

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: see form PCT/ISA/220

PCT

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/IB2022/053995	International filing date (day/month/year) 29.04.2022	Priority date (day/month/year) 03.05.2021
International Patent Classification (IPC) or both national classification and IPC INV. A61K39/12 A61K9/127 A61P31/16		
Applicant PFIZER INC.		

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:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Heder, Andreas Telephone No. +31 70 340-0
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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 43bis.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 13ter.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 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.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 43bis.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 43bis.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:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 34-36

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for the whole application or for said claims Nos. 34-36

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-33

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>1-33</u> |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | <u>1-33</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-33</u> |
| | No: Claims | |
2. Citations and explanations
- see separate sheet**

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)
and / or
2. Non-written disclosures (Rules 43*bis*.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 IV

Lack of unity of invention

The application relates to several inventions:

Invention 1: claims 1-33

Immunogenic composition comprising at least two RNA coding for influenza virus antigen formulated in an LNP, and use

Invention 2: claims 34-36

Method of purifying in vitro transcribed RNA coding for influenza antigen, by ultrafiltration and diafiltration

Rule 13.1 PCT stipulates that when an application relates to a group of inventions, said groups of inventions have to be so linked as to form a general inventive concept. Rule 13.2 PCT specifies that the requirement of unity is fulfilled only when the separate inventions involve one or more of the same or corresponding special technical features. "Special technical features" are those technical features that define a contribution which each of the claimed inventions makes over the prior art.

- 1) The common matter of the separate inventions: The only technical feature linking potential inventions 1 and 2 is that they both relate to RNA coding for influenza virus antigen.
- 2) Examination whether any of the common matter is special: RNA coding for influenza virus antigen is not novel and inventive (see, e.g., D1: Buschmann 2021, Vaccines 9:65, D2: Zhuang 2020, Vaccines 8:123).

Therefore, the feature "RNA coding for influenza virus antigen" is not a special technical feature in the sense of Rule 13.2 PCT. This means that the groups of inventions identified above are not united by providing novel and inventive solutions to one common technical problem. Consequently, the present application lacks unity, and the separate groups of potential inventions have been divided as indicated.

Only invention 1 has been searched.

The present opinion is restricted to invention 1.

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 BUSCHMANN MICHAEL D. ET AL: "Nanomaterial Delivery Systems for mRNA Vaccines", VACCINES, vol. 9, no. 1, 1 January 2021 (2021-01-01), page 65, XP055927791, CH ISSN: 2076-393X, DOI: 10.3390/vaccines9010065
- D2 Zhuang Xinyu ET AL: "mRNA Vaccines Encoding the HA Protein of Influenza A H1N1 Virus Delivered by Cationic Lipid Nanoparticles Induce Protective Immune Responses in Mice", Vaccines, vol. 8, no. 1, 10 March 2020 (2020-03-10), page 123, XP055941881, DOI: 10.3390/vaccines8010123
- D3 FREYN ALEC W. ET AL: "A Multi-Targeting, Nucleoside-Modified mRNA Influenza Virus Vaccine Provides Broad Protection in Mice", MOLECULAR THERAPY, vol. 28, no. 7, 1 July 2020 (2020-07-01), pages 1569-1584, XP055900397, US ISSN: 1525-0016, DOI: 10.1016/j.ymthe.2020.04.018
- D4 POLACK FERNANDO P. ET AL: "Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine", THE NEW ENGLAND JOURNAL OF MEDICINE, vol. 383, no. 27, 31 December 2020 (2020-12-31), pages 2603-2615, XP055820495, US ISSN: 0028-4793, DOI: 10.1056/NEJMoa2034577 Retrieved from the Internet: URL: https://pro.biontech.de/files/Polack_F_et_al.pdf

D1 Buschmann 2021 *** page 13 last para., Tab. 1 *** pub. 19.01.21, lipid delivery of mRNA vaccines, ALC-0315, BNT162b2...Ref. 40, H3N2-HA mRNA vaccine...ref. 130

D2 Zhuang 2020 *** chapter 2.2, 2.3 2.7, 5, Fig. 1 *** ref.130 in Buschmann, influenza H3N2 mRNA/LNP vaccine

D3 Freyn 2020 **** Abstract, Fig. 1-5, page 1579 *** mRNA/LNP influenza H1N1 vaccine, Ag: HA stalk, NA, M2 + NP

D4 BNT162b2

Disclosure of the application

1 mRNA vaccine coding for HA of two or more influenza subtypes

Re: medical use

- 2 Claim 33 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment. Patentability, in particular novelty and inventive step, of said claim has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the substance or composition.

Re: novelty

- 3 The presently available prior art does not disclose compositions of two or more mRNA coding for HA of two or more influenza subtypes. The present claims are therefore formally novel.

Re: inventive step

- 4 The present claims lack inventive step. The H3N2-HA encoding vaccine referred to in D1 (page 13/14) is taken as closest prior art. This vaccine is disclosed in further detail in reference 130 of D1 (herein cited as D2). The difference is that claim 1 requires the presence of two mRNA molecules coding for HA of different subtypes. The technical problem is: the provision of an alternative influenza vaccine. It is common knowledge that seasonal influenza vaccines should at least be trivalent, or quadrivalent, corresponding to current circulating influenza subtypes. An mRNA vaccine having several mRNA molecules coding for different antigenic proteins (in this case, HA, M2, NA, and NP of H1N1), is disclosed in D3. Consequently, it was a matter of routine to modify the closest prior art by including HA-coding mRNA of several subtypes, and there was motivation to do so. In the alternative, D3 could also serve as closest prior art, leading to essentially the same conclusion.

- 5 Further variations referred to in the dependent claims, such as LNP formulation, cap structure, 5' and 3' UTR, polyA, etc., are disclosed, e.g., in D1 and D3, as well, and are within the range of alternatives that anyone faced with the technical problem would have tested. It is noted in particular that the exemplified LNP formulation appears to be identical with that of the BNT162b2 COVID19 vaccine of Biontech/Pfizer which was in public use in the EU and USA at the time of priority (see also D4). The composition of the LNP in BNT162b2 is described in further detail in intermediate document D5 (see item VI) which is merely cited to confirm that the public use of BNT162b2 at the time of priority, implicitly disclosed already at that time said LNP formulation.
- 6 An unexpected technical effect is not seen because the examples merely show immune reactions elicited in vaccinated mice which were predictable. No challenge experiments have been done. For essentially the same reasons, all present claims lack inventive step.

Re Item VI

Certain documents cited

D5 CHAUDHARY NAMIT ET AL: "mRNA vaccines for infectious diseases: principles, delivery and clinical translation", NATURE REVIEWS DRUG DISCOVERY, NATURE PUBLISHING GROUP, GB, vol. 20, no. 11, 25 August 2021 (2021-08-25), pages 817-838, XP037602785, ISSN: 1474-1776, DOI: 10.1038/S41573-021-00283-5 [retrieved on 2021-08-25]

D6 WO 2022/043551 A2 (CUREVAC AG [DE]) 3 March 2022 (2022-03-03)

D5 publ. 25.08.2021 P-doc mRNA vaccine, structure & formulation, incl. ALC-0315, ALC-0159

D6 *** SEQ ID 26944, SEQ ID 26945 *** P-doc, IBIS, CureVac, SEQ ID 26944 100% id w/ SEQ 1 of appl (1-52:2-53), SEQ ID 26945 100% id w/ SEQ 2 of appl (1-295:993-1287), SEQ ID NO 26945 100% id w/ SEQ 3 of appl (1-110:1288-1397)

D5 is an intermediate document which would become prior art in case the priority claim should turn out not to be valid. D5 is cited to confirm the LNP formulation of BNT162b2 which was already in public use at the time of priority.

D6 is an intermediate document disclosing SEQ ID NO: 1, 2, and 3.

Re Item VIII

Certain observations on the international application

Reference to "*fragment[s]*" and "*variant[s]*" in claims 1, 2, and throughout the claim set lacks clarity. The same applies to "*about*" in claim 8, and "*modified*" in claim 9. In claim 17, it is not clear what "*purity*" means. Also, in a mixture of four mRNA, not all of them can be present at an abundance of 85% (see claim 17, Arts. 5 and 6 PCT).

Furthermore, dependent claim 2 is broader than independent claim 1 because it adds "*variant[s]*" which are outside the scope of claim 1.