PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2017/048174	23.08.2017	26.08.2016

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/14 A61K38/48 A61K9/16 A61K9/00 A61K47/34 A61K47/36 ADD. A61K9/113

Applicant
AKINA, 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 43*bis*.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 notifed the International Bureau under Rule 66.1*bis*(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:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Palma, Vera Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2017/048174

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. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-4, 6-8, 10-24, 29, 30, 33-35, 37-44, 46-49
	No:	Claims	1, 5, 9, 25-28, 31, 32, 36, 45, 50, 51
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-51
Industrial applicability (IA)	Yes:	Claims	1-51
	No:	Claims	

2. Citations and explanations

see separate sheet

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 V

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

1 Method of treatment

1.1 Claims 50 and 51 relate to subject-matter considered by this Authority to be covered by the provision 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.

Although claims 50 and 51 are directed to a method of treatment of the human/ animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2 Cited documents

2.1 Reference is made to the following documents:

D1 US 2010/310669 A1 (PAILLARD ALEXANDRA [FR] ET AL) 9 December 2010 (2010-12-09)

D2 JIANJUN WANG ET AL: "Stabilization and encapsulation of human immunoglobulin G into biodegradable microspheres",
JOURNAL OF COLLOID AND INTERFACE SCIENCE,
vol. 271, no. 1, 1 March 2004 (2004-03-01), pages 92-101, XP055092590,
ISSN: 0021-9797, DOI: 10.1016/j.jcis.2003.08.072

D3 US 6 312 708 B1 (DONOVAN STEPHEN [US]) 6 November 2001 (2001-11-06)cited in the application

D4 LU YING ET AL: "Microparticles produced by the hydrogel template method for sustained drug delivery", INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER, AMSTERDAM, NL, vol. 461, no. 1, 11 December 2013 (2013-12-11), pages 258-269, XP028810400, ISSN: 0378-5173, DOI: 10.1016/J.IJPHARM.2013.11.058 cited in the application

D5 US 2016/175410 A1 (HUNT TERRENCE J [US]) 23 June 2016 (2016-06-23)

3 **Novelty (Art. 33(2) PCT)**

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 5, 9, 25-28, 31, 32, 36, 45, 50 and 51 is not new in the sense of Article 33(2) PCT.

3.2 Document D1 discloses a method of formulating polymer microparticles for the controlled delivery of encapsulated proteins, comprising the steps of (whole document; [0026]; [0099]; [0101]; [0116]):

a) dissolving protein (e.g. lysozyme) in an aqueous solution;

b) precipitating said protein;

c) glycofurol ([0101] is seen as a wash solvent for the precipitant;

d) dispersing the precipitant in a solution containing dichloromethane and PLGA to form a polymer-protein dispersion;

e) preparing polymer microparticles encapsulating the protein from the polymer-protein dispersion.

A pharmaceutical composition comprising said polymer microparticles encapsulating protein, as well as its use in the treatment of diseases and disorders, are also disclosed in D1.

The subject-matter of claims 1, 5, 9, 25-28, 32, 36 and 50 is therefore not novel over D1 (Art. 33(2) PCT).

3.3 Document D2 discloses a method of formulating polymer microparticles for the controlled delivery of encapsulated proteins, comprising the steps of (page 93; page 96, right-hand column; page 98, right-hand column, first paragraph; page 99, left-hand column, last paragraph):

a) dissolving protein (IgG) in an aqueous solution;

b) precipitating said protein with zinc acetate;

c) dispersing the precipitant in a solution containing dichloromethane and PLGA to form a polymer-protein dispersion;

d) preparing polymer microparticles encapsulating the protein from the polymer-protein dispersion.

A pharmaceutical composition comprising said polymer microparticles encapsulating protein, as well as its use in the treatment of diseases and disorders, are also disclosed in D2.

The subject-matter of claims 1, 5, 9, 25-27, 31, 36 and 50 is therefore not novel over D2 (Art. 33(2) PCT).

3.4 Document D3 discloses (col. 8, lines 22-44; col. 22, lines 9-65; example 1): a pharmaceutical composition, comprising a plurality of polymer microparticles encapsulating botulinum toxin such as botulinum toxin type A.

The following is noted: where a claim defines a product in terms of the process by which the product is made, the claim should be construed as a claim to the product per se that possesses the characteristics derived from the manufacturing process stated in the claim. Therefore, the patentability of a product defined by a product-by-process claim does not depend on its method of production. A product is not rendered novel merely by the fact that it is produced by means of a new process. If the product in such a claim is the same as, or obvious from, a product described in an item of prior art, the claim is unpatentable even though the product described in the item of prior art was made by a different process (see PCT Guidelines, Appendix A5.26[1]).

In this case, it does not therefore appear that the product defined by claim 36 is novel over document D3.

Moreover, D3 discloses said pharmaceutical formulation for use in treating diseases or disorders such blepharospasm or muscle spasms (col. 14, lines 30-34; col. 18, lines 38-39).

The subject-matter of claims 36, 45, 50 and 51 is therefore not novel over D3 (Art. 33(2) PCT).

3.5 In view of documents D1-D3, the subject-matter of claims 1, 5, 9, 25-28, 31, 32, 36, 45, 50 and 51 is therefore not novel (Art. 33(2) PCT).

