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BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,

HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM,
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MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
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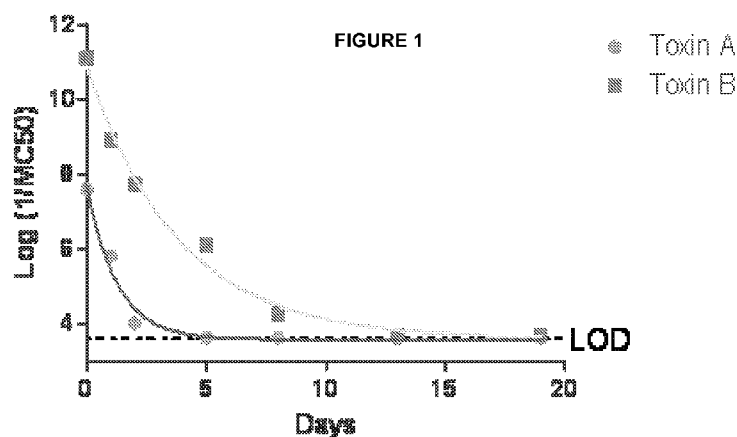
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(88) Date of publication of the international search report:

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(54) Title: TOXOID, COMPOSITIONS AND RELATED METHODS



(57) Abstract: The disclosure relates to generally to the field of toxin inactivation. More specifically, it relates to clostridial toxins, methods of inactivating these toxins and compositions (e.g., vaccines) comprising toxoids (e.g., produced by these methods). Provided are methods of producing a *C. difficile* toxoid comprising inactivating a *C. difficile* toxin with formaldehyde. Toxoids prepared by these methods are stable at high temperature (e.g., 37°C) and remain non-cytotoxic with minimal residual formaldehyde.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/029035

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.:

1-4, 31-36(completely); 9, 10, 14-18(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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/029035

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/08 A61K47/00
ADD.

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 practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, Sequence Search, 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 99/20304 A1 (ORAVAX INC [US]) 29 April 1999 (1999-04-29) page 18	1-4,9, 10, 14-18, 31-36
X	WO 2005/058353 A1 (ACAMBIS INC [US]; THOMAS WILLIAM D JR [US]; GIANNASCA PAUL J [US]; ZHA) 30 June 2005 (2005-06-30) page 14 - page 18 ----- -/--	1-4,9, 10, 14-18, 31-36



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 application or patent 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

Date of the actual completion of the international search

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08/10/2014

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/029035

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	N. G. ANOSOVA ET AL: "Systemic antibody responses induced by a two-component Clostridium difficile toxoid vaccine protect against C. difficile-associated disease in hamsters", JOURNAL OF MEDICAL MICROBIOLOGY, vol. 62, no. Pt 9, 21 March 2013 (2013-03-21), pages 1394-1404, XP055122429, ISSN: 0022-2615, DOI: 10.1099/jmm.0.056796-0 the whole document -----	1-4,9, 10, 14-18, 31-36
A	LORNA E. LANCASTER ET AL: "An assessment of thermal stability of Clostridium difficile toxoid formulations", HUMAN VACCINES, vol. 7, no. 2, 1 February 2011 (2011-02-01), pages 202-210, XP055122446, ISSN: 1554-8600, DOI: 10.4161/hv.7.2.13986 the whole document -----	1-4,9, 10, 14-18, 31-36
A	KOTLOFF K ET AL: "Safety and immunogenicity of increasing doses of a clostridium difficile toxoid administrated to healthy adults", INFECTION AND IMMUNITY, AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 69, no. 2, 1 February 2001 (2001-02-01), pages 988-995, XP002986519, ISSN: 0019-9567, DOI: 10.1128/IAI.69.2.988-995.2001 the whole document -----	1-4,9, 10, 14-18, 31-36

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/029035

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9920304	A1	29-04-1999	
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		WO 2005058353 A1	30-06-2005

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-4, 31-36(completely); 9, 10, 14-18(partially)

Method for inactivating C. difficile toxins A or B by incubating 0.15%-0.5% formaldehyde (w/v) at about 17-32 °C for about 21 days

2. claims: 5-8, 11-13, 19-30(completely); 9, 10, 14-18(partially)

Method for preparing an immunogenic composition comprising toxoid A and toxoid B of C. diffiicle by adding a composition comprising a residual amount of formaldehyde
