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(54) Title: INFLUENZA VACCINES WITH REDUCED AMOUNTS OF SQUALENE

(57) Abstract: Influenza vaccines include hemagglutinin from at least one influenza A virus strain and at least one influenza B virus strain. They also include an oil-in-water emulsion adjuvant with submicron oil droplets, comprising squalene. In some embodiments the hemagglutinin concentration is $>12\mu\text{g/ml}$ per strain. In some embodiments the squalene concentration is $<19\text{mg/ml}$. In some embodiments the vaccine is mercury-free. In some embodiments the vaccine has a unit dose volume between 0.2-0.3mL. In some embodiments the squalene concentration is 9.75mg/mL or 4.88mg/mL. In some embodiments the vaccine includes antigens from two influenza A virus strains and two influenza B virus strains.



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INTERNATIONAL SEARCH REPORT

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PCT/IB2010/000312

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K39/145 A61K39/295 A61P31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/128939 A1 (GLAXOSMITHKLINE BIOLOG SA [BE]; BALLOU WILLIAM RIPLEY [BE]; HANON EMMA) 30 October 2008 (2008-10-30) the whole document	1,8-12, 15,16, 19,20, 22,23
X	WO 2008/068631 A2 (NOVARTIS AG [CH]; TSAI THEODORE F [US]) 12 June 2008 (2008-06-12) the whole document	1,5, 8-12,15, 16,19, 20,22,23
X	WO 2008/043774 A1 (GLAXOSMITHKLINE BIOLOG SA [BE]; BALLOU WILLIAM RIPLEY JR [BE]; HANON E) 17 April 2008 (2008-04-17) the whole document	1,5, 8-12,15, 16,19, 20,22,23
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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/052155 A2 (NOVARTIS VACCINES & DIAGNOSTIC [IT]; CONTORNI MARIO [IT]) 10 May 2007 (2007-05-10) the whole document	1,5, 8-12,15, 16,19, 20,22,23
A	SCHNEIDER M M ET AL: "Antibody response to tetravalent influenza subunit vaccine in patients infected with human immunodeficiency virus type 1" INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, ELSEVIER SCIENCE, AMSTERDAM, NL LNKD- DOI:10.1016/0924-8579(95)00038-0, vol. 6, no. 4, 1 April 1996 (1996-04-01), pages 195-200, XP002493637 ISSN: 0924-8579 the whole document	1,5, 8-12,15, 16,19, 20,22,23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2010/000312

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1(completely); 5, 8-12, 15, 16, 19, 20, 22, 23(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1(completely); 5, 8-12, 15, 16, 19, 20, 22,
23(partially)

An influenza virus vaccine comprising: (i) hemagglutinin from at least two influenza A virus strains and at least two influenza B virus strains; and (ii) an oil-in-water emulsion adjuvant with submicron oil droplets, comprising squalene, where the squalene concentration is <19 mg/ml; and subject-matter related thereto.

2. claims: 2(completely); 5, 8-12, 14, 16-23(partially)

An influenza virus vaccine comprising: (i) hemagglutinin from at least one influenza A virus strain and at least one influenza B virus strain, wherein the hemagglutinin concentration is >12 [micro]g/ml per strain; and (ii) an oil-in-water emulsion adjuvant with submicron oil droplets, comprising squalene, where the squalene concentration is <19 mg/ml; and subject-matter related thereto.

3. claims: 3(completely); 5, 8-12, 14, 16-23(partially)

A mercury-free influenza virus vaccine comprising: (i) hemagglutinin from at least one influenza A virus strain and at least one influenza B virus strain; and (ii) an oil-in-water emulsion adjuvant with submicron oil droplets, comprising squalene, where the squalene concentration is <19 mg/ml; and subject-matter related thereto.

4. claims: 4(completely); 5, 8-14, 16-23(partially)

An influenza virus vaccine comprising: (i) hemagglutinin from at least one influenza A virus strain and at least one influenza B virus strain; and (ii) an oil-in-water emulsion adjuvant with submicron oil droplets, comprising squalene, where the squalene concentration is 9.75 mg/mL or 4.88 mg/mL; and subject-matter related thereto.

5. claims: 6, 7(completely); 8-13, 15, 17, 19, 21-23(partially)

An influenza virus vaccine having a unit dose volume between 0.2-0.3 ml, wherein the vaccine comprises: (i) hemagglutinin from at least one influenza A virus strain and at least one influenza B virus strain; and (ii) an oil-in-water emulsion adjuvant with submicron oil droplets, comprising squalene, where the squalene concentration is <19 mg/ml or 19.5 mg/ml, 9.75 mg/ml or 4.88 mg/ml; and subject-matter related thereto.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2010/000312

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008128939	A1	30-10-2008	AR 066405 A1 19-08-2009
		AU 2008240761 A1 30-10-2008	
		CA 2683075 A1 30-10-2008	
		CN 101678096 A 24-03-2010	
		CR 11122 A 22-03-2010	
		EA 200901161 A1 30-06-2010	
		JP 2010524883 T 22-07-2010	
		KR 20100009576 A 27-01-2010	
		PE 01462009 A1 23-03-2009	
		US 2009136543 A1 28-05-2009	
		US 2010189741 A1 29-07-2010	
WO 2008068631	A2	12-06-2008	AU 2007330494 A1 12-06-2008
		CA 2671629 A1 12-06-2008	
		CN 101553252 A 07-10-2009	
		EA 200900784 A1 30-12-2009	
		EP 2121011 A2 25-11-2009	
WO 2008043774	A1	17-04-2008	AU 2007306381 A1 17-04-2008
		CA 2664619 A1 17-04-2008	
		CR 10726 A 25-05-2009	
		EA 200900350 A1 30-10-2009	
		JP 2010505907 T 25-02-2010	
		KR 20090066323 A 23-06-2009	
		US 2010183667 A1 22-07-2010	
WO 2007052155	A2	10-05-2007	AU 2006310163 A1 10-05-2007
		CA 2628206 A1 10-05-2007	
		EP 1951302 A2 06-08-2008	
		JP 2009514850 T 09-04-2009	
		US 2009304742 A1 10-12-2009	