4 Inventive Step (Art. 33(3) PCT)

4.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-51 does not involve an inventive step in the sense of Article 33(3) PCT.

4.2 Lacking novelty, claims 1, 5, 9, 25-28, 31, 32, 36, 45, 50 and 51 are also not inventive (Art. 33(3) PCT).

4.3 D3, which is seen as the most relevant state of the art in relation to independent claim 47, discloses (col. 8, lines 22-44; col. 22, lines 9-65; example 1): a pharmaceutical composition, comprising a plurality of polymer microparticles encapsulating botulinum toxin and albumin.

The subject-matter of claim 47 differs from D1 in that the plurality of botulinum toxin/albumin are zinc-precipitated.

The effect of this difference is to overcome loss of activity of protein active agents associated with denaturation of water-dissolved proteins that occurs in the interface between water and organic solvent (cf. description page 20, lines 8-11). The objective technical problem can thus be formulated as the provision of a composition comprising botulinum toxin microparticles, with little loss of biological activity.

D3 suggests the use of multivalent metal cations, preferably Zn++, as a stabilizer for botulinum toxin, avoiding a potential loss of activity (col. 22, lines 9-65; col. 23, lines 57-65). Thus, taking D3 alone, the skilled person would be prompted to modify the microparticles disclosed therein, and would arrive to the subject-matter of claim 47 without the exercise of inventive step (Art. 33(3) PCT).

4.4 Dependent claims 2-4, 6-8, 10-24, 29, 30, 33-35, 37-44, 46, 48 and 49 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

The reasons therefor are that the additional features of the said claims are a combination of features obvious to the man skilled in the art in consideration of the disclosure of the prior art named in the present proceedings, or they concern only minor modifications which lie within the normal practice of the man skilled in the art.

E.g., microparticles obtained via the micropatterned hydrogel template method, wherein the micropatterned template comprises poly(vinyl alcohol), are known from D4.

Compositions comprising thermosensitive polymers for sustained release of botulinum toxin are known from D5.

In the absence of a surprising effect, dependent claims 2-4, 6-8, 10-24, 29, 30, 33-35, 37-44, 46, 48 and 49 therefore lack an inventive step (Art. 33(3) PCT).

5 Industrial Applicability (Art. 33(4) PCT)

5.1 The subject-matter of claims 1-51 is industrially applicable in the sense of Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

6 Clarity (Art. 6 PCT) and Sufficiency of Disclosure (Art. 5 PCT)

6.1 The application does not meet the requirements of Article 5 PCT, because the invention is not sufficiently disclosed for a skilled person to be able to execute it. The requirements of Article 6 PCT also are not met, because the subject-matter of the claims is not supported by the description.

The requirements of Article 5 PCT are met if the application discloses the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The requirements of Article 5 PCT are met if:

(a) at least one way is clearly indicated in the patent specification enabling the skilled person to carry out the invention, and

(b) the disclosure allows the invention to be performed in the whole area claimed without undue burden, applying common general knowledge. The description must contain a technical concept fit for generalisation, there must not be an undue burden in carrying out the invention throughout the whole area claimed.

The present invention does not meet the requirements of point (b). The skilled person is given a great number of possibilities among which he has to choose, namely among the type of protein, the type of precipitating agent, the type of wash solvent, the type of polymer, the type of polymer solvent, etc.

The description, on page 14, lines 9-15 and page 17, line 29 - page 18, line 27 gives all possible proteins; on page 22, lines 24-29 all possible precipitants; on page 25, lines 5-10 all possible wash solvents; on page 6, lines 23-29, page 10, line 29 - page 11, line 5 and page 12, line 27 - page 13, line 6 all possible polymers; on page 30, lines 15-20 all possible polymer solvents.

The description resembles therefore a catalogue with a large number of possible alternatives, which all may have an impact on the properties of the microparticle such as biological activity of the protein. They cannot be combined just by routine experimentation giving the desired result.

The patent application does not disclose a technical concept fit for generalisation which makes available to the person skilled in the art the host of variants encompassed in the subject-matter of the claims.

Consequently, the claims encompass subject-matter which is not sufficiently disclosed as it cannot be performed without undue burden (Art. 5 PCT). The application provides support for only a limited number of polymer microparticles which are represented in the examples 1-10, wherein the protein is a combination of botulinum toxin and albumin, the precipitant is zinc chloride and the polymer is PLGA (Art. 6 PCT).

6.2 The application does not meet the requirements of Article 6 PCT, because claims 10, 21-23, 26-28 and 51 are not clear.

6.3 Claim 10 mentions a "non-solvent" when referring to claim 9; however, claim 9 indicates a "non-polymer solvent". This discrepancy renders claim 10 unclear (Art. 6 PCT).

Claim 26 mentions "lends" as a possible biodegradable polymer. It is not clear what is meant by said "lends", a definition not known in the art (Art. 6 PCT).

Claim 51 specifies some diseases and disorders twice, namely hemorrhagic cystitis and interstitial cystitis/ painful bladder syndrome (IC/PBS), rendering the claim unclear (Art. 6 PCT).

The term "about" used in claims 21-23, 27 and 28 is an approximate term and leaves the reader in doubt as to the exact meaning of the technical features qualified by such term, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).