

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference P5706PC00	FOR FURTHER ACTION	See item 4 below
International application No. PCT/EP2016/082664	International filing date (<i>day/month/year</i>) 23 December 2016 (23.12.2016)	Priority date (<i>day/month/year</i>) 23 December 2015 (23.12.2015)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant VALNEVA AUSTRIA GMBH		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).
2. This REPORT consists of a total of 8 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Date of issuance of this report 26 June 2018 (26.06.2018) Authorized officer Nora Lindner e-mail: pct.team5@wipo.int
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2016/082664

International filing date (day/month/year)
23.12.2016

Priority date (day/month/year)
23.12.2015

International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/12 C07K14/005

Applicant
VALNEVA AUSTRIA GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Lewis, Birgit

Telephone No. +49 89 2399-0



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

see separate sheet

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-17</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-17</u>
Industrial applicability (IA)	Yes: Claims	<u>1-17</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item II

Priority

The present application claims 5 priorities.

The first priority (23.12.2015) is not valid because patent application EP15202585 does not relate to Zika virus at all.

The second priority is dated 18.03.2016. EP16161068 relates to Zika virus including an inactivated Zika virus but not to a genome of Zika strain H/PF/2013 (SEQ ID NO: 13 of the present application, accession number KJ776791.1). Example 2 discloses virus growth and purification including a concentration step by chilling in ice for 2 hours after adding 0.5-2mg of protamine sulfate and ultracentrifugation on sucrose gradients at 38.000 g for 18 hours followed by filtration through a 0.22 µm filter. Example 3 relates to virus inactivation by formaldehyde (0.018% at 22°C or 4°C). Example 4 tests the immunogenicity of the virus with aluminium hydroxyde adjuvant but does not show the outcome with regard to % seroprotection. From this concludes that the present set of claims (claims 1-15) can only partially claim this priority, i.e. only when SEQ ID NOs. are referred to that are disclosed in EP16161068. Finally, it is noted that EP16161068 does not relate to the subject-matter of present claims 16 and 17 (relating to '*PS at amounts too low to detect*'). Thus, claims 16 and 17 are not entitled to the priority of 18.03.2016.

The third and fourth priorities were both filed on 23-06-2016.

EP16176025 (PRIO3) is the first disclosure of the idea to use the successful JEV production system IXARIO® as basis for the production of Zika virus. This includes the use of protamine sulfate to remove contaminating DNA and surprisingly as well immature and non-infectious virus particles. The aspect of a purity with '*PS at amounts too low to detect*' is not explicitly mentioned. Therefore, this Authority is of the opinion that claims 16 and 17 are not entitled to the priority of 23-06-2016. PRIO3 also mentions for the first time the Zika strain H/PF/2013 (SEQ ID NO: 13 of the present application, SEQ ID NO: 13 in PRIO3). In order to demonstrate or confirm complete entitlement of present claims 1-15 to claim this priority, the applicant will be asked to identify for each SEQ ID NO: in the claims, the corresponding sequence in EP16176025. If this is not possible, this priority can only be partially claimed.

EP16176049 (PRIO4) deals with the purification of viruses, the examples being directed at Flaviviridae, Zika virus being one of them. Example 2 addresses virus purity after PS treatment. However, it does not relate to the subject-matter of present claims 16 and 17 (relating to '*PS at amounts too low to detect*'). Thus, this Authority is of the opinion that claims 16 and 17 are not entitled to the priority of 23-06-2016.

EP16182845 (PRIO5) of 04-08-2016 addresses the purity of the vaccine with regard to protamine salt and the introduction of an improved sucrose gradient. It will need to be discussed if the disclosures made in EP16182845 are sufficient to entitle the application to the priority date of 04-08-2016. At the moment, this Authority is of the opinion that claims 16 and 17 are not entitled to the priority of 04-08-2016.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- | | |
|----|---|
| D1 | B. D. COX ET AL: "Predicting Zika virus structural biology: Challenges and opportunities for intervention", ANTIVIRAL CHEMISTRY & CHEMOTHERAPY., vol. 24, no. 3-4, 1 August 2015 (2015-08-01), pages 118-126, XP055328128 |
| D2 | SRIVASTAVA A K ET AL: "A purified inactivated Japanese encephalitis virus vaccine made in vero cells", VACCINE, vol. 19, no. 31, 14 August 2001 (2001-08-14), pages 4557-4565, XP027321987 |
| D3 | US 8 765 148 B2 (WIZEL BENJAMIN ET AL) 1 July 2014 (2014-07-01) cited in the application |

D1 is regarded as being the prior art closest to the subject-matter of claim 1, and discloses that Zika virus is in the center of an emerging crisis that requires the development of a vaccine. D1 does not relate to an inactivated Zika virus vaccine. Hence, claims 1 and dependent and related claims 2-17 are new.

