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Datasheet for the decision of 7 December 2022

Case Number: T 2303/19 - 3.3.07

Application Number: 14180710.7

Publication Number: 2851087

IPC: A61K39/00, A61K9/19, A61K39/12, C07K14/005, C12N7/00

Language of the proceedings: EN

Title of invention:
Stabilization of vaccines by lyophilization

Patent Proprietor:
Sanofi Pasteur Biologics, LLC

Opponent:
Dilg, Haeusler, Schindelmann
Patentanwaltsgesellschaft mbH

Headword:
Stabilization of vaccines by lyophilization/ SANOFI

Relevant legal provisions:
RPBA Art. 12(4)
EPC Art. 56, 76(1), 123(2)

Keyword:

Admission of new documents (Yes)
Main request - Inventive step (No)
Auxiliary request 1 - Amendments allowable (Yes)
Auxiliary request 1 - Inventive step (Yes)

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Case Number: T 2303/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 7 December 2022

Appellant: (Patent Proprietor)	Sanofi Pasteur Biologics, LLC 38 Sidney Street Cambridge, MA 02139 (US)
Representative:	J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Respondent: (Opponent)	Dilg, Haeusler, Schindelmann Patentanwaltsgesellschaft mbH Leonrodstrasse 58 80636 München (DE)
Representative:	Maiwald GmbH Elisenhof Elisenstraße 3 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 17 June 2019 revoking European patent No. 2851087 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	Y. Podbielski

Summary of Facts and Submissions

I. European patent No. 2 851 087 was granted on the basis of a set of 13 claims.

Independent claim 1 as granted read as follows:

"1. A freeze-dried composition comprising a live, attenuated flavivirus vaccine, one or more stabilizers, lactose, amorphous mannitol, and one or more buffer components."

II. An opposition was filed under Article 100 (a), (b) and (c) EPC against the granted patent on the grounds that the subject-matter of the granted patent lacked novelty and inventive step, was not sufficiently disclosed, and extended beyond the content of the application as filed.

III. The appeal lies from the decision of the opposition division to revoke the patent.

IV. The decision was based on the claims as granted as main request and eight auxiliary requests.

V. The documents cited during the opposition proceedings included the following:

D1: WO 2008/057550 A2 (parent application as originally filed)
D6: Yu (2001) Adv. Drug Delivery Rev. 48: 27-42
D8: Excerpt from Rote Liste 2004 relating to Stamaril®
D9: US 4,500,512
D10: Excerpt from Rote Liste 1998 relating to Stamaril®

D11: Summary of Product Characteristics of Varilrix®
D12: Product monograph for Priorix®
D14: Kim et al. (1998) J. Pharm. Sci. 87(8): 931-935
D15: Lueckel et al. (1998) Pharm. Dev. Technol. 3(3): 337-346
D16: Cleland et al. (2000) J. Pharm. Sci. 90(3): 310-321
D18 Al-Hussein and Gieseler (2012) J. Pharm. Sci 101(7), 2534-2544
D20 Handbook of Pharmaceutical Excipients
D23 Annex A
D24 Annex B

VI. According to the decision under appeal, claims 4 and 5 of the main request complied with Articles 76(1) and 123(2) EPC. As the new objections under Article 100(c) EPC against claims 1, 2, 10 and 12 were late filed and *prima facie* not relevant, the opposition division disregarded these objections under Article 114(2) EPC.

D3 did not anticipate the claimed subject-matter.

With regard to inventive step, the difference over D8-D10 was the additional presence of amorphous mannitol in the claimed formulation. The data provided in the patent did not allow a direct comparison with the data of D9. Therefore, the general technical problem to be solved was the provision of an alternative stable formulation of live, attenuated flavivirus. The claimed solution was obvious, in view of in particular D6 and D14. The subject-matter of claim 1 of the main request did not involve an inventive step.

The objections raised by the opponent under Article 76(1) EPC against auxiliary request 1 were considered as being *prima facie* relevant and were admitted. Claims

8 and 9 of auxiliary request 1 did not comply with Article 100(c) EPC in relation with Article 76(1) EPC.

Auxiliary request 2 was not inventive. The addition of a further well-known stabiliser, HSA, could indeed not confer an inventive step on the subject-matter of claim 1 of auxiliary request 2.

Auxiliary requests 3-6 were not admitted into the opposition proceedings under Rule 116(1) EPC. Auxiliary request 7 was not inventive and auxiliary request 8 contravened Article 76(1) EPC .

VII. The patent proprietor (hereinafter the appellant) filed an appeal against said decision. With the statement setting out the grounds of appeal dated 24 October 2019, the appellant submitted auxiliary requests 1-9 and the following item of evidence:

D28: "Lyophilisation; Introduction and Basic Principles" (Jennings, 2002, pages 29 to 33).

Claim 1 of auxiliary request 1 read as follows, the difference(s) compared with claim 1 as granted shown in bold::

"1. A freeze-dried composition comprising a live, attenuated flavivirus vaccine, ~~**one or more stabilizers**~~ **human serum albumin (HSA)**, lactose, amorphous mannitol, and one or more buffer components." (emphasis by the Board)

VIII. With a letter dated 19 February 2020, the opponent (hereinafter the respondent) submitted the following evidence:

D29: Williams & Dean; Vial Breakage by Frozen Mannitol Solutions: Correlation with thermal characteristics and effect of Stereoisomerism, Additives, and Vial Configuration; J. Parenteral Science & Technology Vol. 45(2), 1991, pages 94-100.

IX. A communication from the Board, dated 18 August 2022, was sent to the parties. In it the Board expressed its preliminary opinion that *inter alia*, the main request was not inventive.

X. With a letter dated 3 November 2022, the appellant submitted an annex which contained an annotated version of Figure 1 of document D9.

XI. The parties were summoned to attend oral proceedings at the EPO premises. The appellant requested in its letter dated 3 November 2022 that the oral proceedings take place by videoconference. The respondent did not consent to this request and suggested a mixed mode format. Thereafter the appellant indicated that if the hearing were to take place in mixed mode the appellant's representative would attend in person, and asked for the appellant's in-house Counsel to attend remotely. In a communication dated 24 November 2022 the Board informed the parties that it had decided to hold the oral proceedings in person.

XII. Oral proceedings took place at the premises of the EPO on 7 December 2022. At the beginning the Chairman asked the parties whether they wished to comment on the format of the oral proceedings. The parties said that they did not.

XIII. The arguments of the appellant may be summarised as follows:

Admission of D28 into the appeal proceedings

D28 was a textbook extract concerning the use of mannitol as a bulking agent in lyophilised formulations, and was cited in direct response to the decision of the opposition division with regard to the obviousness of the solution to add amorphous mannitol to the formulations of the prior art.

Main request - Inventive step

Each of D8, D9 or D10 could be considered as the closest prior art . There was a technical effect shown over D9, especially in view of Tables 8 and 9 of the contested patent. Thus, the problem to be solved should have been formulated as the provision of a formulation having improved stability over the prior art, in particular during storage at elevated temperatures.

Even in the absence of an improved stability over the compositions of the prior art, the compositions were not obvious. The skilled person would indeed not have added any stabilising agent to the composition of D8-D10 in the expectation of producing a suitable alternative. D11 and D12 would not have motivated the skilled person to add amorphous mannitol to existing compositions. Furthermore, the prior art discouraged the skilled person from including amorphous mannitol as stabiliser, as illustrated by D6, D14 or D28.

Auxiliary request 1 - Inventive step

D9 clearly taught that HSA would destabilise a freeze-dried composition comprising a live attenuated flavivirus and for this reason taught away from the solution.

XIV. The arguments of the respondent may be summarised as follows:

Admission of D28 and D29 into the appeal proceedings

D28 was not *prima facie* more relevant than the documents already on file and had not been filed in reaction to an unexpected finding of obviousness of claim 1, and could have been filed much earlier during the opposition proceedings; it brought also a new point relating to the breakage of vials during lyophilization with mannitol. If D28 was admitted into the appeal proceedings, D29 should be admitted, since it was filed in reaction to D28.

Main request - Inventive step

No comparative data had been provided to support an advantageous effect over the prior art documents, in particular D9, but also D8 or D10. Accordingly, the technical problem underlying claim 1 of the main request was considered to be the provision of an alternative stable formulation of live, attenuated flavivirus. The claimed solution was obvious in view of D11, D12, D15 or D16.

Auxiliary request 1 - Amendments

This request did not meet the requirements of Article 76(1) EPC and 123(2) EPC in view of the subject-matter of claims 1, 8 and 9.

Auxiliary request 1 - Inventive step

No effect was shown for the addition of HAS, which was obvious in view of D25, D11 or D12. D9 did not teach away the solution in view of Figure 1.

XV. Requests

The appellant (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained as granted (main request), or that the patent be maintained on the basis of one of auxiliary requests 1-9 filed with the statement of grounds of appeal dated 24 October 2019.

They also requested that document D28, also filed with the statement of grounds of appeal, be admitted into the proceedings.

The respondent (opponent) requested that the appeal be dismissed. They also requested that D28 not be admitted into the proceedings. They furthermore requested that D29 be admitted in case D28 is admitted.

Reasons for the Decision

1. Format of the oral proceedings

The appellant's reasons for requesting that the oral proceedings take place by videoconference were two-fold. Firstly, this format would facilitate attendance at the hearing by the appellant's in-house counsel. Secondly, it would reduce the risk of any last minute travel disruption which may occur due to the uncertainty surrounding Covid-19 cases.

The Board agrees with the respondent that at the relevant time there were no Covid-19 related travel restrictions which would impair the parties' possibilities to attend in person oral proceedings at the EPO premises, and that in person oral proceedings are for now the optimum format as expressed in decision G 1/21. The Board also considers that the possible attendance of an accompanying person cannot determine the format of the oral proceedings. The Board thus decided that the oral proceedings take place in person.

2. Admission of D28 and D29 into the appeal proceedings

2.1 D28 was filed by the appellant at the earliest stage of the appeal proceedings with its statement of grounds of appeal and is an excerpt from a book dealing with lyophilization.

It relates to the use of mannitol as bulking agent, and discloses particularly that mannitol is the most common bulking agent used in lyophilized formulations, and that if the formulation is frozen slowly, the mannitol becomes crystalline. Moreover, the document mentions that the crystalline structure of the mannitol provides

a supporting structure for the active constituent (see pages 29 and 30).

Hence D28 was filed to show that mannitol is used as a bulking agent in crystalline form since it provides a good structure to the lyophilised cake. This document has been filed in response to the decision of the opposition division with regard to the assessment of inventive step, in particular the obviousness of the solution to use amorphous mannitol as a stabilizing agent for the claimed vaccine composition. In the appellant's view, D28 shows the opposite, i.e that mannitol is normally used as a bulking agent, and not as a stabilising agent, and in crystalline form, instead of its amorphous state.

In the Board's view, D28 is evidence of common general knowledge, filed in direct response to a point raised during the opposition proceedings and present in the decision of the opposition division, this point still being relevant in the appeal proceedings. Consequently, the Board admits D28 into the appeal proceedings (Article 12(4) RPBA 2007).

2.2 D29 is a document filed by the respondent in reply to the statement of grounds of appeal and the filing of document D28. It relates to a point mentioned in D28, namely the possible breakage of vials comprising mannitol during the lyophilization.

In view of its subject which might be of possible interest in the appeal proceedings, and the early submission in response to the filing of a new document in the appeal proceedings, the Board decides to admit D29 into the appeal proceedings (Rule 12(4) RPBA 2007).

3. Main request - Inventive step

3.1 The claimed invention relates to stabilized compositions comprising live, attenuated flavivirus vaccine.

3.1.1 D8-D10 were cited as possible closest prior art documents in the decision of the opposition division. The appellant and the respondent used D9 as closest prior art in the appeal proceedings.

3.1.2 D9 relates to stabilizing agents for live viruses, and to the stabilized vaccines so-obtained. It discloses in particular a lyophilized vaccine formulation containing attenuated live yellow fever virus in a stabilizing agent constituted by a phosphate buffer solution (PBS) containing calcium and magnesium ions, 4% lactose, 2% sorbitol and about 0.005M to 0.05M final concentration of at least one amino acid, with a preference for histidine and alanine at a final concentration of 0.02 M (see claim 1, col. 3, lines 58-61, and col. 5, lines 6-17).

Tables 3 and 4 of D9 show the stability of the formulations. Table 4 shows in particular the stability of anti-yellow fever vaccines at 37°C; the titer loss in log UFP/ml after 14 days of the stabilised compositions is comprised between 0.148 and 0.464:

TABLE 4

Anti-yellow fever vaccine
Stability test at 37° C.
(titer in log UFP/ml: averages of 4 titrations)

Batch no	Vaccine prepared in	Control stored at −60° C.	titer loss after heating at 37° C. 7 days	14 days
18	Distilled water	5.541	1.037	2.412
	Stabilizer	5.717	0.284	0.282
25	Distilled water	5.543	0.876	1.575
	Stabilizer	5.875	0.140	0.148
26	Distilled water	5.357	0.730	1.090
	Stabilizer	5.638	0.352	0.464
27	Distilled water	5.417	0.679	1.076
	Stabilizer	5.710	0.280	0.362
28	Distilled water	5.109	0.604	0.977
	Stabilizer	5.426	0.237	0.292

3.1.3 D8 and D10 give the composition of the anti-yellow fever vaccine Stamaril® comprising in particular lactose, sorbitol, Histidine, alanine, and a phosphate buffer.

3.1.4 None of the documents D8-D10 disclose the presence of amorphous mannitol in their compositions. The compositions shown in D8 and D10 are identical to the compositions disclosed in D9, without however any disclosure as to the amounts of excipients and without any explicit stability test. In view of the more complete disclosure of D9, this document will be considered as the closest prior art.

3.2 The appellant defines the problem as the provision of a formulation having improved stability, in particular during storage at elevated temperatures.

According to the respondent and to the opposition division in its decision, the problem to be solved is

the provision of an alternative stable formulation of live attenuated flavivirus.

3.3 The claimed solution to any of these problems is the presence of amorphous mannitol in the claimed freeze-dried composition comprising a live, attenuated flavivirus vaccine.

3.4 The appellant relies on Tables 8 and 9 of the patent in support of an improved effect, and considers it furthermore not appropriate to compare the stability results shown in the Tables of the patent with the stability results shown in D9 such as in Table 4.

3.4.1 Table 8 shows accelerated stability data of a composition comprising 4% lactose, 2% sorbitol, 10 mM histidine, 10 mM alanine and 50 mM potassium glutamate (see [0063]). Such composition shows a Log loss at 37°C of 1.67 after 14 days. The same composition with 0.1% HSA (Human Serum Albumin) shows an improvement in stability, with a Log loss at 14 days of 0.43. This Table does not provide any comparison with a composition comprising amorphous mannitol.

3.4.2 Table 9 gives a comparison of the accelerated stability data at 37°C between several compositions, and in particular between:
- a composition with 4% lactose, 2% sorbitol, 10 mM histidine, 10 mM alanine, 50 mM potassium glutamate and 0.1% HSA
- a composition with 4% lactose, 3% mannitol, 10 mM histidine, and 0.1% HSA.

Table 9 highlights that the composition comprising mannitol has an improved stability, with a Log loss of

0.15, while the composition with sorbitol has a Log loss of 0.42 after 14 days.

Both compositions differ however not only in the sugars used, but also in the concentration of said sugars and in the presence or absence of alanine and potassium glutamate. Accordingly these compositions cannot be compared to each other; they cannot serve for the same reason as a comparison with the composition disclosed in D9. In view of these differences, it appears indeed impossible to draw a conclusion as to whether the substitution of sorbitol by mannitol, or the presence of other components, is responsible for the effect on stability; comparative examples must indeed show clearly that the desired technical effect is linked with the distinguishing feature, which is here the presence of amorphous mannitol and no other technical feature.

In this regard, the Board cannot follow the appellant's argument that the different amounts of sugar in Table 9, namely 2% of sorbitol versus 3% of mannitol, constituted only a small and insignificant difference in particular in view of Figure 4 of the patent which demonstrates a small stability difference between compositions comprising 3 and 4% of lactose;. In the Board's view, it is indeed difficult to consider that a difference of 50% in the amount of sugar (i.e. 2% of sorbitol vs 3% of mannitol) never has an incidence on the stability of the composition. This is for instance confirmed by the same Figure 4 of the patent which show a significant difference in stability between a composition comprising 2% of lactose and a composition comprising 3% of lactose.

3.4.3 Consequently, it is not possible to conclude that there is an improved effect on stability linked to the use of amorphous mannitol; the problem is therefore as defined by the opposition division in its decision, namely the provision of an alternative stable formulation of live attenuated flavivirus.

3.5 It remains to consider whether the skilled person faced with this technical problem would have arrived at the subject-matter of claim 1 in an obvious manner.

3.5.1 D6 relates to the stabilization of labile substances during processing and storage using additives, the prevention of crystallization of the excipients that must remain amorphous for their intended functions and the selection of appropriate storage conditions under which amorphous solids are stable (see Abstract). Mannitol is listed among the excipients useful to protect proteins, peptides and organisms during freeze-drying processes (page 37, paragraph 4.1). D6 also mentions that certain excipients (e.g. mannitol) have a strong tendency to crystallize, leading to phase separation and loss of stabilizing power (see page 38, point 4.4). D6 further explains how mannitol can be made amorphous by deliberately preventing crystallization (see page 29, paragraph "2.Preparation"). It indicates in particular that the process conditions can influence the amount of amorphous material in the end product, and that the introduction of an annealing step may promote crystallization, in particular of mannitol, as also explained in the contested patent in paragraph [0068] and [0069]. In view of this document, as acknowledged in the decision of the opposition division, the skilled person would have recognized amorphous mannitol as a

stabilizing agent for freeze-dried compositions and avoided crystalline mannitol.

3.5.2 D11 relates to the vaccine Varilrix® comprising an attenuated varicella vaccine and excipients, namely framycetin sulfate, human serum albumin, lactose, sorbitol, mannitol, amino acids and red Phenol, while D12 relates to the vaccine Priorix® comprising combined live attenuated measles, mumps and rubella vaccines. The excipients used therein are amino acids, human albumin, lactose, mannitol, neomycin sulphate and sorbitol. An indication of the nature of mannitol, i.e. crystalline or amorphous, is however not given in any of these documents.

3.5.3 D14 relates to the lyophilization of mannitol. It discloses that mannitol is one of the most commonly used excipients in freeze dried pharmaceutical products. It further indicates that instability of the drug in the presence of mannitol is to be attributed in part to continued crystallization of mannitol, and that in particular annealing during the freeze-drying process promotes crystallization, and is associated with marked loss of activity (see page 931 "Introduction"). It mentions also the difficulties to make lyophilized amorphous mannitol compositions (see page 932, last par.). Hence, the disclosure of this document confirms the possible stabilizing effect of mannitol on freeze-dried compositions, and the necessity to keep it as amorphous as possible.

3.5.4 D15 discloses the use of mannitol to stabilize compositions comprising Interleukin-6. It mentions in particular that, during freeze-drying, the most effective protection against aggregation was provided by completely amorphous formulations consisting of

trehalose or sucrose either alone or in combination with glycine or mannitol (see Abstract).

3.5.5 D16 mentions on page 314 that a low concentration of mannitol may remain amorphous and in the same phase as the protein during drying, providing protection to the protein. In support of this, D16 cites another study which determined that mannitol at 60 mM in a lyophilized rhuMAb HER2 formulation was only 7% crystalline.

3.5.6 D18 is a study on the effect of mannitol crystallization in mannitol-sucrose systems on LDH stability during freeze-drying with and without annealing. It mentions in particular that the destabilizing effect of mannitol crystallization on LDH during freeze-drying can likely be attributed to removal of mannitol from the amorphous phase containing the protein (see "Summary and conclusions"). It shows also that the crystallization of mannitol depends on its weight ratio to sucrose as shown below:

Table 3. Crystallinity of Mannitol (% ± SD) in Samples Containing Different Weight Ratios of Mannitol to Sucrose Freeze-Dried with and Without Annealing

	Crystallinity of Mannitol (%) ± SD	
Formulation (Mannitol: M, Sucrose: S)	With Annealing (Polymorphic Form)	Without Annealing (Polymorphic Form)
M100	83 ± 3.4(β)	69 ± 2.7(β)
M90/S10	73 ± 3(β)	65 ± 1.5(β)
M70/S30	47 ± 2.5(δ)	41 ± 0.6(δ)
M50/S50	33 ± 3(δ)	13 ± 2(δ)
M30/S70	11 ± 1.3(δ)	3 ± 0.4(δ)
M10/S90	2 ± 0.7(β)	0 (–)

The corresponding dominant polymorphic form of mannitol is provided in brackets.

In the appellant's view, a passage of D18 provided evidence that mannitol should remain generally in its crystalline state since it is used as a bulking agent and not as a stabilizing agent in the claimed invention. D18 explains indeed at page 2534, right-hand column, second paragraph that: "A central goal of freeze-drying is to retain the protein activity during storage while obtaining an elegant final product. This goal is commonly achieved by using amorphous cryoprotectants and/or lyoprotectants, often in combination with crystalline bulking agents. Crystalline excipients support the physical stability during freeze-drying and provide product elegance, whereas amorphous excipients commonly serve as a protein stabilizer during both freezing (cryoprotectant) and drying (lyoprotectant)".
This passage does however not cite mannitol, and the appellant's interpretation is at odds with the remaining teaching of D18 summarized above, and regarding the stabilizing effect of amorphous mannitol.

3.5.7 D28 mentions the common use of mannitol as a bulking agent in freeze-dried formulations, and discloses that if the formulation is frozen slowly, the mannitol becomes crystalline (see pages 29-30). It further mentions that the crystalline structure of the mannitol provides a supporting structure for the active constituent and prevents loss of product from the container and that if a solution containing mannitol is frozen rapidly enough to prevent crystallization of the mannitol, then breakage of the vial can occur. D28 was filed by the appellant to show that mannitol is used as a bulking agent in crystalline form since it provides good structure to the lyophilised cake. In the appellant's view the possible breakage of the vial would dissuade the skilled person from using amorphous

mannitol. However, as pointed out by the respondent, the skilled person was also aware of simple methods for preventing this breakage (see D29 abstract). Furthermore, D28 is totally silent as to the stability concern of the freeze-dried compositions. In the Boards's view, D28 does not support a teach-away for the use of amorphous mannitol in lyophilised vaccines.

3.5.8 In view of these documents, it appears that mannitol in general was known as a component of freeze-dried formulations comprising live attenuated vaccines, as shown in D11 or D12.

Moreover, the use of mannitol as a stabilizing agent is explicitly disclosed in particular in documents D6 and D14, which were cited in the decision of the opposition division with regard to the obviousness of the claimed solution, but also in D15, D16 and D18.

The necessity of keeping mannitol in its amorphous state to keep its stabilizing effect is furthermore explicit from D6 and D14, and also from D15, D16 and D18.

3.6 Consequently, the claimed solution was known from the prior art. Considering that the problem to be solved has been defined as the provision of an alternative, the simple selection of a known solution is devoid of any inventive character and the main request does not meet the requirements of Article 56 EPC.

4. Auxiliary request 1 - Inventive step

4.1 Claim 1 of auxiliary request 1 has been amended by the specification that the the stabilizer is human serum albumin (HSA).

4.2 Starting from document D9, the appellant defines the problem as the provision of a formulation with improved stability under long-term storage, particularly at elevated temperatures, whereas the respondent considers that there is no evidence for any advantage over D9.

4.3 The claimed solution is the use of amorphous mannitol and human serum albumin (HSA) in freeze-dried composition comprising a live, attenuated flavivirus vaccine.

4.4 Even though it appears convincing in view of the experimental results of Table 8 of the contested patent, as well as of Tables 7 or 4, that the addition of HSA provides an improvement on the stability of the claimed vaccine formulations, the Board will, in the respondent's favour, nevertheless start from the assumption that a combination of HSA and amorphous mannitol as claimed in claim 1 of auxiliary request 1 request does not provide an improved stability. The problem will therefore be considered as the the provision of an alternative stable formulation of live attenuated flavivirus.

4.5 HSA is known as component of lyophilized vaccine composition as shown in D11 or D12. It is also known as cryoprotectant for drug lyophilization, as shown in D25 (cf. page 6, section 7).

The closest prior art D9 teaches however away the use of HSA as stabilizing agent. D9 discloses indeed that the protective effect exerted by its stabilizing solution of the viral preparation is essentially due to the presence of the amino acids and of the calcium and magnesium ions present in the buffer (cf. D9, col. 5, lines 48-52). It emerges furthermore from the studies performed in D9 that the addition of HSA to different stabilizing compositions systematically leads to a greater titer loss of the lyophilized vaccines, therefore a decreased stability of the vaccine compositions. This is expressed by the results shown in Figure 1 of D9 which shows a greater titer loss of a lyophilized vaccine composition comprising lactose or saccharose with HSA in comparison to the corresponding compositions comprising only lactose or saccharose (see Figure 1 or col. 7, line 62 - col. 8, line 20). Figure 1 also shows that the replacement of lactose in a stabilizing composition according to the invention of D9 comprising lactose and sorbitol by a combination of sorbitol with HSA leads also to a greater titer loss. Hence, D9 clearly teaches that HSA will destabilise a freeze-dried composition comprising a live attenuated flavivirus, and presents clearly an incitation not to incorporate HSA.

Moreover, the claimed solution, i.e the addition of amorphous mannitol and HSA, represents two changes over the disclosure of D9. In the Board's view the skilled person concerned with the issue of stability of the compositions would not make a second significant change to the compositions of D9 which goes against the teaching of D9 itself. As is clear from Table 7 of the patent, not all known stabilisers will provide a formulation of acceptable stability. Freeze-dried compositions comprising HSA and amorphous mannitol all

provided better stability than similar compositions comprising other known stabilisers such as porcine gelatin and recombinant human gelatin.

Consequently, the claimed solution, namely the use of amorphous mannitol and human serum albumin (HSA) in freeze-dried composition comprising a live, attenuated flavivirus vaccine is not obvious and auxiliary request 1 meets the requirements of Article 56 EPC.

5. Auxiliary request 1 - Amendments

5.1 The subject-matter of claims 1, 8 and 9 was objected to by the respondent under Article 123(2) EPC and Article 76(1) EPC.

5.2 Claims 1, 8 and 9 of auxiliary request 1 read:

"1. A freeze-dried composition comprising a live, attenuated flavivirus vaccine, human serum albumin (HSA), lactose, amorphous mannitol, and one or more buffer components."

"8. The composition of claim 1, wherein the pH of said composition is 7.9-8.1."

"9. A method of preparing a composition according to any one of claims 1 to 8, said method comprising subjecting a composition comprising a live, attenuated flavivirus vaccine, one or more stabilisers, lactose, amorphous mannitol, and one or more buffer components to a freeze-drying process."

5.3 The subject-matter of claim 1

5.3.1 A basis for the subject-matter of claim 1 can be found explicitly in claim 1, in combination with the subject-matter of dependent claims 2, 7 and 28 of the parent application WO2008/057550 A2 (D1). Claim 2 provides basis for the presence of HSA, claim 7 recites indeed the presence of mannitol and lactose as bulking agents, and claim 28 that the composition must be freeze-dried.

The amorphous state of mannitol is furthermore disclosed on page 8, lines 1-11 as a preferred embodiment of the invention and its incorporation in the subject-matter of claim 1 is, for this reason, derivable directly and unambiguously in combination with the remaining features of claim 1.

Consequently, the subject-matter of claim 1 is directly and unambiguously derivable from the parent application.

5.3.2 The same basis can be found in the patent application in the "aspects" on pages 31-35 corresponding to the claims of the parent application (see pages 31-35). The amorphous state of mannitol is also disclosed on page 8, lines 1-11 as a preferred embodiment.

Consequently, the subject-matter of claim 1 is directly and unambiguously derivable from the patent application.

5.4 The subject-matter of claim 8

The subject-matter of this claim finds a direct and explicit basis in dependent claim 29 of the parent application D1 which reads:

"29. The composition of claim 1, wherein the pH of said composition is 7.9-8.1".

The same disclosure is found on page 32, line 29 of the "aspects" of the patent application.

The fact that claim 29 does not refer back to claim 28 of the parent application, as argued by the respondent, does not effect the assessment of added-subject-matter. Claims 28 and 29 are dependent claims regarding two different and preferred aspects of the invention claimed with regard to claim 1, namely the freeze-dried state of the composition (claim 28) and the pH (claim 29). In the Board's view these preferred aspects can be incorporated individually or simultaneously in the subject-matter of claim 1 without infringing Article 76(1) EPC or Article 123(2) EPC.

5.5 The subject-matter of claim 9

This claim finds a basis in claim 54 of the parent application which reads:

"54. A method of preparing a therapeutic composition, said method comprising subjecting the composition of claim 1 or claim 30 to a freeze-drying process."

An explicit disclosure for the use of amorphous mannitol can be found on page 8, lines 1-11 as a preferred embodiment, and its inclusion in the method claim for preparing the composition of claim 1 is derivable directly and unambiguously from the parent application under Article 76(1) EPC. The same conclusions apply for the basis in the patent application under Article 123(2) EPC, (cf. page 8,

lines 1-11 of the application and the "aspects" on page 34, lines 9-10).

5.6 Consequently, auxiliary request 1 meets the requirements of Article 76(1) EPC and Article 123(2) EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of auxiliary request 1 filed with the statement of grounds of appeal dated 24 October 2019 and a description to be adapted thereto.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated