

PATENT COOPERATION TREATY

From the:
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)
13 January 2016

Applicant's or agent's file reference
P-71-PCT-7

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/IB2015/057682

International filing date (*day/month/year*)

08 October 2015

Priority date (*day/month/year*)

09 October 2014

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

**C07H 3/06 (2006.01) C08B 37/00 (2006.01) C07K 14/33 (2006.01) C07K 14/34 (2006.01) A61K 39/02 (2006.01)
A61P 31/04 (2006.01)**

Applicant

MSD WELLCOME TRUST HILLEMANN LABORATORIES PVT. LTD.

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 <i>bis</i> .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 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 66.1*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

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Date of completion of this opinion

13 January 2016

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/IB2015/057682

Box No. I Basis of this 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 (under 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 filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☐ in electronic form
 - b. (time)
 - ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
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 in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY		International Application No. PCT/IB2015/057682									
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 <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%; vertical-align: top;"> Novelty (N) </td> <td style="width: 50%; vertical-align: top;"> Claims 1-13 Claims 14-15 </td> <td style="width: 20%; text-align: center; vertical-align: top;"> YES NO </td> </tr> <tr> <td style="vertical-align: top;"> Inventive step (IS) </td> <td style="vertical-align: top;"> Claims NONE Claims 1-15 </td> <td style="text-align: center; vertical-align: top;"> YES NO </td> </tr> <tr> <td style="vertical-align: top;"> Industrial applicability (IA) </td> <td style="vertical-align: top;"> Claims 1-15 Claims NONE </td> <td style="text-align: center; vertical-align: top;"> YES NO </td> </tr> </table>			Novelty (N)	Claims 1-13 Claims 14-15	YES NO	Inventive step (IS)	Claims NONE Claims 1-15	YES NO	Industrial applicability (IA)	Claims 1-15 Claims NONE	YES NO
Novelty (N)	Claims 1-13 Claims 14-15	YES NO									
Inventive step (IS)	Claims NONE Claims 1-15	YES NO									
Industrial applicability (IA)	Claims 1-15 Claims NONE	YES NO									
2. CITATIONS AND EXPLANATIONS: <u>CITATIONS</u> D1: WO 2005/003775 A2 (INSTITUT PASTEUR et al.) 13 January 2005 D2: Wright K et al. 'Preparation of synthetic glycoconjugates as potential vaccines against <i>Shigella flexneri</i> serotype 2a disease' Organic Biomolecular Chemistry, 2004, Vol 2, page 1518-1527 D3: Bélot F et al. 'Synthesis of two linear PADRE conjugates bearing a deca- or pentadecasaccharide B epitope as potential synthetic vaccines against <i>Shigella flexneri</i> serotype 2a infection' Chemistry - A European Journal, 2005, Vol 11, page 1625-1635 <u>NOVELTY (N)</u> The subject matter of claims 14 and 15 is not new and does not meet the requirements of article 33 (2) of the PCT with regard to novelty. This claim is directed to the product of a process and is construed as a claim to the product per se. A product is not rendered novel merely by the fact that it is produced by means of a new process. D1 discloses oligosaccharide-protein conjugates 501-503, 401, 601-602, 708-713, 801. Conjugate 501 for example, has a oligosaccharide to protein ratio of approximately 0.33 (w/w). D2 discloses oligosaccharide-protein conjugates 1-3 [scheme 5]. Conjugate 1 for example, has a oligosaccharide to protein ratio of approximately 0.33 (w/w). Therefore claims 14 and 15 are not novel in light of the disclosures of any of D1 to D2. D3 discloses oligosaccharide-protein conjugates 1-2 [scheme 1]. Therefore claim 14 is not novel in light of the disclosure of D3. D1 – D3 do not disclose a conjugation process with the specific combinations of features of claims 1-13, specifically none of D1- D3 discloses the conjugation process time of 14 to 22 hours. Therefore the subject matter of the aforementioned claims is new and meets the requirements of article 33 (2) of the PCT with regard to novelty. <u>INVENTIVE STEP (IS)</u> Claims 14 and 15 lack an inventive step for the reasons given above. An invention is necessarily obvious in light of its disclosure. Consequently the subject matter of claims 14-15 is obvious and does not meet the requirements of article 33 (3) of the PCT with regard to inventive step. Claims 1-13 are not inventive in light of D1-D3 considered individually. D1 discloses (see for example figure 23 and page 104-106) a. reacting an oligosaccharide having a terminal amine linker (compound 518) with a reagent having at least one reactive thiol functional group [SAMA-Pfp] to form an activated oligosaccharide (figure 23 step a and c – the free sulfhydryl group is generated using NH₂OH.HCl during the conjugation step c) compound 538 is obtained in 53% yield [page 104 line 28].											

- b. reacting a carrier protein (PADRE-Lys) with an aliphatic hetero bifunctional crosslinker [maleimide butyric acid] to obtain an activated carrier protein having reactive maleimide functional group (compound 508) in figure 23 step b.
- c. carrying out conjugation reaction (figure 23 step c) of said activated synthetic oligosaccharide of step (a) with said activated carrier protein of step (b) to obtain a synthetic oligosaccharide-protein conjugate (compound 501) having thioether linkage.

D1 discloses that this reaction produces the oligosaccharide-protein conjugate in 62% yield [page 106, line 8] and is effective in inducing antibody production, and is used in vaccines [page 143], thereby showing the oligosaccharide-protein conjugate displays significantly high antibody titer.

The difference between D1 and the instant claims is in the reaction time and/or the reagents used and at which step in the process the conversion of the thiol on the oligosaccharide to the sulfhydryl group occurs. The instant claims are to where 'said process of conjugation is completed in a range of 14 hours to 22 hours', D1 has a conjugation reaction time of 1 hour and a total synthesis reaction time of approximately 7 hours. As the instant specification claims that one of the advantages of the method of the instant claims is a reduced reaction time it is considered that a reaction time of 14-22 hours is not considered inventive in light of D1 which discloses a considerably shorter reaction time.

The conversion to sulfhydryl group occurs in the instant claims before the conjugation step compared to the method taught in D1 where it occurs during the conjugation step in the absence of any surprising result, this is considered to be a workshop variation and cannot be considered to involve an inventive step. Similarly the use of SATA and BMPS are considered to be technical equivalents to the SAMA-Pfp and maleimide butyric acid reagents taught in D1 and gel filtration is considered to be a technical equivalent of HPLC separation taught in D1, therefore in the absence of any surprising result cannot be considered to involve an inventive step. Therefore claims 1, 5-9 and 13 are not inventive in light of D1.

D1 as discussed previously discloses the method of claim 1 to make oligosaccharide-protein conjugates using protein groups and sugar groups that mimic the antigenic properties of saccharides from *Shigella flexneri*, including those that have 4 to 8 repeating units [pages 4-5]. These conjugates can be used to make a vaccine against *S. flexneri* [page 6 line 4-6]. Therefore the difference between claims 2 and 3 is in the choice of the saccharide units used, however the person skilled in art seeking to create a vaccine against other pathogenic species, such as *Neisseria meningitidis* or *Haemophilus influenzae* in light of the teachings of D1 would find it obvious to utilise saccharides from these species, or saccharides that mimic the antigenic properties of these species. Furthermore the person skilled in the art would expect that these conjugates would inherently induce IgG antibodies and SBA activity, D1 demonstrates that protection is conferred upon systemic immunization or administration of specific immune serum (page 122 line 20-123 line 13) therefore the person skilled in the art would expect these properties to be present. Therefore in the absence of any problem to overcome, surprising advantage gained or disadvantage avoided, the substitution of one antigenic sugar group for another in order to target a different pathogen cannot be considered to involve an inventive step. Additionally from the teachings of D1 the person skilled in art would expect a reasonably high yield of said conjugates. Therefore in light of the disclosure of D1 claims 2-3 and 10-12 are not inventive in light of D1.