The problem to be solved by the present invention may be regarded as the provision of a safe and efficient Zika virus vaccine.

The solution to this problem proposed in claim 1 of the present application, namely an inactivated Zika virus vaccine that is able to confer seroprotection on at least 70% of subjects is not considered as involving an inventive step because from D1 it was already known that Zika virus belongs to the genus Flavivirus, like DENV or JEV (D1: p. 119, left col. §2). From D2 it was further known, how to produce a successful Flavivirus vaccine. Hence it is considered that the skilled person looking to develop a

Zika virus vaccine would turn to D2 to find a strategy for the development of a Flavivirus vaccine with a reasonable expectation of success and without the exercise of inventive skill, in order to solve the problem posed.

Having regard to the dependent and related claims, it appears that none of the claims relates to features that are not readily derivable from either document D1 or D2 or document D3 (which discloses the specific adjuvants of claims 13 and 14). This includes at least some of the sequences listed in claims 3 and 4 (note that D1 already states that many Zika virus sequences are known). Finally, it is noted that the sequences of claims 3 and 4 are not shown in the application as having any surprising effect with regard to the development of a vaccine. Hence, they are obvious selections that become available to the skilled person as soon as a new strain is identified and published, and cannot establish an inventive step.

Re Item VI

Certain documents cited

- | | |
|----|---|
| D4 | WO 2016/145149 A1 (THE US SECRETARY OF THE ARMY ON BEHALF OF THE WALTER REED ARMY INST OF) 15 September 2016 (2016-09-15) |
| D5 | WO 2017/009873 A1 (BHARAT BIOTECH INT LTD) 19 January 2017 (2017-01-19) |
| D6 | CN 105 749 268 A (SINOVAC RES & DEV CO LTD) 13 July 2016 (2016-07-13) |
| D7 | RAFAEL A. LAROCCA ET AL: "Vaccine protection against Zika virus from Brazil", NATURE, vol. 536, no. 7617, 28 June 2016 (2016-06-28), pages 474-478, XP055314483 |

WO 2016/145149 (D4) published on 15 September 2016 claims the priority of 11-03-2015. Its priority is, thus before the first priority of the present application.

It discloses a vaccine comprising at least on inactivated Dengue virus and one inactivated non-Dengue virus, for example Zika virus. The Flavivirus is grown in Vero cells, treated with protamine sulfate (2mg/ml), purified over a sucrose gradient and activated by formaldehyde treatment (5mM formalin at 22°C for 10 days). The vaccine is formulated with aluminium hydroxyde as adjuvant.

WO 2017/009873 (D5) published on 19 January 2017 claims the priority of 16 July 2015. Its priority is, thus before the first priority of the present application.

It discloses a vaccine comprising an inactivated Zika virus, f. ex. formaldehyde deactivated.

CN 105 749 268 (D6) published on 13 July 2016 claims the priority of 11 April 2016. Its priority is, thus before the priorities PRIO3 and PRIO4 of the present application.

It discloses an inactivated (f. ex. formaldehyde inactivated) Zika virus vaccine. Purification is done by sucrose gradient centrifugation and the vaccine may be formulated with an aluminium salt.

Larocca et al. (D7) published on 28 June 2016, discloses an inactivated Zika virus vaccine (PIV) which shows complete protection after one single administration in a mouse model. The strain used was Puerto Rican PRVABC59 Zika virus which is SEQ ID NO: 4 in the present application, it was passaged in Vero cells, formalin inactivated (0.05%, 22°C for 7 days) and formulated with alum.

Re Item VIII

Certain observations on the international application

Claim 1 does not meet the requirements of Article 6 PCT because the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved (*'seroprotection on at least 70% of subjects'*), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

It is clear from the description and the examples, that the advantageous immunogenicity and safety of the inactivated Zika virus vaccine lies in the preparation and purification and not in the strain selection or the corresponding genomes and E proteins. Hence, dependent claims 2-4 cannot provide features to overcome the clarity objection concerning claim 1.

Dependent claims 5-9 address the inactivation step. The respective features (*'inactivated by ...'*), however, relate to a method and cannot *per se* serve to characterize a product. Hence, also claims 5-9 are unclear in the sense of Article 6 PCT.

