprises EGF and, optionally, also attachment factors, in particular when the primary cells are adherent cells (see [0033] of the amended specification). The board is convinced that this passage of the amended description provides support, within the meaning of Article 84 EPC, for the amended claims 1 and 5, and that there is no need for either claim 1 or claim 5 to specify any particular "cell type". As regards paragraph [0068], which is part of Example 4, it should be noted that in the amended specification this example is marked as a reference example and that, therefore, it does not serve the purpose of supporting the amended claims.

*Claim 5*

16. Appellant I's further objection of lack of clarity concerning the term "attachment factor" in amended claim 5 is not justified. The term "attachment factor" has a clear meaning in the relevant art: it designates a compound that promotes adhesion of cells to a solid support. Neither the fact that the term in question is not defined in the patent, nor the fact that different structurally unrelated compounds - as listed in document (58) - can function as attachment factors may be regarded as prejudicial to the clarity of claim 5.

17. In sum, having considered the arguments put forward by the parties in appeal proceedings, the board concludes that the claims of the main request meet the requirements of Article 84 EPC.

*Article 83 EPC*

18. The findings on Article 83 EPC in section 20.2 of the decision under appeal were contested by appellant I arguing that the invention as claimed in claim 1 cannot be carried out over the whole scope of the claim because certain poxviruses cannot grow in **any** primary avian cell, but only in particular cells.

19. It is specified in claim 1 that the primary avian cells used in the method are cells that allow the productive replication of the poxvirus to be amplified. In its communication in preparation of the oral proceedings, the board stated that the notional person skilled in the art in the technical field of the invention could be considered to be an experienced practitioner who is aware of which particular cells under specific conditions allow the productive replication of

particular poxviruses. This has not been contested by the appellants. Nor have they disputed that the application as filed clearly discloses the replication of MVA in CEF cells. Neither the passage of the application as filed to which appellant I referred (see page 7, lines 13 to 23, which corresponds to paragraph [0024] of the patent in suit) nor any of the documents on file cast doubts that the method of claim 1 can be applied to amplify MVA in CEF cells.

20. Appellant I argued further that the disclosure in the application as filed was insufficient as regards the attachment factor, the EGF and/or the fibronectin concentration in the medium, and further components of the serum-free medium required for a particular cell type. This objection cannot be accepted either. As stated in the board's communication, at the relevant date various attachment factors were known in the art (see document (58)), and the knowledge of particular medium components required by specific cells belonged to the common general knowledge of the skilled person at that time. This was not disputed by appellant I. As regards EGF and fibronectin, concentrations suitable for carrying out the invention are disclosed in the application as filed (see passage from page 9, line 24 to page 10, line 4), and there is no evidence on file supporting appellant I's contention that finding out the optimal EGF and fibronectin concentration in a medium used for a specific combination of poxvirus and primary avian cell would require inventive skills or more than routine experiments.

21. Finally, appellant I asserted that a skilled person could not put into practice a method according to claims 9 to 12 because the patent did not teach precisely how the "extracts" specified in these claims

contribute to the solution of the technical problem. Even if this objection were to be considered as relating to Article 83 EPC – rather than, possibly, to Article 56 EPC, there is no evidence on file which may raise doubts on the feasibility of amplifying a poxvirus in an avian primary cell using a serum-free medium comprising EGF and a microbial or plant extract or an extract from a non-mammalian animal. Hence, appellant I's argument cannot be accepted.

22. Summarising the above, the arguments put forward by appellant I to support its objection of lack of sufficient disclosure fail to convince the board.

*Article 87 EPC*

23. While the findings concerning the correction of the priority declaration (see section 18.1.1 of the decision under appeal) were not contested in appeal proceedings, appellant I maintained its objection that the priority rights could not be validly claimed. In its view, the Danish application filed on 5 September 2002 was not the first application within the meaning of Article 87(1) and (4) EPC, because the earlier application PCT/EP02/07280 (document (1) in these proceedings) already disclosed the claimed invention.

24. Appellant I's view is not shared by the board. Document (1) discloses a process for improving the propagation of a poxvirus in a cell culture by reducing the temperature of the culture after infection below 37°C. In Example 1, the effect of the temperature on the multiplication of MVA in primary CEF cells is described. Primary CEF cells are cultivated in VP-SFM medium (a serum-free medium comprising EGF), and then

infected with MVA using serum-free RPMI medium. It is undisputed that the RPMI medium does not comprise EGF.

25. The board cannot acknowledge in the passage on page 17, lines 9 to 25 of document (1) a clear and unambiguous disclosure of the use of a serum-free medium containing EGF in either the infection or the propagation step (steps (b) and (c) of the method of amended claim 1 of the patent in suit). The fact that neither the removal of the VP-SFM medium comprising EGF, nor a washing step between the cultivation step and the subsequent steps of infection with the virus and cultivation of the infected cells, are mentioned in this passage cannot be regarded as a clear teaching that EGF is to be added to the medium used during the viral infection and replication, as required by amended claim 1. Contrary to appellant I's view, the passage on page 10, lines 9 to 14 of document (1) gives no indication whatsoever that the medium used for the cultivation of the cells before infection and for the production of the virus may be a serum-free medium comprising EGF.

26. In view of the above, the Danish priority application is considered to be the first application disclosing the method according to the present invention. Hence, the priority right is validly claimed, and the priority date is the relevant date for the assessment of novelty and inventive step. Consequently, document (1), a European application filed under the Patent Cooperation Treaty on 2 July 2002 and published on 30 January 2003 is to be regarded as comprised in the state of the art only for the assessment of novelty (Article 54(3) (4) EPC 1973).

*Article 54(3)(4) EPC 1973*

27. As stated in paragraphs 24 and 25 above, document (1) does not disclose, clearly and unambiguously, a method for the amplification of a poxvirus which comprises the step of infecting primary avian cells with poxvirus, and cultivating the infected cells in a serum-free medium containing EGF. Hence, document (1) does not prejudice the novelty of the subject-matter of claim 1.

*Article 56 EPC*

28. The findings on Article 56 EPC in the decision under appeal were contested by both appellants relying on document (15) as the closest state of the art. Alternatively, appellant I relied on document (55). Both lines of argument fail to convince the board.

*Document (15) as the closest state of the art*

29. Document (15) relates to paramunity, an antigen non-specific mechanism developed by warm-blooded animals, especially mammals and birds, which allows the animal to mount an immediate defence when confronted with foreign substances, infectious pathogens, toxins or transformed cells of the animal itself (see page 1, first and second paragraph). It describes multipotent paramunity inducers based on combinations of poxvirus components, a method for preparing the paramunity inducers, and their use as therapeutics in human and veterinary medicine. The paramunity inducers described in document (15) are based on the observation that the combination of poxvirus components derived from various poxvirus strains brings about not only an additive or supplementary effect, but a potentiation of the

respective paramunizing action (see page 4, first paragraph).

30. According to document (15), poxviruses used as components for the multipotent paramunity inducers can be propagated in both primary and secondary cell cultures or in permanent cell lines, using known techniques (see passage from page 12, line 27 to page 14, line 27). Example 1 describes the propagation of the attenuated avipox strain HP1 in chicken embryo fibroblast (CEF) cultures by cultivating the fibroblasts in *"... a totally synthetic medium comprising 10% BMS (serum substitute medium), 10% lactalbumin hydrolyzate and MEM (minimal essential medium)*" (see page 22, lines 7 to 9). After inoculation with the virus, MEM is used as medium for maintenance until progeny poxvirus is produced (see page 22, lines 11 and 12).

31. It was common ground that the method described in document (15) differs from the method according to claim 1 in that the medium used in steps (a) to (c) of the latter contains EGF. It was however a subject of dispute whether a medium containing BMS as described in document (15) can be regarded as a "serum free medium" as specified in claim 1.

32. In the decision under appeal, the opposition division found that BMS is a complex medium that includes an important protein fraction of the serum, and that, therefore, "... *BMS does not fall into the scope of a 'serum-free medium'*" (see page 14, sixth paragraph, lines 5 to 7 of the decision). The appellants questioned the opposition division's interpretation of the term "serum free medium" relying on documents (36) and (62) to (68). However, this evidence does not

support their view that BMS is to be considered to be a serum free medium as specified in claim 1.

33. According to the established jurisprudence of the Boards of Appeal, the terms used in patent documents should be given their normal meaning in the relevant art. If a term is ambiguous or unclear, the description and the drawings may be used for interpreting the claims (see, e.g., decisions T 23/86, OJ 1987, 316).

34. It is apparent from the documents to which the appellants referred that the term "serum free" may be given different meanings depending on the focus of the particular publication, and that the terms "serum free" and "serum substitute" are sometimes used indiscriminately, even though the meaning of the latter term is more general as it refers to media in which whole serum has been replaced by either a serum fraction or non-serum components. For instance, in documents (65) and (66), which focus on media with a reduced protein content in order to facilitate purification of the monoclonal antibodies produced by hybridomas, no clear distinction is made between media commercialized as "serum free" or as "serum substitute". The same is true for document (37). It should be noted that a clear distinction is, in some cases, not possible because the exact composition of media commercialized as serum free media is not provided by the manufacturers (see document (66), page 136, "Determination of protein content"; and document (36), page 1, first paragraph under the heading "Content of Serum-Free Media").