D1 discloses that the protein portion of the oligosaccharide-protein conjugate may be any protein or peptide comprising at least one T-helper cell epitope, for example, tetanus toxoid or CMR197 [page 11 line 4-18] furthermore page 135 outlines the synthesis of conjugates containing tetanus toxoid. Therefore claim 4 is not inventive in light of D1.

D1 discloses several other oligosaccharide-protein conjugates synthesised in a similar manner, see for example, 502, 503, 401, 601, 602, 708-713, 801.

A similar objection applies in regards to D2 and D3 which disclose the similar reactions in scheme 5 and scheme 1, respectively. See also Introduction, Experimental of D2 and scheme 1, 3, 4, Introduction, page 1634 column 2 of D3.

Therefore the subject matter of claims 1-13 is obvious and does not meet the requirements of article 33 (3) of the PCT with regard to inventive step.

INDUSTRIAL APPLICABILITY (IA)

The invention defined in the claims is considered to meet the requirements of Industrial Applicability under Article 33(4) of the PCT because it can be made by, or used in, industry.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY Box No. VIII Certain observations in the international application	International Application No. PCT/IB2015/057682
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: Claims 1-15 do not comply with PCT Article 6 because they are not fully supported by the description. The scope of the claims must not be broader than is justified by the description and they must be enabled by the description across their <u>entire</u> scope. However it is considered that it is not reasonable to predict that all variants covered by the claim will possess the properties or uses suggested, that is, a sound prediction cannot be made in respect of the entire scope of the claim. Consequently the search performed was limited to the supported subject matter, that is, the search was performed based on the examples provided in the complete specification. Although the person skilled in the art could, based on the examples provided, substitute different reagents, proteins and oligosaccharides to arrive at oligosaccharide-protein conjugates different to those provided in the examples, however claim 1 and dependant claims 2-13 require that the process of conjugation is completed in a range of 14 to 22 hours and must have higher yields than conventional conjugates, and that the conjugate display significantly high antibody titer, including functional antibodies. The person skilled in the art, although able to make other conjugates would not be able to reasonably predict that all variants of the process of synthesising oligosaccharide protein conjugates covered by the claims will have the properties mandated by claim 1, similarly the products of this process (as defined by claims 14 and 15) cannot be reasonably predicted to possess the required properties. Furthermore it is not defined what ‘significantly high’ means nor which ‘conventional conjugates’ are referred to for the yields to be higher than, therefore the person skilled in the art is not able to determine the full scope of the claims. For the purposes of providing an opinion any yield greater than 20% was considered higher as per table 7 which demonstrates that the yields of conjugates of the present invention to be 20% or greater, and any detectable antibodies were considered ‘significantly high’. Claims 2 and 3 do not comply with PCT Article 6 because the person skilled in the art is not able to determine the entire scope of claims 2 and 3. These claims define the invention wherein the oligosaccharide mimics the natural polysaccharides of gram negative bacteria. There are no teachings of how to identify said oligosaccharides, nor which property or properties are being mimicked. Furthermore claims 9-12 do not comply with PCT Article 6 because they are not fully supported by the description. The scope of the claims must not be broader than is justified by the description and they must be enabled by the description across their entire scope. Claims 9-12 include a broad statement that includes all possible means without qualification for solving the problem facing the inventor. These claims therefore merely re-state the problem or the desired result. It appears that claim 9-12 re-state results achieved by the examples from the specification; however these claims are appended to claim 1 which is much broader than is enabled by the complete specification. Claim 5 is unclear as it lacks antecedent for SATA in step (b). Step (a) refers to at least one sulphydrilating agent, whereas step (b) refers to remove unreacted SATA. For the purposes of providing an opinion it was considered that step (b) meant to refer to removing unreacted sulphydrilating agent.	