Dependent claims 10-15 relate to the adjuvant and/or excipient. Adjuvants and excipients often have an effect on the performance of a vaccine but they cannot serve to characterize the inactivated virus particle in order to overcome the objection concerning claim 1.

PATENT COOPERATION TREATY

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see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
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FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2016/082664

International filing date (day/month/year)
23.12.2016

Priority date (day/month/year)
23.12.2015

International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/12 C07K14/005

Applicant
VALNEVA AUSTRIA GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
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For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Lewis, Birgit

Telephone No. +49 89 2399-0



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
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 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
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5. Additional comments:

Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

see separate sheet

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-17</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-17</u>
Industrial applicability (IA)	Yes: Claims	<u>1-17</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item II

Priority

The present application claims 5 priorities.

The first priority (23.12.2015) is not valid because patent application EP15202585 does not relate to Zika virus at all.

The second priority is dated 18.03.2016. EP16161068 relates to Zika virus including an inactivated Zika virus but not to a genome of Zika strain H/PF/2013 (SEQ ID NO: 13 of the present application, accession number KJ776791.1). Example 2 discloses virus growth and purification including a concentration step by chilling in ice for 2 hours after adding 0.5-2mg of protamine sulfate and ultracentrifugation on sucrose gradients at 38.000 g for 18 hours followed by filtration through a 0.22 µm filter. Example 3 relates to virus inactivation by formaldehyde (0.018% at 22°C or 4°C). Example 4 tests the immunogenicity of the virus with aluminium hydroxyde adjuvant but does not show the outcome with regard to % seroprotection. From this concludes that the present set of claims (claims 1-15) can only partially claim this priority, i.e. only when SEQ ID NOs. are referred to that are disclosed in EP16161068. Finally, it is noted that EP16161068 does not relate to the subject-matter of present claims 16 and 17 (relating to '*PS at amounts too low to detect*'). Thus, claims 16 and 17 are not entitled to the priority of 18.03.2016.

The third and fourth priorities were both filed on 23-06-2016.

EP16176025 (PRIO3) is the first disclosure of the idea to use the successful JEV production system IXARIO® as basis for the production of Zika virus. This includes the use of protamine sulfate to remove contaminating DNA and surprisingly as well immature and non-infectious virus particles. The aspect of a purity with '*PS at amounts too low to detect*' is not explicitly mentioned. Therefore, this Authority is of the opinion that claims 16 and 17 are not entitled to the priority of 23-06-2016. PRIO3 also mentions for the first time the Zika strain H/PF/2013 (SEQ ID NO: 13 of the present application, SEQ ID NO: 13 in PRIO3). In order to demonstrate or confirm complete entitlement of present claims 1-15 to claim this priority, the applicant will be asked to identify for each SEQ ID NO: in the claims, the corresponding sequence in EP16176025. If this is not possible, this priority can only be partially claimed.

EP16176049 (PRIO4) deals with the purification of viruses, the examples being directed at Flaviviridae, Zika virus being one of them. Example 2 addresses virus purity after PS treatment. However, it does not relate to the subject-matter of present claims 16 and 17 (relating to '*PS at amounts too low to detect*'). Thus, this Authority is of the opinion that claims 16 and 17 are not entitled to the priority of 23-06-2016.

EP16182845 (PRIO5) of 04-08-2016 addresses the purity of the vaccine with regard to protamine salt and the introduction of an improved sucrose gradient. It will need to be discussed if the disclosures made in EP16182845 are sufficient to entitle the application to the priority date of 04-08-2016. At the moment, this Authority is of the opinion that claims 16 and 17 are not entitled to the priority of 04-08-2016.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- | | |
|----|---|
| D1 | B. D. COX ET AL: "Predicting Zika virus structural biology: Challenges and opportunities for intervention", ANTIVIRAL CHEMISTRY & CHEMOTHERAPY., vol. 24, no. 3-4, 1 August 2015 (2015-08-01), pages 118-126, XP055328128 |
| D2 | SRIVASTAVA A K ET AL: "A purified inactivated Japanese encephalitis virus vaccine made in vero cells", VACCINE, vol. 19, no. 31, 14 August 2001 (2001-08-14), pages 4557-4565, XP027321987 |
| D3 | US 8 765 148 B2 (WIZEL BENJAMIN ET AL) 1 July 2014 (2014-07-01) cited in the application |

D1 is regarded as being the prior art closest to the subject-matter of claim 1, and discloses that Zika virus is in the center of an emerging crisis that requires the development of a vaccine. D1 does not relate to an inactivated Zika virus vaccine. Hence, claims 1 and dependent and related claims 2-17 are new.

The problem to be solved by the present invention may be regarded as the provision of a safe and efficient Zika virus vaccine.

The solution to this problem proposed in claim 1 of the present application, namely an inactivated Zika virus vaccine that is able to confer seroprotection on at least 70% of subjects is not considered as involving an inventive step because from D1 it was already known that Zika virus belongs to the genus Flavivirus, like DENV or JEV (D1: p. 119, left col. §2). From D2 it was further known, how to produce a successful Flavivirus vaccine. Hence it is considered that the skilled person looking to develop a

Zika virus vaccine would turn to D2 to find a strategy for the development of a Flavivirus vaccine with a reasonable expectation of success and without the exercise of inventive skill, in order to solve the problem posed.

Having regard to the dependent and related claims, it appears that none of the claims relates to features that are not readily derivable from either document D1 or D2 or document D3 (which discloses the specific adjuvants of claims 13 and 14). This includes at least some of the sequences listed in claims 3 and 4 (note that D1 already states that many Zika virus sequences are known). Finally, it is noted that the sequences of claims 3 and 4 are not shown in the application as having any surprising effect with regard to the development of a vaccine. Hence, they are obvious selections that become available to the skilled person as soon as a new strain is identified and published, and cannot establish an inventive step.

Re Item VI

Certain documents cited

- | | |
|----|---|
| D4 | WO 2016/145149 A1 (THE US SECRETARY OF THE ARMY ON BEHALF OF THE WALTER REED ARMY INST OF) 15 September 2016 (2016-09-15) |
| D5 | WO 2017/009873 A1 (BHARAT BIOTECH INT LTD) 19 January 2017 (2017-01-19) |
| D6 | CN 105 749 268 A (SINOVAC RES & DEV CO LTD) 13 July 2016 (2016-07-13) |
| D7 | RAFAEL A. LAROCCA ET AL: "Vaccine protection against Zika virus from Brazil", NATURE, vol. 536, no. 7617, 28 June 2016 (2016-06-28), pages 474-478, XP055314483 |

WO 2016/145149 (D4) published on 15 September 2016 claims the priority of 11-03-2015. Its priority is, thus before the first priority of the present application.

It discloses a vaccine comprising at least on inactivated Dengue virus and one inactivated non-Dengue virus, for example Zika virus. The Flavivirus is grown in Vero cells, treated with protamine sulfate (2mg/ml), purified over a sucrose gradient and activated by formaldehyde treatment (5mM formalin at 22°C for 10 days). The vaccine is formulated with aluminium hydroxyde as adjuvant.

WO 2017/009873 (D5) published on 19 January 2017 claims the priority of 16 July 2015. Its priority is, thus before the first priority of the present application.

It discloses a vaccine comprising an inactivated Zika virus, f. ex. formaldehyde deactivated.

CN 105 749 268 (D6) published on 13 July 2016 claims the priority of 11 April 2016. Its priority is, thus before the priorities PRIO3 and PRIO4 of the present application.

It discloses an inactivated (f. ex. formaldehyde inactivated) Zika virus vaccine. Purification is done by sucrose gradient centrifugation and the vaccine may be formulated with an aluminium salt.

Larocca et al. (D7) published on 28 June 2016, discloses an inactivated Zika virus vaccine (PIV) which shows complete protection after one single administration in a mouse model. The strain used was Puerto Rican PRVABC59 Zika virus which is SEQ ID NO: 4 in the present application, it was passaged in Vero cells, formalin inactivated (0.05%, 22°C for 7 days) and formulated with alum.

Re Item VIII

Certain observations on the international application

Claim 1 does not meet the requirements of Article 6 PCT because the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved (*'seroprotection on at least 70% of subjects'*), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

It is clear from the description and the examples, that the advantageous immunogenicity and safety of the inactivated Zika virus vaccine lies in the preparation and purification and not in the strain selection or the corresponding genomes and E proteins. Hence, dependent claims 2-4 cannot provide features to overcome the clarity objection concerning claim 1.

Dependent claims 5-9 address the inactivation step. The respective features (*'inactivated by ...'*), however, relate to a method and cannot *per se* serve to characterize a product. Hence, also claims 5-9 are unclear in the sense of Article 6 PCT.

Dependent claims 10-15 relate to the adjuvant and/or excipient. Adjuvants and excipients often have an effect on the performance of a vaccine but they cannot serve to characterize the inactivated virus particle in order to overcome the objection concerning claim 1.