35. Document (36), to which both appellants referred, is concerned with ethical issues related to animal welfare. In this context, the statement on which the

appellants relied ("*By definition serum-free medium lacks whole serum as an ingredient, but it may not be entirely free of serum-derived* products"; see page 1, second paragraph under the heading "Content of Serum-Free Media") is to be understood, rather than as a definition, as a warning that even culture media labelled as "serum-free" by the manufacturer may still contain residual serum components. This applies also to the identical wording in the passage of document (64) on page 942, left-hand column, second full paragraph from the bottom.

36. In documents (62) and (63), it is stated that serum free media may contain serum constituents (see document (62), page 157, lines 2 and 3 of the second paragraph under the heading "Introduction"; and document (63), page 56, left-hand column, lines 12 to 16). However, it is also stated that "*... those constituents are known, and the level of each component is precisely defined*" and "*... for the most part highly purified*" (see document (63), page 57, left-hand column, lines 3 to 9; and sentence bridging centre and right-hand columns).

37. It follows from the above that, as used in the art, the term "serum free medium" refers clearly to a medium which does not contain whole serum, but the term seems to be rather vague as regards the possible content of serum components. In such a situation and according to the jurisprudence of the Boards of Appeal, the meaning of the term "serum free medium" has to be determined from the point of view of a skilled person who reads claim 1 in the context of the application and against the background of his/her common general knowledge (see T 1599/06 of 13 September 2007, point 3.1 of the Reasons).

38. It is clear from the statements in the second and third paragraph on page 3 of the application as filed that the method of the invention addresses the problem of a potential risk of contamination with pathogenic agents, if poxviruses intended for use as vaccines are prepared using a medium containing serum, e.g. bovine or fetal calf serum. In particular, the agent causing bovine spongioforme encephalopathy (BSE) is mentioned as one of the many potential problems associated with the use of bovine serum supplement (see page 3, lines 19 to 23 of the application). Having in mind that the agent causing BSE is suspected to be a protein, a person skilled in the art reading the application understands that the term "serum free medium" as used therein can only mean a medium containing neither whole serum, nor any serum fraction comprising a significant amount of uncharacterized proteins.

39. The medium used in Example 1 of document (15) comprises 10% BMS, which is described as a serum substitute medium (see page 22, lines 7 and 8). BMS, which was commercialized as a "serum alternative", is derived from fetal bovine serum (FBS) ("*Using only fractions of FBS, ...*"; see product datasheet filed as document (31)). Although its total protein and IgG content is significantly lower than that of FBS (it contains only one third of the proteins associated with serum), BMS still contains a substantial part of (uncharacterized) serum proteins. Hence, a person skilled in the art would not regard a medium containing BMS as a "serum free medium" within the meaning of claim 1.

40. Thus, the method described in document (15) differs from that defined in claim 1 in that the latter uses a

serum free medium for growing, infecting and cultivating the primary avian cells after infection, and that the medium used in all three steps contains EGF.

41. The technical effect associated with these features is a substantial reduction of the risk of contamination with pathogenic agents such as viruses, while maintaining poxvirus yields that are at least comparable to those obtained using a medium containing animal sera.

42. Appellant II disputed that the poxvirus yields disclosed in the application could be compared to those described in document (15) arguing that the experimental conditions were not the same. However, it did neither contest the statement in the application as filed that primary avian cells grow poorly in serum free medium without additional growth factors (see page 6, lines 21 to 23), nor argued, let alone filed any evidence that the virus titers disclosed in the application as filed for the method of the invention (see Examples 7 and 8 in the application as filed) are not comparable to those obtained in medium containing serum. Appellant II's further argument that the presence of EGF in steps (b) and (c) of the method according to claim 1 has no technical effect whatsoever is also unconvincing. Claim 1 requires that the medium used in steps (a) to (c) is a serum free medium which comprises EGF. The technical effect achieved by the use in all three steps of a serum free medium comprising EGF is a reduction of the risk of viral contamination, compared to a method using a medium that contains serum fractions as described in document (15).

43. Even though document (15) does not mention a potential contamination of cell cultures used for the production of vaccines with pathogenic agents as a problem, it was not a subject of dispute between the parties that, at the relevant date, this was a matter of general concern. Consequently, starting from the method described in document (15) the objective problem to be solved by the skilled person can be formulated as the provision of an effective and reliably safe method for the amplification of poxviruses in primary avian cells. Neither appellant has convincingly disputed that this problem is solved by the method of claim 1.

44. Having considered the evidence on which the appellants relied, the board is not persuaded that the solution proposed in claim 1 was obvious to a person skilled in the art at the relevant date.

45. Both appellants referred to document (5) which describes animal cell culture media comprising plant-derived nutrients that substitute animal-derived products. As possible components of the medium, document (5) mentions growth factors, interleukins, colony-stimulating factors, interferons and lymphokines. EGF is one of the ten growth factors mentioned in this document. Like the opposition division in the decision under appeal, the board observes that document (5) does not relate to media for the amplification of viruses, but to media for the cultivation of animal cells. It is not apparent to the board why a person skilled in the art seeking to amplify poxviruses would – without the benefit of hindsight – have not only turned to document (5), but also chosen among the numerous cell culture media described therein specifically a medium comprising EGF. Moreover, even if the skilled person might have

considered using such a medium, he/she would not have derived from document (5) anything that gave him/her a reasonable expectation to be able to effectively amplify poxviruses in primary avian cells, i.e. to obtain viral titers comparable to those obtained in serum containing media. Hence, the appellants' objection of lack of inventive step based on a combination of document (15) with document (5) must fail.

46. Document (28), to which appellant II referred, describes VP-SFM, a cell culture medium formulated without any human or animal derived components other than human recombinant EGF and human recombinant insulin. Among the advantages of VP-SFM, document (28) mentions a reduced risk of viral contamination and equivalent virus titers compared to serum supplemented media. It is stated in document (28) that VP-SFM is designed specifically for the growth of VERO, COS-7, MDBK, BHK-21, HEp2 and other important **cell lines**, which require little or no adaptation to the culture medium, whereas for other cell lines sequential adaptation may be necessary. It should be noted that, while immortalized cell lines can be adapted to a medium by subculturing, primary cells cannot be subcultured. Thus, a person skilled in the art reading document (28) would not have reasonably expected to be able to use VP-SFM for cultivating primary avian cells and amplifying poxviruses. Consequently, the claimed invention cannot be regarded as obvious in view of document (15) combined with document (28).

47. Appellant I relied also on documents (22) and (25). Document (22) concerns a serum free or serum depleted medium containing growth factors that stimulate the proliferation of stromal cells and cells from a variety

of tissues or organs, *inter alia*, epidermal growth factor (EGF), and document (25) describes that the addition of EGF and insulin to cultures of normal chicken heart mesenchymal cells causes these cells to proliferate at a rate comparable to that of their Rous sarcoma virus-infected counterparts. However, neither document (22) nor document (25) suggests that the media described therein may be suitable for an effective amplification of poxviruses in primary avian cells. Thus, combining document (15) with either document (22) or document (25) can only be considered obvious with the benefit of hindsight.

*Document (55) as the closest state of the art*

48. Appellant I relied – for the first time in appeal proceedings – on document (55) as the closest state of the art in combination with document (28).
Document (55) is the publication in the Bundesanzeiger of a European Community directive concerning particular requirements for the manufacture and testing of vaccinia virus vaccines used for pre-vaccination. According to section 2.2 of the directive, MVA vaccines are amplified in primary CEF cells using a chemically defined, protein-free culture medium ("*... unter einem chemisch weitgehend definierten, eiweißfreien Kulturmedium ...*"). Contrary to appellant I's view, the board does not consider that a combination of the teachings of documents (55) and (28) was obvious to a skilled person. Even if – for the sake of argument - the board were to accept that the skilled person had a motivation to combine the two documents, for the reasons given in paragraph 46 above there was no reasonable expectation that VP-SFM could be used for cultivating primary avian cells and amplifying poxviruses.

49. Summarizing the above: the arguments and evidence brought forward by the appellants fail to convince the board that the method of claim 1 lacks an inventive step within the meaning of Article 56 EPC.

*Article 113(1) EPC*

50. In its communication pursuant to Article 15(1) RPBA, the board expressed a reasoned provisional opinion on the issues to be discussed at the oral proceedings. The reasons given by the board in the present decision were known to the appellants, as they are essentially those given in the decision under appeal and/or in the board's communication. The appellants were given the opportunity to make written and/or oral submissions in respect of the grounds and evidence on which the present decision is based. However, they neither replied in substance to the board's communication nor attended the oral proceedings. Under these circumstances, the board considers that the provisions of Article 113(1) EPC are complied with.

**Order**

**For these reasons it is decided that:**

The appeals are dismissed.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated