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Datasheet for the decision of 24 October 2013

Case Number: T 1149/09 - 3.3.04

Application Number: 02796552.4

Publication Number: 1418942

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Title of invention:
Poxvirus-containing compositions and process for their preparation

Patent Proprietor:
Bavarian Nordic A/S

Opponents:
TRANSGENE S.A.
Sanofi Pasteur, Inc.

Headword:
Vaccinia virus formulation/BAVARIAN NORDIC

Relevant legal provisions:
EPC Art. 56, 108
EPC R. 101(1)
RPBA Art. 13(1)

Keyword:
Inventive step - main request, auxiliary requests 2 to 4 (no)
Admissibility of appeal of opponent 02 - statement of grounds (not filed)

Decisions cited:
G 0002/98, T 0377/95, T 0333/97

Catchword:

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Case Number: T 1149/09 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 24 October 2013

Appellant I: (Patent Proprietor)	Bavarian Nordic A/S Boegeskovvej 9 3490 Kvistgaard (DK)
Representative:	Zeman, Steven M. Grünecker, Kinkeldey, Stockmair & Schwanhäusser Leopoldstrasse 4 80802 München (DE)
Appellant II: (Opponent 01)	TRANSGENE S.A. Boulevard Gonthier d' Andernach Parc d'innovation CS80166 67405 ILLKIRCH GRAFFENSTADEN CEDEX (FR)
Representative:	Puech, Cécile Cabinet Regimbeau 20, rue de Chazelles 75847 Paris Cedex 17 (FR)
Other party: (Opponent 02)	Sanofi Pasteur, Inc. 1 Discovery Drive, Knerr Building 1 Swiftwater, PA 18034 (US)
Representative:	Bösl, Raphael Konrad Isenbruck Bösl Hörschler LLP Patentanwälte Prinzregentenstrasse 68 81675 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 30 March 2009 concerning maintenance of the European Patent No. 1418942 in amended form.**

Composition of the Board:

Chairman:	C. Rennie-Smith
Members:	R. Morawetz
	B. Claes

Summary of Facts and Submissions

I. The appeals of the proprietor (hereafter "appellant I") and of opponent 01 (hereafter "appellant II") lie against the decision of the opposition division whereby European patent No. EP 1418942 was maintained in amended form on the basis of the first auxiliary request filed during the oral proceedings before the opposition division on 16 December 2008.

II. The patent at issue has the title "Poxvirus-containing compositions and process for their preparation". It was granted on European application No. 02796552.4 which originated from international application PCT/EP2002/013434 published as WO 2003/053463 (hereinafter "application as filed") and claims priority from DK 200101831 (hereinafter "previous application"). Claim 1 as granted read:

"1. A formulation, comprising (i) a vaccinia virus having a titer of at least 10^6 $TCID_{50}$ per mg total protein, (ii) a disaccharide, (iii) a pharmaceutically acceptable polymer and (iv) a buffer, wherein the buffer is not a phosphate buffer."

III. The patent was opposed under Article 100(a) EPC 1973 on the grounds of lack of novelty (Article 54 EPC 1973) and inventive step (Article 56 EPC 1973) and under Article 100(b) EPC 1973.

IV. The opposition division held that the claims as granted (main request) failed the requirements of Article 56 EPC and maintained the patent in amended form on the basis of the auxiliary request filed during oral proceedings (which corresponds to auxiliary request 2 in the appeal proceedings, see section XI

below). Claim 1 of the auxiliary request read (amendments compared to claim 1 as granted indicated in bold by the board):

"1. A formulation, comprising (i) a vaccinia virus having a titer of at least 10^6 $TCID_{50}$ per mg total protein, (ii) a disaccharide, (iii) a pharmaceutically acceptable polymer and (iv) a buffer, wherein the buffer is not a phosphate buffer, **wherein the vaccinia virus is a MVA strain or strain Elstree, the disaccharide is sucrose and the polymer is dextran and wherein the formulation further comprises glutamic acid.**"

V. Opponent 02 filed a notice of appeal on 9 June 2009 and paid the appeal fee on the same date. No statement of grounds of appeal was filed by opponent 02 and the notice of appeal contained nothing that could be regarded as statement of grounds of appeal pursuant to Article 108 EPC. Opponent 02 requested in its notice of appeal that the decision under appeal be set aside and the patent be revoked.

VI. Appellant I filed its statement of grounds of appeal on 7 August 2009 and requested that the patent be maintained as granted (main request) and alternatively according to the auxiliary request filed by letter of 8 February 2008 (renamed auxiliary request 1 with letter of 31 May 2013). Claim 1 of auxiliary request 1 read (amendments compared to claim 1 as granted indicated in bold by the board):

"1. A formulation, comprising (i) a vaccinia virus having a titer of at least 10^6 $TCID_{50}$ per mg total protein, (ii) a disaccharide, (iii) a pharmaceutically acceptable **soluble** polymer and (iv) a buffer, wherein

the buffer is not a phosphate buffer."

VII. Appellant II filed its statement of grounds of appeal on 17 July 2009.

VIII. By communication dated 27 August 2009, sent by registered letter with advice of delivery, the registry of the board informed opponent 02 that no statement of grounds of appeal had been filed and that it was to be expected that the appeal would be rejected as inadmissible pursuant to Article 108, third sentence, EPC in conjunction with Rule 101(1) EPC.

IX. With a letter of 16 January 2012 appellant II provided further arguments regarding lack of inventive step.

X. By a communication of 16 January 2013 the parties were summoned to oral proceedings to be held on 24 October 2013.

XI. On 31 May 2013 appellant I filed a further written submission together with auxiliary requests 2 to 4, wherein auxiliary request 2 corresponded to the auxiliary request maintained by the opposition division (see section IV above). Claim 1 of auxiliary request 3 read (amendments compared to claim 1 as granted indicated in bold by the board):

"1. A formulation, comprising (i) a vaccinia virus having a titer of at least 10^6 $TCID_{50}$ per mg total protein, (ii) a disaccharide, (iii) a pharmaceutically acceptable polymer and (iv) a buffer, wherein the buffer is not a phosphate buffer, **wherein the vaccinia virus is a MVA strain, the disaccharide is sucrose and the polymer is dextran and wherein the formulation further comprises glutamic acid.**"

Claim 1 of auxiliary request 4 read (amendments compared to claim 1 as granted indicated by strikethrough or in bold by the board):

"1. A formulation, comprising (i) a vaccinia virus having a titer of at least 10^6 $TCID_{50}$ per mg total protein, (ii) a disaccharide, (iii) a pharmaceutically acceptable polymer and (iv) a buffer, ~~wherein the buffer is not a phosphate buffer~~, **wherein the vaccinia virus is a MVA strain, the disaccharide is sucrose and the polymer is dextran, wherein the formulation further comprises glutamic acid, and wherein the buffer is TRIS.**"

XII. With a telefax received on 27 September 2013 opponent 02 announced that it would not attend the oral proceedings.

XIII. Oral proceedings before the board were held on 24 October 2013 in the absence of opponent 02. Document (D17) was admitted into the appeal proceedings by agreement of the parties. After the board announced its view on the main request, appellant I withdrew auxiliary request 1.

XIV. The following documents are referred to in this decision:

(D1) US 6,258,362, July 2001
(D3) Rexroad, J. et al., Cell Preservation Technology, July 2002, vol. 1, pages 91-104
(D14) Burke C.J. et al., Critical Reviews™ in Therapeutic Drug Carrier Systems, 1999, vol. 16, pages 1-83
(D15) R. Pushker, Clinical Microbiology Newsletter,

1994, vol. 16, pages 121-124

(D16) Iyer L.M. et al., Journal of Virology, December 2001, vol. 75, pages 11720-11734

(D17) Ober, B.T. et al., Journal of Virology, August 2002, vol. 76, pages 7713-7723

XV. The arguments of appellant I can be summarised as follows:

Main request - claim 1
Priority

Page 10, lines 8 to 10 of the priority document stated that the virus was further purified. This disclosure constituted a direct and unambiguous disclosure of values for $TCID_{50}$ per mg total protein recited in the claims. Page 11, lines 19 to 20 of the priority document made it clear that poxviruses were contained in the formulation in a concentration of *inter alia* $> 10^6$ $TCID_{50}$/ml.

Inventive step

The invention lay in the field of poxviruses, in particular vaccinia virus (see paragraphs [0002] and [0013] of the patent specification). The main objective of the patent in suit was the provision of a stable vaccinia formulation (see paragraphs [0013] and [0014]). The technically relevant and substantiated teaching of document (D1) related to herpes simplex virus 2 (HSV-2). Although document (D1) disclosed formulations which were identical to the claimed formulations, in real life, the skilled person would start from the virus not from the formulation. Therefore document (D1) did not represent the closest prior art.

The skilled person interested in stabilizing vaccinia virus formulations for human use would rather start from document (D14). Document (D14) set out multiple formulations for poxviruses on page 54. The stabilisation values for each formulation in the table was numerically indicated in the "Log loss" column. Without knowing the claim, the skilled person looking for a stable formulation would start from the formulation in line 1 and not from the one in line 3 on page 54. Choosing the formulation with the most features in common with claim 1 involved hindsight. Document (D14) stated that development of formulations for live vaccines was empirical by nature (see page 7). The poxvirus in the formulation according to the invention was at least partially purified and had a titer of at least 10^6 $TCID_{50}$ per mg total protein. Document (D14) provided no level of purification only log loss during storage. During oral proceedings the problem to be solved was defined as the provision of a vaccinia virus formulation being pure enough to allow direct administration upon reconstitution while being stable enough to prevent loss of viral titre during storage. It was plausible that the effect was achieved over the whole scope of claim 1 and thus that the problem was solved over its whole scope. The burden of proof was on appellant II to show that certain buffers or disaccharide or polymers would not solve the problem.

The skilled person interested in stabilising vaccinia virus would not consider document (D1). The skilled person knew that the outer membrane structure was important for the stabilisation. The envelopes of poxviruses and herpes viruses were different (see documents (D15), (D16)). Poxviruses were twice as large

as HSV (see document (D15), Table 1). The difference of the membranes was reflected in their different ether sensitivity. Document (D16) stated (see page 11721, left hand column, at the end of the first partial paragraph) that the shape was different. The skilled person would understand that formulation conditions sufficient for herpes viruses were not transferable to a poxvirus setting. Therefore the skilled person reading document (D1) would not apply any teaching obtained with HSV-2 to poxviruses/vaccinia.

Moreover, when looking at document (D1), the skilled person would look at example 2 and not at example 5, because example 2 provided the better stabilisation. Examples 4 to 6, while relating to partially purified viruses, provided less stabilisation.

Auxiliary request 2 - claim 1
Inventive step

Document (D14) represented the closest prior art. It was conceded that the problem solution approach stipulated that the correspondence of the features was one of the criteria to be considered. The claimed subject-matter had been narrowed down to a defined set of components (dextran and sucrose), Na-glutamate and specific viruses. The development of viral formulations was empirical by nature (see document (D14), page 7, 1st paragraph, lines 7 and 8; 2nd paragraph, line 1; page 8, third paragraph, lines 13 and 14), which meant that it was impossible to predict what would work. In other words, one had to try to know what worked. Even if the skilled person started from the formulation in line 3 on page 54 he/she had to get rid of peptone, add buffer, and add the viral titer. The number of changes required indicated the presence of an inventive step.

The effect of the difference and the problem to be solved were the same as for the main request. Even if the skilled person would have looked at other documents he would not have looked at document (D1), because it related to herpes viruses. As regards the formulations in document (D1), the skilled person would have started with those that worked best.

Auxiliary requests 3 and 4
Admissibility

These requests were occasioned by the submission of appellant II of 16 January 2012, in particular its arguments on pages 7 and 8. The amendments carried out were designed to focus more closely on specific embodiments in the patent for which advantageous technical effects had been documented and should address the inventive step objections. These requests narrowed the claims based on features already in the claims as maintained in opposition. The appellant II was already aware of the subject-matter and no new subject-matter had been introduced. The requests should be admitted because they placed no undue burden on appellant II.

Auxiliary requests 3 and 4 - claim 1
Inventive step

The main advantage of the MVA formulation was a better retention of viral titer through the process of lyophilisation. This was a result of the increased viral stability achieved by the claimed formulation. Maintaining viral stability and thus titer was a problem that plagued the skilled person. The specific effect was obtained using MVA in formulations with TRIS

buffer, dextran, sucrose and glutamic acid (see Table 3).

The problem to be solved was the same as before. Starting from document (D14) the skilled person would try the formulation of example 2 of document (D1) because it had the better results and thus end up with a formulation comprising a phosphate buffer. Documents (D1), (D14) and (D17), i.e. three documents, had to be combined to arrive at all features of claim 1.

XVI. The arguments of appellant II (opponent 01) can be summarised as follows:

Main request - claim 1
Priority

The disclosure on page 10, lines 8 to 10 of the priority document did not discloses a minimum value for $TCID_{50}$ /mg. Page 11, lines 18 to 21 of the priority document related to concentration ranges of the poxviruses in aqueous formulations given in $TCID_{50}$ /ml and did not allow to deduce any minimum value of $TCID_{50}$ per mg protein because the presence of other components was not excluded.

Inventive step

Document (D1) was the closest prior art because it aimed at the same objective as the invention and had the most characteristics in common. The patent aimed at providing a stable and safe poxvirus containing formulation, see paragraph [0013]. Document (D1) aimed at the same objective. Although document (D1) aimed particularly at herpes viruses it did mention that the formulations were useful for poxviruses.

If document (D14) represented the closest prior art, the formulation disclosed on page 54, line 3 was the best starting point. The formulation in line 1 on page 54 differed more from claim 1 than the formulation in line 3. According to the problem solution approach the closest prior art had to have the most features in common. Therefore the composition in line 3 was the appropriate starting point. The only difference with regard to claim 1 appeared to be the purification of the virus and the buffer. The effect of this difference was according to paragraph [0013] of the patent in suit that the virus was stable and that the formulation comprised a low amount of non-poxvirus associated proteins. Accordingly, the problem was the provision of a vaccinia virus formulation for direct administration which had a certain stability. It had to be assessed whether the problem was solved across the entire scope. Claim 1 was drafted using open language (comprising), accordingly the presence of serum, animal proteins, and peptone was not excluded. It was not plausible that all compositions falling within the scope of claim 1 were stable. The $TCID_{50}$ given in claim 1 allowed for the presence of animal proteins. A $TCID_{50}$ of 10^6 per mg total protein corresponded to a partially purified vaccinia virus, see paragraph [0029] of the patent in suit. The characteristics of purity given in claim 1 were not high enough to solve the problem. Therefore the problem had to be reformulated and could be seen as the provision of a vaccinia virus formulation with a partially purified virus and a certain stability.

Document (D1) would have been looked at by the skilled person faced with this problem because it lay in a neighbouring field and aimed at the same objective as the invention. It was routine for the skilled person to

look at formulations tested for other viruses (see the prior art cited in document (D1)). The skilled person would look at formulations which had been tested for viruses which were close to poxvirus. Both herpes viruses and poxviruses were enveloped and had a DNA genome. The presence of an envelope led in both cases to the same problem of stabilising an envelope which comprised lipids and proteins, even if their exact structure was different. Documents (D14) and (D3) underlined that the envelope was important for the stabilisation. There was no evidence for the difference of the envelope or a possible effect on the stability. All documents focused on whether viruses were enveloped or not, this was the only relevant difference in the context of stabilisation of formulations. The size of the two viruses was very similar, see figure 1 of document (D14). The skilled person would therefor have been motivated to test formulation which had been shown to work for herpes virus on poxviruses. Document (D1) related to the same problem, i.e. the provision of stabilised virus preparations free of animal proteins (see abstract, column 3, lines 60 to 61, column 4, lines 19 to 20 and 40 to 41, column 6, lines 40 to 42, examples). Document (D1) invited the skilled person to test the formulation on poxviruses, it stated that the invention was particularly applicable to poxviruses (column 6, lines 17 to 18). Document (D1) could thus be combined with document (D14). The compositions disclosed in document (D1) included examples which were free from protein (other than any protein forming part of the active vaccine component) in particular free from gelatin or other animal protein (see column 4, lines 19 to 20, examples 4 to 6). The skilled person would have tested these formulations as they related to purified viruses, while example 2 did not. Vaccinia virus was the prototype poxvirus. The combined teaching

of documents (D14) and (D1) rendered the subject-matter of claim 1 obvious. By testing the formulations disclosed in document (D1) the skilled person would have arrived at the claimed solution in an obvious manner. That the success was certain was not required and a reasonable expectation of success was given.

Auxiliary request 2 - claim 1
Inventive step

During the oral proceedings document (D1) was no longer pursued as closest prior art. Document (D14) was considered to represent the closest prior art, in particular one of the vaccinia virus formulations of reference (404) disclosed in Table 3 on page 54. The problem solution approach stipulated that the formulation with the most features in common was chosen as closest prior art. Accordingly the selection of the formulation in line 3 was not based on hindsight. The subject-matter of claim 1 differed from the formulation of document (D14) in that it contained a partially purified virus, dextran instead of peptone, and a buffer without phosphate. The effect of these differences was that the titer and the dextran aimed at the elimination of animal proteins while the buffer aimed at increasing the stability. There were no data in the patent that showed that the effect was achieved across the entire scope of the claim. Alleged advantages should be supported by sufficient evidence, otherwise they needed not to be considered (see decision T 20/81). The claim stipulated no concentrations of the compounds. The formulation of the patent was not better than the formulation disclosed in document (D14). Starting from document (D14) the problem to be solved was the provision of vaccinia virus formulations without animal proteins and with a

certain stability. This problem was not solved across the entire scope of the claim. A $TCID_{50}$ of 10^6 per mg total protein corresponded to a partially purified vaccinia virus, see paragraph [0029] of the patent in suit. The formulation was open to the addition of other components due to the word "comprising". Peptone, sorbitol, and animal serum could still be present, nothing needed to be excluded. The problem needed to be reformulated and could be seen as the provision of vaccinia virus formulations wherein the vaccinia virus was a partially purified vaccinia strain with a certain stability. The solution was obvious for the same reason as set out for the main request. The two claimed vaccinia strains were well known and the ones most interesting from an industrial point of view. Document (D17) disclosed that MVA was the "gold standard" of recombinant vaccinia viruses in clinical development while Elstree had been used during worldwide smallpox eradication (see abstract). The skilled person was looking for an alternative with an acceptable stability.

Auxiliary requests 3 and 4
Admissibility

These requests were late filed. It was not clear how they addressed the inventive step objections.

Auxiliary request 3 - claim 1
Inventive step

This claim differed from claim 1 of auxiliary request 2 in that the virus had been limited to a MVA strain. This did not change the reasoning that had been brought forward for auxiliary request 2. The problem to be solved was the same as before, i.e. the provision of

vaccinia virus formulations without animal proteins and with a certain stability. This problem was not solved across the entire scope of the claim for the same reasons as set out for auxiliary request 2. The problem needed to be reformulated and could be seen as the provision of vaccinia virus formulations wherein the vaccinia virus was a partially purified vaccinia strain with a certain stability. The solution was obvious for the same reason as set out for auxiliary request 2. The skilled person would have used the formulations disclosed for HSV in examples 4 to 6 of document (D1). Document (D17) disclosed that MVA was the "gold standard" of recombinant vaccinia viruses in clinical development (see abstract).

Auxiliary request 4 - claim 1
Inventive step

This claim differed from claim 1 of auxiliary request 2 in that the virus had been limited to a MVA strain and buffer limited to TRIS. The formulation was not more stable than the formulation of document (D14). The problem to be solved was the same as before. This problem was not solved across the entire scope of the claim for the same reasons as before. The problem needed to be reformulated and could be seen as the provision of vaccinia virus formulations wherein the vaccinia virus was a partially purified vaccinia strain with a certain stability. The solution was obvious for the same reason as set out for auxiliary requests 2 and 3. The skilled person would have used the formulations disclosed for HSV in examples 4 to 6 of document (D1). Document (D1) prompted the skilled person to test these formulations on poxviruses. These formulation contained TRIS buffer. The skilled person had a reasonable expectation that a certain stability could be achieved.

Only two documents had to be combined, documents (D1) and (D14). The skilled person specialised in poxviruses knew that MVA was used for clinical developments, that it was the gold standard. Therefore, document (D17) illustrated the common general knowledge.

XVII. Opponent 02 filed no arguments during the appeal proceedings.

XVIII. Appellant I requested that the decision under appeal be set aside and the patent be maintained as granted or alternatively that the decision under appeal be set aside and the patent be maintained on the basis of one of its auxiliary requests 2, 3, or 4 filed with its letter of 31 May 2013. Appellant II requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Admissibility of the appeal of opponent 02

1. As no written statement setting out the grounds of appeal has been filed, the appeal of opponent 02 is rejected as inadmissible (Article 108 EPC, third sentence, in conjunction with Rule 101(1) EPC). It could not therefore maintain its request that the decision under appeal be set aside and the patent be revoked but as an "other party" only request that the appeal of appellant I be dismissed. In the event, opponent 02 took no part in the appeal proceedings after filing its notice of appeal.

Admissibility of the appeals of the proprietor (appellant I) and of opponent 01 (appellant II)

2. These appeals are admissible.

Main request (claims as granted) - claim 1
Priority

3. In the decision under appeal the opposition division decided that the claimed subject-matter was not entitled to the claimed priority. Appellant I has contested this decision.

4. Claim 1 relates to a formulation comprising a vaccinia virus having a titer of at least 10^6 $TCID_{50}$ per mg total protein. Appellant I relied on page 10, lines 8 to 10 and page 11, lines 19 to 20 of the previous application as providing priority for the feature "at least 10^6 $TCID_{50}$ per mg total protein".

5. The previous application discloses on page 10, lines 8 to 10 that "*Especially for vaccination of human beings it is thus preferred that the virus is further purified before it is included into a formulation according to the present invention*". In the board's judgement, the mere indication that the virus is further purified does not directly and unambiguously disclose a minimum value of $TCID_{50}$ per mg total protein, let alone a formulation comprising a vaccinia virus having a titer of at least 10^6 $TCID_{50}$ per mg total protein.

6. Page 11, lines 18 to 21 of the earlier application discloses that "*The poxviruses are contained in the aqueous formulation in a concentration range of 10^5 to 10^9 $TCID_{50}$/ml, preferably in a concentration*

range of 10^6 to $5x10^8$ $TCID_{50}$/ml, most preferably in a concentration range of 10^7 to 10^8 $TCID_{50}$/ml". This disclosure relates to concentration ranges of poxviruses with defined lower and upper endpoints in aqueous formulations given in $TCID_{50}$/ml. It does however not allow the deduction of any minimum value of $TCID_{50}$ per mg total protein since the presence of proteins of non-viral origin is not excluded.

7. For the above reasons the feature "at least 10^6 $TCID_{50}$ per mg total protein" can not be derived directly and unambiguously from the previous application, which therefore does not relate to the same invention (see opinion G 2/98 of the Enlarged Board of Appeal, OJ 2001, 413, Headnote). Therefore the effective date of claim 1 as granted is the filing date. Accordingly, documents (D3) and (D17) belong to the state of the art pursuant to Article 54(2) EPC.

Inventive step
Closest prior art

8. The opposition division considered document (D1) to represent the closest prior art. On appeal the parties disagreed as to which document constituted the closest prior art. While appellant I considered document (D14) to represent the closest prior art, appellant II considered document (D1) to represent the closest prior art.

9. From the patent as a whole it is understood that the purpose of the present invention is the provision of a poxvirus-containing formulation for freeze-drying which leads to a stable freeze-dried product, wherein the poxvirus is preferably a purified or at least partially purified virus comprising low amounts of non-poxvirus

associated proteins, and is in particular a vaccinia virus (see paragraphs [0009], [0013], [0014] of the patent in suit).

10. Document (D1) relates to preparations of viruses, e.g. for vaccines, to their stabilisation and to their use (see column 1, lines 11 to 15). Document (D1) discloses (see abstract, examples 4 to 6) stabilized dried pharmaceutical compositions dispersible in aqueous liquid which comprise - besides purified virus - sucrose, dextran, sodium glutamate, and Tris buffer. Compositions disclosed in document (D1) include compositions free from protein (other than any protein forming part of the active vaccine component). According to column 6, lines 17 to 18 of document (D1) "*The invention is particularly applicable for example to herpesviruses and poxviruses among others*". In the examples, the virus used is not a poxvirus but HSV-2, a herpes virus. It is undisputed that examples 4 to 6 of document (D1) disclose formulations which - except for the virus - are identical to the claimed formulations.

11. Document (D14), a review article, relates to the formulation, stability and delivery of live attenuated vaccines for human use. According to document (D14), the inherent lability of live organisms presents a particular formulation challenge in terms of stabilizing and preserving vaccine viability during manufacturing, storage and administration (see abstract). Document (D14) examines pharmaceutical approaches to the stabilization, formulation, and lyophilisation of biological macromolecules in general, as well as the specific applicability of these principles to live attenuated viral and bacterial vaccines. Finally, document (D14) discloses examples of accelerated and real-time storage stability testing of

various viral preparations, including various vaccinia virus formulations, *inter alia* a formulation comprising the Elstree strain, 5% Na-glutamate, 1.25% sucrose and 5% peptone (see Table 3 on page 54).

12. Both documents thus relate to the stabilization of live viral vaccines and provide stable formulations comprising live viruses. While document (D1) discloses formulations which - except for the virus - are identical to the claimed formulation (see examples 4 to 6), document (D14) discloses stable formulations which comprise a vaccinia virus, but differ from the claimed formulations in their chemical composition (see Table 3).

13. According to established case law of the Boards of Appeal, when deciding which of two documents (here documents (D1) and (D14)), has to be regarded as closest prior art, it has to be considered which document the skilled person would have **realistically** taken as a starting point under the circumstances of the claimed invention (Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, I.D. 3.4.2). Among these "circumstances", aspects such as the subject-matter of the invention, the formulation of the original problem, the intended use and the effects to be obtained should generally be given more weight than the maximum number of identical technical features. In the present case, where the stated purpose of the invention is the provision of stable poxvirus containing formulations, in the board's judgement, the realistic starting point for the skilled person is a stable vaccinia virus formulation as disclosed in document (D14).

14. Hence, the board concludes that document (D14) not only discloses subject-matter conceived for the same purpose but is also the most promising springboard towards the invention. Therefore the board decides that document (D14) represents the closest state of the art for the purpose of the assessment of inventive step of the subject-matter of claim 1.

15. The parties also disagreed on which of the formulations disclosed in document (D14) qualified as the closest prior art. Appellant I considered the formulation comprising an Elstree strain (a vaccinia virus), 5% peptone (a pharmaceutically acceptable polymer) and 5% sorbitol disclosed in line 1 on page 54 of document (D14) to represent the closest prior art. Appellant II considered the formulation comprising an Elstree strain (a vaccinia virus), 5% Na-glutamate, 1.25 % sucrose (a disaccharide), and 5% peptone (a pharmaceutically acceptable polymer) disclosed in line 3 on page 54 of document (D14) to represent the closest prior art.

16. In the board's judgement, the formulation comprising an Elstree strain, 5% Na-glutamate, 1.25 % sucrose, and 5% peptone requires less structural modifications to arrive at the claimed invention than the formulation comprising an Elstree strain, 5% peptone, and 5% sorbitol, and is accordingly considered to represent the closest prior art. Pursuant to paragraph [0047] of the patent in suit the term "stable, poxvirus containing composition" is used to define poxvirus containing compositions in which the overall loss in virus titer at an incubation temperature of 37°C during 28 days is less than 0,5 logs. According to Table 3 of document (D14) the loss in virus titer of the formulation is 0,4 at an incubation temperature of 37°C during 4 weeks. Accordingly, this formulation is

stable.

17. Appellant I's contention that the selection of this formulation is based on hindsight is not tenable, since the Boards of Appeal have established that, in circumstances such as the present, the prior art requiring the minimum of structural modifications to arrive at the claimed invention qualifies as the closest prior art (see Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, I.D.3.1).

Technical problem and solution

18. The subject-matter of claim 1 differs from the formulation disclosed in line 3 on page 54 of document (D14) in that the virus has a titer of at least 10^6 $TCID_{50}$ per mg total protein and in the presence of the buffer. Appellant I took the view that these differences resulted in a vaccinia virus formulation that was pure enough to allow direct administration upon reconstitution while being stable enough to prevent loss of viral titer during storage and formulated the problem accordingly.

19. The first issue to be addressed is whether the effect is achieved across the scope of the claim, in other words whether the problem is plausibly solved across the scope of claim 1.

20. The board notes that claim 1 relates to a formulation defined as **comprising** *inter alia* a vaccinia virus having a titer of at least 10^6 $TCID_{50}$ per mg total protein, a disaccharide, a pharmaceutically acceptable polymer, and a buffer. Accordingly, the presence of serum, animal proteins, or peptone is not excluded.

Indeed, according to the patent in suit a titer of at least 10^6 $TCID_{50}$ per mg total protein corresponds only to a partially purified virus (see paragraph [0029] of the patent in suit).

21. The patent in suit reports stabilization of Modified Vaccinia Virus Ankara (MVA) with a dilution buffer comprising dextrane, sucrose, and L-glutamic acid, termed DSG. The dilution buffer DSG was used at various defined final concentrations, wherein the $TCID_{50}$/ml of the final formulation was adjusted to 5 x 10^8 $TCID_{50}$/ml with a physiological Tris-buffer (see paragraphs [0066] and [0067], Table 6). However, neither the nature nor the concentrations of any of the components of the formulation, i.e. the disaccharide, the polymer or the buffer are specified in claim 1. Therefore in the board's judgement, the results obtained in the accelerated stability test carried out in the patent in suit with six defined formulations can not be plausibly extended to all formulations falling within the scope of claim 1.

22. According to the case law of the Boards of Appeal, alleged advantages to which the patent proprietor merely refers, without offering sufficient evidence to support the comparison with the closest prior art, cannot be taken into consideration in determining the problem underlying the invention and therefore in assessing inventive step (Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, I.D.4.4.2). The board concludes that the problem as formulated by appellant I (see point 18 above) is not plausibly solved by all formulations falling within the scope of claim 1. Accordingly, the problem has to be reformulated to a less ambitious problem which can be considered as being plausibly solved (Case Law of the

Boards of Appeal of the European Patent Office, 7th edition 2013, I.D.9.8.1). In the board's judgement, accordingly, this problem is the provision of a vaccinia virus formulation comprising a partially purified virus and having some degree of stability. The board is satisfied that this problem is solved.

Obviousness

23. It remains to be assessed whether the skilled person, when faced with the technical problem defined in point 22 above, would have modified the teaching in the closest prior art document (D14) - possibly in the light of other teachings in the prior art - so as to arrive at the claimed invention in an obvious manner.

24. It is undisputed that document (D1) discloses formulations which - except for the virus - are chemically identical to the formulation of claim 1 (see examples 4 to 6). The key question to be addressed is whether the skilled person, when embarking on finding a solution to the above problem, would have considered the teaching of document (D1).

25. The board notes that document (D1) relates to the stabilization of herpes virus preparations and thus lies in a neighbouring technical field. The compositions disclosed in document (D1) include compositions free from protein (other than any protein forming part of the active vaccine component), in particular free from gelatin or other animal protein or its hydrolysate or other material of animal origin (see column 4, lines 19 to 22, examples 4 to 6). In other words, the compositions contain purified viruses. Lyophilization of the virus containing preparations of document (D1) leads to stable compositions wherein the

titer of the virus lies within 0.5 of a log of the titre found immediately after lyophilisation. Finally, document (D1) discloses that the invention, i.e. the stabilised virus formulations, are particularly applicable for herpes viruses and poxviruses (see column 6, lines 17 to 18).

26. Document (D1) thus teaches stabilised purified virus preparations that are also suitable for poxviruses. Vaccinia virus is the prototype poxvirus. In the board's judgement, the skilled person faced with the problem formulated above would therefor have been motivated to test the preparations of document (D1) on vaccinia virus.

27. As pointed out repeatedly in document (D14), the development of live vaccine formulation is empirical by nature (see e.g. page 7, lines 6 to 9 of first paragraph; line 1 of the second paragraph; page 17, third paragraph). The person skilled in the field of the development of live vaccine formulation would therefore have been aware that any formulation, and thus also the formulations disclosed in document (D1) to stabilize HSV-2, would have to be tested with vaccinia viruses to determine whether or not they also stabilize these viruses. In situations like the present, the skilled person would have either some expectation of success or, at worst, no particular expectation of any sort, but a "try and see" attitude, which does not equate with an absence of a reasonable expectation of success (see decisions T 333/97 of 5 October 2000 and T 377/95 of 24 April 2001). Accordingly, the skilled person would have arrived at a formulation comprising purified Elstree strain, dextran, sodium glutamate, sucrose, and Tris buffer (a buffer which is not a phosphate buffer), and thus at a

formulation falling within the scope of claim 1, without the exercise of any inventive activity.

28. As a first line of argument, appellant I submitted that the skilled person interested in stabilising vaccinia virus would not have considered document (D1) because he or she knew that the outer membrane structure was important for the stabilisation of the virus and that the envelopes of poxviruses and herpes viruses were different. Therefore the skilled person reading document (D1) would not have applied any teaching obtained with HSV-2 to vaccinia viruses.

29. The board is not persuaded by this line of reasoning. Document (D14) consistently distinguishes between live viral vaccines which are based either on nonenveloped or on enveloped viruses (page 7, lines 1 to 3; page 8, lines 15 to 18 of last paragraph, page 17, third paragraph). A summary of stability observations of various enveloped viruses is presented in Table 3 of document (D14). Document (D14) also discloses that, in general, enveloped viruses are more labile than those lacking an envelope (page 24, third paragraph). Also document (D3) considers enveloped viruses as an entity as regards stabilisation (see page 97, left hand column, first full paragraph). In the board's judgement it can be concluded from documents (D14) and (D3) that the skilled person interested in the stabilisation of viruses distinguished mainly between enveloped and nonenveloped viruses. Herpes viruses and poxviruses are both enveloped viruses. The board is not convinced that possible differences in the size of the viruses, the chemical structure of the envelopes or the shape of the viruses would have discouraged the skilled person from transferring the formulation conditions disclosed in document (D1) for herpes viruses to a poxvirus setting.

Finally, the board notes that document (D1) does not list poxviruses amidst a long, arbitrary list of viruses to which the invention is applicable. To the contrary, document (D1) specifically proposes that the invention is particularly applicable for only two classes of viruses, namely herpes viruses and poxviruses (see column 6, lines 17 to 18).

30. As a second line of argument appellant I submitted that if the skilled person had considered the teaching of document (D1), he or she would have chosen the formulation giving the best stabilisation, i.e. the formulation disclosed in example 2 of document (D1) and not the formulations of examples 4 to 6 which, while relating to partially purified viruses, provided less stabilisation.

31. The board is not persuaded by this argument either. Example 2 of document (D1) is silent as to whether the virus is purified or not. To the contrary, examples 4 to 6 relate to the stabilisation of a purified virus. The formulations of these examples stabilize the virus as can be seen from the log loss after storage of the lyophilised preparation for 25 or 40 weeks. Therefore, the skilled person, interested in providing a solution to the problem of providing a vaccinia virus formulation comprising a partially purified virus and having some degree of stability would have tested the formulations provided in examples 4 to 6 and not the formulation provided in example 2 of document (D1).

32. For these reasons the subject-matter of claim 1 is found to lack an inventive step and thus the main request is not allowable under Article 56 EPC.

Auxiliary request 2 - claim 1
Inventive step

33. Claim 1 of this request differs from claim 1 of the main request in that the formulation is more narrowly defined as further comprising glutamic acid, the disaccharide sucrose, the polymer dextran and as the vaccinia virus a MVA strain or strain Elstree. This request corresponds to the request considered allowable by the opposition division.

34. The parties agreed that document (D14) represented the closest prior art. The board sees no reason to disagree. The subject-matter of claim 1 differs from the formulation disclosed in Table 3 on page 54 of document (D14) in that it contains a partially purified virus, dextran instead of peptone, and a buffer without phosphate. Appellant I submitted that the effect of the difference was the same as for the main request and formulated the problem accordingly as the provision of a vaccinia virus formulation pure enough to allow direct administration upon reconstitution while being stable enough to prevent loss of viral titer during storage.

35. The board notes that, although in present claim 1 the components are more narrowly defined than in claim 1 of the main request, the concentrations of these components are not indicated, the virus is only partially purified, and the definition of the formulation allows for the presence of *inter alia* peptone, serum or animal proteins. The board is thus not satisfied that the problem as formulated by the appellant is solved across the whole scope of claim 1 (see points 19 to 22 above). Accordingly, the problem needs to be reformulated (see point 22 above) and is

defined as the provision of a vaccinia virus formulation comprising a partially purified virus and having some degree of stability. The board is satisfied that this problem is solved.

36. It has been established (see points 23 to 32, above), that the skilled person faced with this problem would have combined the teaching of document (D14) with the teaching of document (D1), in particular examples 4 to 6 of document (D1), thus arriving at a formulation falling within the scope of present claim 1 in an obvious manner.

37. Appellant I submitted that the skilled person starting from the formulation disclosed in document (D14) had to get rid of peptone, and add dextran, the buffer and the viral titer in order to arrive at the claimed formulation. The sheer number of changes required spoke for the presence of an inventive step. The board notes that the presence of peptone is not excluded from the formulation of claim 1. As regards the dextran, the buffer and the viral titer, the board considers that document (D1) teaches the skilled person that it is the combination of dextran, sodium glutamate, sucrose and Tris buffer that stabilizes a purified virus (see examples 4 to 6). Therefore, the skilled person when testing the formulations disclosed in examples 4 to 6 of document (D1) with vaccinia viruses would have made all the changes required to arrive at a formulation which stabilizes the virus. Accordingly, the board is not persuaded by the argument of appellant I.

38. For these reasons the subject-matter of claim 1 is found to lack an inventive step and thus auxiliary request 2 is not allowable under Article 56 EPC.

Auxiliary requests 3 and 4
Admissibility

39. Claim 1 of auxiliary request 3 corresponds to claim 1 of auxiliary request 2, in which the option that the vaccinia virus is Elstree has been removed from the claim, thus limiting the vaccinia strain to a MVA strain. Auxiliary request 4 corresponds to auxiliary request 3 in which claim 1 has been additionally amended to specify that the buffer is TRIS. The board is satisfied that these amendments are a *bona fide* attempt to address the objections under inventive step, that they are straightforward and do not lead to any surprising turn of events or a fresh case. Under these circumstances the board decides to admit these requests in the proceedings in the exercise of its discretion under Article 13(1) RPBA.

Auxiliary request 3 - claim 1
Inventive step

40. This claim differs from claim 1 of auxiliary request 2 only in that the vaccinia strain is limited to a MVA strain.

41. The problem to be solved is the same as formulated above for auxiliary request 2 (see point 35 above). The board is satisfied that this problem is solved.

42. It has been established (see points 23 to 32, above), that the skilled person faced with this problem would have combined the teaching of document (D14) with the teaching of document (D1), in particular examples 4 to 6 of document (D1), thus arriving at a formulation which differs from the formulation according to claim 1 merely in that the vaccinia strain is Elstree and not

MVA. It thus needs to be established whether or not the choice of the MVA strain instead of the Elstree strain can justify the acknowledgement of an inventive step. Document (D17), which can be taken to represent the common general knowledge of the skilled person at the relevant date, discloses that MVA is the "gold standard" of recombinant vaccinia viruses in clinical development (see abstract). In the board's judgement, the fact that MVA was the "gold standard" of recombinant vaccinia viruses in clinical development at the relevant date would have prompted the skilled person, when faced with the problem formulated above (see points 41 and 35), to provide a vaccinia virus formulation comprising a MVA strain. Accordingly, the board considers the choice of the MVA strain as obvious to a person skilled in the art.

43. Appellant I submitted that documents (D14), (D1) and (D17) and, thus, three documents had to be combined to arrive at the claimed solution. The board understands this as an implicit argument to the effect that the combination of more than two documents to arrive at the claimed solution indicated the presence of an inventive step. The board notes that in the present case document (D17) is merely cited to illustrate the common general knowledge of the skilled person working in the field of vaccinia viruses at the relevant date. Accordingly, two documents are combined with the common general knowledge of the skilled person. In any case, the board is not persuaded that a requirement to combine more than two documents to arrive at the claimed solution would automatically guarantee the acknowledgement of an inventive step. As pointed out above (see point 23), the relevant question to be answered is whether or not the skilled person, in the expectation of solving the problem, would have modified the teaching in the

closest prior art document in the light of other teachings in the prior art so as to arrive at the claimed invention. The board is satisfied that this is the case (see point 42).

44. For these reasons the subject-matter of claim 1 is found to lack an inventive step and thus auxiliary request 3 is not allowable under Article 56 EPC.

Auxiliary request 4 - claim 1
Inventive step

45. This claim differs from claim 1 of auxiliary request 3 only in that the buffer is defined as being TRIS.

46. Since the buffer used in examples 4 to 6 of document (D1) is TRIS, no inventive step can be acknowledged for this request for the same reasons as given above for auxiliary request 3 (see points 40 to 44 above). Therefor auxiliary request 4 is not allowable under Article 56 EPC.

47. In the absence of an allowable request the patent has to be revoked.

Order

For these reasons it is decided that:

1. The appeal of opponent 02 is rejected as inadmissible.

2. The decision under appeal is set aside and the patent is revoked.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith

Decision electronically authenticated