THE PATENTS ACT, 1970

&

The Patents Rules, 2003

(SECTION 25(1) and RULE 55)

In the matter of the application for Patent **5057/CHENP/2007** filed by **ONO PHARMACEUTICALS CO., LTD., JAPAN & E.R. SQUIBB & SONS, L.L.C, U.S.A**

And

In the matter of representation by way of opposition u/s 25(1) to the grant of patent thereon by **INDIAN PHARMACEUITCAL ALLIANCE, MUMBAI**

And

In the matter of representation by way of opposition u/s 25(1) to the grant of patent thereon by **PANKAJ KUMAR SINGH, NEW DELHI**

And

In the matter of representation by way of opposition u/s 25(1) to the grant of patent thereon by **RESTECH PHARMACEUTICALS, AHMEDABAD**

And

In the matter of representation by way of opposition u/s 25(1) to the grant of patent thereon by **DR. REDDY'S LABORATORIES LIMITED, HYDERABAD**

ONO PHARMACEUTICALS CO., LTD.,
1-5, Doshomachi 2-chome, Chuo-ku, Osaka-shi,
Osaka 541-8526 Japan …. Applicant

AND

E.R. SQUIBB & SONS, L.L.C
Route 206 & Province Line Road,
Princeton, New Jersey 08540, U.S.A …. Applicant

INDIAN PHARMACEUITCAL ALLIANCE
a society registered under the Societies Registration Act having mailing address
C/o VISION CONSULTING GROUP,
201 Darvesh Chambers, 743 P D Hiduja Road,
Khar (W), Mumbai 400 052 …. Opponent 1

PANKAJ KUMAR SINGH
an Indian citizen of
House No. 152/9, Kishan Garh, Vasant Kunj, New Delhi-110070 …. Opponent 2

RESTECH PHARMACEUTICALS
whose proprietors are
PAVAN PATEL AND M.R. PATEL
Having office at plot no. 407, new Ahmedabad Industrial Estate,
Sarkhej-Bavla Road, Moraiya-
382-210, Dt. Ahmedabad …. Opponent 3

DR. REDDY'S LABORATORIES LIMITED
an Indian Company with its principal place of business at 8-2-337 Road No. 3
Banjara Hills, Hyderabad …. Opponent 4

Present:

Archana Shanker, Gitika Suri & Devender Rawat	…..	Agents for Applicants
Nayan J. Rawal & Dr. Dhawal	…..	Agents for Opponent 1
Hariharan Subramaniam & Vihan Dang	….	Agents for Opponent 3
S. Majumdar, Amrita Majumdar & Dominic Alvares	…..	Agents for Opponent 4
P. Jyothish Kumar	……	Examiner of Patents & Designs

HEARING HELD BEFORE
Dr. SHARANA GOUDA,
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

DECISION

The applicant **M/s ONO PHARMACEUTICALS CO., LTD., JAPAN & M/s. E.R. SQUIBB & SONS, L.L.C, U.S.A** filed a national phase application No.5057/CHENP/2007 on 9th November, 2007 in pursuance of their PCT application No. PCT/JP06/309606 for granting of a patent for their invention entitled "HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1 (PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS" having the conventional priority of US application No. 60/679,466 dated 9th May, 2005, US application No. 60/738,434 dated 21st November, 2005 and US application no. 60/748,919 dated 8th December, 2005. A request for examination was filed by the applicants on 13th April, 2009. An opposition to the grant of a Patent under section 25(1) was filed by

(1) **INDIAN PHARMACEUITCAL ALLIANCE** a society registered under the Societies Registration Act having mailing address C/o VISION CONSULTING GROUP, 201 Darvesh Chambers, 743 P D Hiduja Road, Khar (W), Mumbai 400 052;

(2) **PANKAJ KUMAR SINGH** an Indian citizen of House No. 152/9, Kishan Garh, Vasant Kunj, New Delhi-110070;

(3) **RESTECH PHARMACEUTICALS** whose proprietors are PAVAN PATEL AND M.R. PATEL Having office at plot no. 407, new Ahmedabad Industrial Estate,

Sarkhej-Bavla Road, Moraiya- 382-210, Dt. Ahmedabad; and

(4) **DR. REDDY'S LABORATORIES LIMITED** an Indian Company with its principal place of business at 8-2-337 Road No. 3 Banjara Hills, Hyderabad.

The first examination report (FER) was issued on 28th June, 2013 and the applicant's agent replied to the FER vide their letter dated 27th June, 2014 along with amended claims. The representations under section 25(1) have been forwarded to Applicant's agent as per Rule 55 of Patent Rules 2003 and the Applicant has submitted the reply statements. The applicants have filed Interlocutory petition and also request for amendment of complete specification by filing amendments in the SEQ listing.

The amended/revised set of claims on record filed on 18th February, 2019 along with written submissions to the 4th Opposition hearing held on 4th January, 2019:

1. An isolated monoclonal antibody or an antigen-binding portion thereof that binds specifically to human Programmed Death (PD-1), comprising:

a) a heavy chain CDR1 consisting of the amino acid sequence set forth in SEQ ID NO: 18;

b) a heavy chain CDR2 consisting of the amino acid sequence set forth in SEQ ID NO: 25;

c) a heavy chain CDR3 consisting of the amino acid sequence set forth in SEQ ID NO: 32;

d) a light chain CDR1 consisting of the amino acid sequence set forth in SEQ ID NO: 39;

e) a light chain CDR2 consisting of the amino acid sequence set forth in SEQ ID NO: 46; and

f) a light chain CDR3 consisting of the amino acid sequence set forth in SEQ ID NO: 53.

2. The monoclonal antibody or antigen-binding portion thereof as claimed in claim 1, which comprises:

(a) a heavy chain variable region comprising an amino acid sequence derived from a human VH 3-33 germline sequence and/or a human VH JH4b germline sequence;

And

(b) a light chain variable region comprising an amino acid sequence derived from a human VK L6 germline sequence and/or a human VK JK4 germline sequence.

3. The monoclonal antibody or antigen-binding portion thereof, as claimed in claim 1, which comprises:

a) a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 4; and

b) a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO: 11.

4. The monoclonal antibody or antigen-binding portion thereof as claimed in any one claims 1-3, which is a human antibody or a portion thereof.

5. The monoclonal antibody or an antigen-binding portion thereof, as claimed in any one claims 1- 4, which is an IgGl or an IgG4 antibody or a portion thereof.

6. The antigen-binding portion as claimed in any one claims 1-5, which is selected from a Fab, a F(ab')2, a Fv fragment, and a single chain Fv (scFv).

7. A composition comprising the monoclonal antibody or antigen-binding portion thereof as claimed in any one claims 1-6 and a pharmaceutically acceptable carrier.

8. An isolated nucleic acid encoding the monoclonal antibody or antigen-binding portion thereof as claimed in any one claims 1- 7, wherein the nucleic acid sequence encoding the heavy chain comprises sequence defined in Figure 4A and that encoding the light chain comprises sequence defined in figure 4B.

The written submissions submitted after hearing along with the opposition/representation and reply statements submitted during the proceedings are considered for deciding the matter under section 25(1) of the Patents Act, 1970:

A. WRITTEN SUBMISSIONS OF ARGUMENTS DURING HEARING BY THE OPPONENTS 1, 3 AND 4

B. WRITTEN SUBMISSIONS OF ARGUMENTS BY THE APPLICANT DURING HEARING FOR OPPOSITION 1, 2, 3 and 4

C. AFFIDAVITS SUBMITTED:

i. BY APPLICANT'S AGENT:

1. Dr. David Feltquate [PGO-1]
2. Dr. Brian T Fife [PGO-1]
3. Ms. Sarah Roques [PGO-1]
4. The second affidavit of Dr. Fife [PGO-2]
5. The third affidavit of Dr. Fife [PGO-3]
6. The fourth affidavit of Dr. Fife [PGO-4] and
7. The fifth affidavit of Dr. Fife [PGO-4]

ii. By OPPONENT'S AGENTS:

1. Dr. Datta Madamwar [PGO-3]
2. Dr. Sateesh Kumar Natarajan [PGO-4]
3. Dr. Jeanne M. Novak [PGO-4]
4. Dr. Vikas Kumar [PGO-4]

FINDINGS OF THE PROCEEDINGS:

Considering the representations by way of Opposition u/s 25(1) along with Applicant's reply statements, expert evidences by way of affidavits and written submissions by all Opponents and Applicants of the arguments including the interlocutory matters discussed along with case laws presented during the hearing, the summary of my findings are as following:

Interlocutory Petition by Applicant requesting for not to take on record the rejoinder and opinion of Dr. Vikas:

During hearing the Applicant's agent argued that the rejoinder along with opinion of Dr. Vikas Kumar filed by the Opponent 4 is not as per the procedure provided in the Act and the Rules, and unnecessarily delays the procedure of a pregrant be dismissed and not be taken on record. Applicant's agent also stated their submissions that "the procedure to be adopted in pre-grant enquiry under Section 25(1) is a summary procedure/proceedings" and "*There is NO PROVISION of any rejoinder being filed by the person opposing the grant of Patent, production of any further documents or evidence. The Act or the Rules do not prescribe for the same and the same therefore should not be allowed.* The applicant has placed arguments by relying on the decision of the Bombay High Court in Glochem Industries Ltd. V Cadila Healthcare Ltd. dated 6th November 2009.

In reply, the opponent submitted that "the pre-grant proceedings being in the nature of quasi-judicial proceedings are imbued with the principles of natural justice. It is submitted that the Applicant along with the reply statement filed therewith 5 affidavits of Dr. Fife, one affidavit by Roques and one affidavit by Feltquate, wherein additional data and 'information' was provided to portray the alleged superiority of the alleged invention (5C4 monoclonal antibody) over prior art antibodies and which additional data by way of the

aforesaid affidavits formed an important and integral part of the pleadings of the reply statement in reply to the various grounds of Opposition. The said additional data particularly by Dr. Fife when evaluated by the expert Dr. Vikas Kumar and whose affidavit is filed with the Rejoinder, which is the subject of the instant Interlocutory Petition, pointed out the numerous discrepancies with the aforesaid data and thus its irrelevance to the impugned application and statements based on such data made in the reply statement thus being incorrect. The Opponent has relied on such affidavit of Dr. Vikas Kumar when replying the various statements made in the reply statement based on such additional data. Thus, in the event the Rejoinder along with the affidavit of Dr. Vikas Kumar is not taken on record the Opponent will suffer grave prejudice as it will not have a chance to address the technical affidavits, which include new and additional data, filed by the Applicant. On the other hand in the event the said Rejoinder along with the affidavit of Dr. Vikas Kumar is taken on record the Applicant will suffer no prejudice whatsoever and in fact will be helpful in properly appreciating the matter on merits". To justify and counter the arguments of Applicant, the Opponent relied on the judgements of Hon'ble Bombay High Court in Neon Laboratories Pvt. Ltd. and Anr. V/s TroikaaPharma Limited and Ors along with case law of Hon'ble Bombay High Court Judgment dated 8th October, 2013 in Tata Chemicals Ltd V/s Union of India & Others. The Opponent further stated that "Thus for the reason that admittedly no hearing was given to the Opponent (Petitioner) in that matter on the additional affidavit and also no opportunity was given to make submissions on the additional affidavit i.e. their say, the Order of the Ld. Controller was found to be in violation of the principles of natural justice. In the present case, additional and new data is sought to be introduced which did not form part of the instant opposition proceedings in India such as by way of an Affidavit of Dr. Fife and the Opponent in the instant case could

not counter such technical new and additional data and point out the numerous discrepancies and un-reliability in the absence of a technical Affidavit of an expert Dr. Vikas Kumar. Further the Reply Statement includes numerous submissions based on such affidavits and thus the Rejoinder also based on the Affidavit of expert Dr. Vikas Kumar is relied upon when countering such submissions of the Reply Statement".

The arguments of the applicant and the opponent 4, as well as the relevant Sections and rules along with the case laws cited have been considered carefully and I am in agreement with the opponent's argument that the proceedings of the section 25 (1) of the Patents Act, 1970 are primarily to assist the Controller for taking the informed decision to grant the good and valid patents only. The opposition under section 25 (1) of the Patents Act, 1970 can be filed by any person up to the grant of a patent, once the documents along with matter pertaining to the grounds given under section 25 (1) of the Patents Act, 1970 has been brought to the Controller's notice before grant of the Patent, the Controller is bound to take it on record. Therefore, considering that, the rejoinder along with opinion of Dr. Vikas Kumar filed by the opponent 4 is taken on record.

OTHER MATTERS BROUGHT/DISCUSSED BY OPPONENTS:

The following points/issues are also raised by Opponents:

i. The Opponent 1 on added subject matter and voluntary amendment of claims.

ii. The Opponent 3 stated that the claim amendments widening the scope of method claim 9: Present claim 9 directed to a method for producing monoclonal antibody is not allowable under Section 59 r/w Section 57 of The Patents Act, 1970.

iii. The Opponent 4 has objected for the allowability of amendment of SEQ listing by way of correction/explanation by filing Form-13.

iv. The Opponent 4 has also objected for the request of the applicant for the auxiliary claim request.

On the raised points/issues of amendment of the complete specification and allowability of auxiliary request by the Controller, there is no specific ground of opposition as per the provisions of Section 25(1) of the Patents Act, 1970 and hence these points/issues are considered during the examination procedure in examination of the present application by the Examiner and Controller.

The Opponent 2 did not attend the hearing and there are no written submissions from that opponent for consideration.

The Opponents 1, 3 and 4's agents during hearing mainly emphasized and based their arguments on the following specific grounds of opposition under section 25 (1) of the Patents Act, 1970:

1. **LACK OF NOVELTY** [Section 25 (1) (b)] [PGO 3 and 4]

2. **OBVIOUSNESS/LACK OF INVENTIVE STEP** [Section 25 (1) (e)] –PGO 1, 3 and 4]

3. **NOT PATENTABLE/NOT AN INVENTION** [Section 25(1)(f)]- PGO 1, 3 and 4

4. LACK OF SUFFICIENCY AND CLARITY [Section 25 (1) (g)] - PGO 1 and 3

5. FAILED TO DISCLOSE INFORMATION UNDER SECTION 8 [Section 25 (1) (h)]-PGO 4

1. LACK OF NOVELTY [Section 25 (1) (b)] [PGO 3 and 4]

1.1 Opponent 3 w.r.t to lack of Novelty of claims stated as following:

LACK OF NOVELTY

Section 25(1)(b) and (d)- the claims 1-11 of the opposed application are anticipated in view of document D3 and admissions made by the Applicants during prosecution of D3 and the opposed application

(A) Applicants admissions that Document D3 is Nivolumab

3.1 It is respectfully submitted that the Applicants have made admissions and statements before various judicial and quasi-judicial authorities stating that document D3 i.e. ***EP 1537878 B1 [corresponding to WO 2004004771 (WO '771); Date of publication- January 15, 2004]*** discloses, teaches and enables Nivolumab which is the monoclonal anti-PD 1 antibody for treatment of cancer allegedly covered in the opposed specification.

3.2 It is the Applicants' case, in paragraph 14 of the Reply Statement and further supported in paragraph 21 of the Evidence Affidavit filed on behalf of the Applicants by Mr. Brian T. Fife under cover of letter dated 15 January 2018, that Nivolumab is disclosed in the present specification. Surprisingly, the Applicants' have earlier submitted during the European prosecution of D3 and before the Courts in United States of America (U.S.A.) that D3 discloses Nivolumab. This constitutes an admission on the part of the Applicants' that D3 anticipates the alleged invention of the opposed specification.

3.3 Reliance is placed on the submissions made by the Applicants during the EP prosecution.

The relevant portion is reproduced herein below for the ease of reference of the Learned Controller:

> *"…Furthermore, even though the priority application filed on July 3, 2002 might notdisclose an anti-PD-1 antibody, no undue experimentation is required to carry out the claimed invention. As explained herein above, the priority application provides sufficient information to generate an anti-PD-1 antibody of the invention (see page 9, line 18 to page 12, line 22). The subject of the claims is the use of an anti-PD-1 antibody in the treatment of cancer."*
>
> (Emphasis Supplied) (**D5, page 438, last paragraph of Opponent's Documents**)

Thus, the Applicants believed during prosecution of D3, that as early as 2002, much prior to the opposed specification, D3 provides sufficient information to generate any anti-PD-1 antibody. Thus, anti-PD-1 antibodies and the process of making such antibodies of the opposed specification are disclosed, enabled and taught in document D3. The fact that D3 may have covered within its purview many anti-PD-1 antibodies is irrelevant, what is relevant is that D3 also specifically covers Nivolumab.

3.4 The Applicants have also relied upon data from the opposed specification WO 2006/121168 (WO'168; corresponding WIPO publication of IN 5057/CHENP/2007) to demonstrate novelty and inventive step of document D3 during the European Prosecution. The relevant portions from the submissions in Europe is reproduced herein below for the ease of reference of the Learned Controller:

> *"With respect to inventive step, with our petition dated January 7, 2008, a copy of WO-A-2006/121168 has been filed, which demonstrates anti-tumor activity of* ***human anti-human PD-1 antibody*** *in vivo. The* ***results indicated by Fig. 47 in WO-A-2006/121168*** *show that tumor cells grafted to mice did not increase at all by administering any concentration of* ***humanized anti-human antibody****. Therefore,* ***tumor growth is completely suppressed in vivo by the activity of the anti- PD-1 antibody claimed in claims 1 and 2 of the present application****."* (Emphasis Supplied)
> (**D4, pages 431-432, bridging paragraph of Opponent's documents**)

3.5 It is further submitted that Example 18 of WO 2006/121168, which is the corresponding WIPO publication of the opposed application IN 5057/CHENP/2007, has been submitted as additional data during examination to demonstrate the inventiveness of the invention allegedly claimed in prior patent application D3. The relevant portions from the submissions in Europe is reproduced herein below for the ease of reference of the Learned Controller:

> *" …Further* ***support of the anticancer activity of anti-human PD-1 antibody*** *can also be found* ***in Example 18 and Figure 47 of WO-A-2006/121168*** *(a copy of which is attached to this petition)"*
> (Emphasis Supplied)
> (**D4, page 434, fourth paragraph of the Opponent's documents**)

Thus, **the data from the opposed application IN 5057/CHENP/2007 has been submitted to demonstrate inventiveness of a prior patent No. EP 1537878 B1, corresponding to WO 2004004771 (WO ' 771) which is D3**. This is a clear admission of the fact the claimed subject matter of D3 is Nivolumab and therefore, it can no longer be reclaimed as a novel and inventive compound in the present opposed application.

3.6 It is also pertinent to point out that for obtaining regulatory approval for Nivolumab from the US FDA, the Applicant has relied upon experimental data similar to Example 18 of the opposed application. Please refer document **D33, page 1270 of the Defendant's documents**. Thus, the presentation of the said data before the US FDA is also testimony to the fact that the Applicant has averred that Nivolumab is covered by the document D3.

3.7 The Applicants on the present application have filed suits before the US Courts claiming patent infringement of US Patents corresponding to D3 family. During these proceedings, the Applicants have specifically averred that these patents cover Nivolumab. Reliance is placed on the US Court decisions annexed as D7, D8 and D9 of the Opponent's documents and the relevant extracts are reproduced herein below for the ease of reference of the Learned Controller:

*"…5. **The plaintiffs put this scientific breakthrough into practice by developing an anti-PD-1 antibody called nivolumab, the first anti-PD-1 antibody approved anywhere in the world for cancer treatment**….*

*13. On May 20, 2014, the United States Patent & Trademark Office ("USPTO") duly and legally issued United States Patent No. 8,728,474 (the "474 patent" (Exhibit 1)) titled "Immunopotentiative Composition" **The inventors of the 474 patent showed for the first time that anti-PD-1 antibodies were useful in methods to treat cancer**. Ono is an assignee of the 474 patent. BMS is an exclusive licensee of the 474 patent. The 474 patent claims methods for treating cancer with an antibody against PD-1.*

*14. **Plaintiffs have put the invention of the 474 patent into practice by developing the breakthrough biologic drug nivolumab. Nivolumab is a monoclonal antibody that recognizes and binds to the PD-1 protein**. When nivolumab binds to the PD-1 protein, that PD-1 protein cannot interact with its natural binding partners. Using nivolumab to block the interaction between PD-1 and its binding partners allows a more robust T cell response by the patient's own immune system…"*

(Emphasis Supplied) (**D7, pages 459, 461 of the Opponent's documents**)

Thus, the Applicants have admitted that Nivolumab was already disclosed and claimed in the patent document D3.

3.8 The Applicants have applied for a Patent Term Extension for the Japanese Patent No. 4409430 which belongs to the D3 patent family. A bare reading of the said document makes it amply clear that the product for which the patent term extension is sought is Nivolumab. Please refer **D29, pages 1120 and 1122 of the Opponent's documents**.

Thus, the Applicants own statements and admissions before the European Patent Office, the US District Courts and the Japanese Patent Office are clear testimony to the fact that document D3 discloses, enables and teaches Nivolumab. Having made these admissions during various judicial and quasi-judicial proceedings, the Applicants are bound by these statements under the principles of prosecution history estoppel and they cannot now go back and claim not to have made these statements.

In view of the Applicants own admissions, it is clear that document D3 discloses, enables and teaches the alleged invention Nivolumab of the opposed specification.

(B)Claims of the Opposed Specification lack novelty in view of document D3

3.9 In summary:

(a) anti-human anti-PD-1 antibodies are known for the treatment of cancer from the teachings of document D3. The said document clearly discloses and in fact presupposes that anti-human anti-PD 1 antibodies are known in the art;

(b) the compound disclosed and claimed in D3 is Nivolumab;

(c) process of making anti-PD 1 antibodies as disclosed in example 1 of the opposed specification is same as the process disclosed in document D3. There is no material difference between the process steps disclosed in the two patent specifications;

(d) the said document D3 also discloses, enables and teaches a substance which can target PD-1 and which has excellent specificity for PD-1.

(e) the data from Example 18 of the opposed specification has been used to demonstrate the inventiveness of prior patent. No. EP 1537878 B1, corresponding to WO 2004004771 which is D3.

(f) example 18 of the opposed specification relates to the same compound as D3.

(g) only apparent difference between D3 and the opposed specification is that the sequence is provided in the opposed specification.

(h) it is a well-established principle that specifically identifying a sequence does not constitute an invention.

3.10 Even assuming arguendo that the claimed antibodies with the 6 sequences in the CDRs are novel, the said antibodies are nothing more than inherent features of the recombinant mouse model and thus, are inherently anticipated.

Thus, the opposed specification is liable to be refused on the ground of being anticipated by document D3 alone.

1.2 Opponent 4 w.r.t Lack of Novelty of Claims stated as following:

I. **Section 25(1)(b): ANTICIPATION /LACK OF NOVELTY**

a. The Opponent submits that D1 discloses immunopotentiating agents and composition thereof that inhibit the immunosuppressive signals induced by PD-1, PD-LI or PD-L2 having therapeutic potential of treating cancer. Particular reference is made to claims 9 and 20 of D1, which recite human antihuman PD-l antibody for use in the treatment of cancer/tumour. Further at paragraph 3, page 11 [page 302-(xi) of the Pre-Grant Representation Volume] the antibody to PD-1 is remarked as "excellent substance in specificity".

b. D1 further discloses at page 302-(xv) & (xix) of the Pre-Grant Representation Volume that –

> ‘‘When non-human antibody is used to treat for human, it is indispensable to decrease the antigenicity of the antibody. Since the immune reaction to patient's antibody often shortens an effective treatment period, the process of decreasing the antigenicity of the antibody by making the antibody humanize or completely human type is necessary. The humanized antibody modified to be acceptable for administering to human is the antibody which is modified so that the decrease of antigenicity or the blood movement may improve to extent that can be allowed in pharmacology when the antibody is administered to human.
> Human PD-1 antibody or human PD-L1 antibody in specification of the present invention includes the humanized or the complete human type antibody, too.
> …….
>
> The complete human type antibody can be prepared by using mice (XenoMouse (Chemical Biology (2000), vol. 7, issue 8, p. R185-6.), HuMAb-Mouse (Infection and Immunity (2002), vol. 70, issue 2,

p.612-9.), TC mouse (Biotechnology and Genetics EnginneringRevew (2002), vol. 19, p. 73-82.), and KM mouse (Cloning Stem Cells (2002), vol. 4, issue 1, p. 91-102.)) of which a constant region gene of human immunoglobulin have been transferred, and a target antibody can be mass-produced by making the antibody production lymphocytes separated from mice to hybridomas. It can be prepared by phage display method (FEBS Letter (1998), vol. 441, p. 20-24.). In this method, by using phages of which the human antibody gene have been incorporated into a cyclic single strand DNA, the human type antibody can be expressed on the surface of the phage as a form fused with coat protein of the phages.''

c. The Opponent relies on Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals; issued by the Office of the Controller General of Patents, Designs and Trademarks (October 2014)

7.5 Inherent anticipation: Sometimes the prior art may inherently disclose the subject matter of an invention. In one case before the IPAB, it was held that '' patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. The prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating prior art. It is not necessary that inherent anticipation requires that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. But it is necessary that the result is a necessary consequence of what was deliberately intended in the invention" i.e. 3 [paragraph 58 of the decision of the IPAB in Enercon (India) Limited vs AloysWobben ORA/6/2009/PT/CH ,ORDER (No. 18 of 2013) . (Page 11)

…

10.6 While interpreting what is ''efficacy'', the Hon'ble Supreme Court in the Novartis case held that in the context of the pharmaceutical patenting the ''efficacy'' should be understood as "therapeutic efficacy''. 14 In Paragraph 180 of the order it was held: What is ''efficacy''? Efficacy means "the ability to produce a desired or intended result". Hence, the test of efficacy in the context of Section 3(d) would be different, depending upon the result the product under consideration is desired or intended to produce. In other words, the test of efficacy would depend upon the function, utility or the purpose of the product under consideration. Therefore, in the case of a medicine that claims to cure a disease, the test of efficacy can only be "therapeutic efficacy''. ……It may be noted that the text added to Section 3(d) by the 2005 amendment lays down the condition of

"enhancement of the known efficacy''. Further, the explanation requires the derivative of ''differ significantly in properties with regard to efficacy''. What is evident, therefore, is that not all advantageous or beneficial properties are relevant, but only such properties that directly relate to efficacy, which in case of medicine, as seen above, is its therapeutic efficacy. While dealing with the explanation as provided in Section 3(d) it must also be kept in mind that each of the different forms mentioned in the explanation have some properties inherent to that form, e.g., solubility to a salt and hygroscopicity to a polymorph. These forms, unless they differ significantly in property with regard to "therapeutic efficacy'', are expressly excluded from patentability. Hence, the mere change of form with properties inherent to that form would not qualify as "enhancement of efficacy" of a known substance. In other words, the explanation is meant to indicate what is not to be considered as therapeutic efficacy. [Page 29]

Thus clearly 'inherent anticipation' has been recognized by the Indian Patent Office.

Given the basis above, the Opponent submits that D1 inherently anticipates the impugned invention for the reasons below:

a. While applying for the SPC based on EP1537878 [D1's equivalent in Europe], the Applicant submitted that the product is Nivolumab, thus conceding that the antibody was inherently disclosed in D1 [UK SPC number: SPC/GB15/081 on EP
1537878 disclose that the product identified is 'nivolumab'. SPC in other European countries, including UK, is referenced in entirety as Annexure X]

b. In fact, Applicant also asserted in Complaints filed before US Courts that, US patents (US8728474, US9073994 and US9067999) were put into practice by developing an anti-PD-1 antibody called Nivolumab, the first anti-PD-1 antibody approved anywhere in the world for cancer treatment. These patents are equivalents of D1.

c. Further, the Applicant, in itsdeposition to an earlier opposition, stated that a 3rd party preparing Nivolumab would infringe EP1537878.

''A 3rd party, if they prepare Nivolumab and also use Nivolumab for treatment of cancer will infringe EP 1537878 B1 (D3) as well as the corresponding EP patent of the present application''.

d. Also, during the prosecution of the EP equivalent of D1, the Applicant referred to experimental data in the present, impugned specification in order to substantiate the anticancer activity.

Regarding the anticancer activity of the anti-human PD-1 antibody claimed in new claims 1 to 3, enclosed please find a test report which shows the immunopotentiative activity of anti-human PD-1 antibody. As can be seen from the results of test report, as anti-human PD-1 antibody increases INF- γ production, it clearly has an anticancer activity. Further support of the anticancer activity of anti-human PD-1 antibody can also be found in Example 18 and Fig. 47 of WO-A-2006/121168 (a copy of the PCT publication which is attached to this petition).

It is submitted that while responding to notice of opposition against EP equivalent of Dl (EP1537878), Applicant stated that the disclosure of EP'878 'directly and unambiguously' enables a person skilled in the art to obtain a human anti-PD 1 antibody and also test it for its specificity and anti-cancer properties.
Therefore, the opponent submits that Nivolumab is inherently disclosed in D1 as evident from the applicant's own admissions and assertions. The Applicant's contention that D1 does not disclose "CDRs", and hence not anticipatory of the impugned claims is wholly without merit.

e. The Opponent relies on Section 58 of the Indian Evidence Act, 1872 to show that when the Applicant itself admits something across jurisdictions about their own alleged invention including when prosecuting an application before EPO then the same need not be proved i.e.

"58. Facts admitted need not be proved. —No fact need to be proved in any proceeding which the parties thereto or their agents agree to admit at the hearing, or which, before the hearing, they agree to admit by any writing under their hands, or which by any rule of pleading in force at the time they are deemed to have admitted by their pleadings: Provided that the Court may, in its discretion, require the facts admitted to be proved otherwise than by such admissions."

f. The Opponent further relies on Avtar Singh And Ors vs Gurdial Singh And Ors; 2007(1)AWC434(SC)
''Admission, it is well known forms the best evidence. It may be that admission does not create any title. but the nature of the land can form subject matter of admission.

Section 58 of the Evidence Act postulates that things admitted need not be proved.''

g. The Opponent thus submits that the impugned patent application ought to be rejected on this ground.

1.3 APPLICANT'S SUBMISSIONS FOR NOVELTY OF THE CLAIMS

1.3.1 Applicant's submissions w.r.t Novelty of Claims stated as following in PGO-3:

3. **Novelty**

x. D3 (EPI53787881) is a document that is in relation to "Use of an anti-PD-1 antibody for cancer treatment" On reading of document D3 for anticipation, it is clear that said document cannot anticipate the present invention in the absence of any disclosure of any specific human anti human-PDI antibody let alone an antibody having the specific CDR sequences for 5C4

SAID DOCUMENT REGARDING 5C4 ANTIBODY. This is evident from the fact that the Opponent had to rely on postdated documents to make an attempt to deal with the novelty issue.

xi. The only antibodies referred to in D3 are in Example 2 which is a **mouse antibody JllO.** (International trust number: FERM BP-8392) & Examples 12 and 13 of D3 which is **J43 a hamster antibody that binds to mouse PD-1** and another **anti-mouse antibody.** (See Page 419 of the Opposition).

xii. Due to the absolute lack of teaching or disclosure of the 5C4 (human anti-PO-l human antibody) CDR sequences in the D3, its disclosure cannot be considered as an enabling disclosure.

xiii. Again, the Opponent has misconstrued the document D4 which is the prosecution history of D3 and 05 which is part of the Opposition proceeding filed in respect of D3. In the prosecution of D3 the applicant relied upon a later filed application (corresponding to the present invention) to show to the patent office that the **use of anti-POt antibody for treatment of cancer is not speculative and that the applicant has post published data which is disclosed in the present application to show that anti PDt antibody can be used for treating cancer.** (Page 434 of the Opposition compilation)

xiv. We would like to refer to the following pages of the Opponents compilation to show that D4/D5 only confirms that D3 is a document directed to **USE of anti PD1 antibody for treatment of 9!..!!.££!:** and does not in any way suggest that D3 disclosed 5C4 antibody.

1.3.2 Applicant's submissions w.r.t Novelty of Claims stated as following in PGO-4:

THE PRESENTLY CLAIMED INVENTION IS NOVEL IN VIEW OF D1

112. The claimed antibody comprising the six CDRs of the 5C4 antibody of the present application is not anticipated at the at the priority date of the application.

113. Any prior art document, in order to be an anticipating document, has to enable a person skilled in the art to perform the invention without exercise of any inventive ingenuity on the priority date of the invention. The said disclosure has to be an "unambiguous clear and a direct disclosure (enabling disclosure)." That is, **ANTICIPATION HAS TO BE BASED ON THE PRIORITY DATE OF THE DOCUMENT.**

"…the earlier publication **must give the requisite knowledge clearly**, and it is not enough that it merely gives the means of attaining such knowledge. It must give sufficient information to a workman skilled in the particular art or craft in order to **enable him to carry out the invention**. How far that knowledge anticipates the new invention is again a question of fact depending on the facts and circumstances of each case. **Even where the prior document and the present specification are identical or nearly identical in language, it does not necessarily follow that the Court must conclude that the first is an anticipation of the second**, and often expert evidence is necessary to help the Court to consider what knowledge the prior publication could have conveyed to the mind of a person who had not the knowledge given by the invention in dispute."

115. The IPAB in India in Ideal Cures Vs. M/S.Colorcon Ltd. held that:

"*30. The novelty as per the leading case laws is defined as below; Novelty: An invention shall be taken to be*

1. New if it does not form part of the state of the art.

2. The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (anywhere in the world) by written or oral description, by use or in any other way.

31. The law of novelty is concisely stated by Lord Hoffmann in Smithkline Beecham plc's (Paroxetine Methanesulfonate) Patent [2005] UKHL 59, [2006] RPC 10. In summary, and for present purposes:

(1) There are two requirements for anticipation, which is very important to consider separate, (a) disclosure and (b) enablement;

(2) So far as disclosure is concerned, the prior art must disclose subject-matter which, if performed, would necessarily result in an infringement of the patent,

32. The law of novelty was again explained by the House of Lords in Synthon v Smithkline Beecham

[2005] UKHL 59; [2006] RPC 323 the specification should meet two

requirements.

First, the matter relied upon as prior art must disclose subject matter which, if performed, would necessarily result in an infringement of the patent. Second, that disclosure must have been enabling, that is to say the ordinary skilled person would have been able to perform the invention if he attempted to do so by using the disclosed matter and the common general knowledge.

Enablement

33. For "enablement", a person skilled in the art must have been able to perform the invention without any undue burden of trials. The question at this stage is how much trial and error or experimentation is permitted. If an inventive step were required to get to the invention of the subsequent patent from the specification of the first patent, then this first patent does not provide an enabling disclosure. The entire prior patent must provide enough information to allow a person skilled in the art to perform or make the subsequently claimed invention without "undue burden". The skilled person may use his common general knowledge of the relevant art at the relevant time to supplement information contained in the prior patent and may conduct routine trials without being considered an undue burden, but prolonged or arduous trial and error experiments would not be considered routine."

116. It is denied that D1 anticipates the claims of the present invention. The Applicants submit as follows:

117. At the outset, in para 7.23 the Opponent has admitted that the sequence of the antibody claimed is not disclosed in D1 and therefore admitted novelty. The anticipation argument should be dismissed on this ground alone.

118. D1 references hybridoma identified by International Trust Number FERM BP-8392. The FERM BP-8392 does not produce antibodies with the specific sequences of the antibodies as presently claimed comprising the CDR's of the 5C4 antibody. The antibodies disclosed in D1 are

a) J110: FERM BP-8392 hybridoma disclosed in D1 produces the J110 antibody, which is a murine anti-human PD-1 antibody. The sequences for that antibody - the heavy chain variable region and light chain variable region are SEQ ID NO: 2 and SEQ ID NO: 4 in US2008/0025979 (corresponding to WO2004/072286). A copy of the publication and sequence is enclosed herewith as **Annexure L;** and

b) J43: J43 is a hamster antibody that binds to mouse PD-1, and has a different CDR with very low alignment, as provided in table below (Exhibit 36):

Antibody of prior art	Heavy Chain			Light Chain		
	CDR1	CDR2	CDR3	CDR 1	CDR2	CDR3
J43	20	47	50	27	29	0

119. Due to the absolute lack of teaching of the 5C4 CDR sequences in the cited references, D1

does not anticipate the present invention, particularly claim 1. Also, as all other claims depend directly or indirectly on the main claim 1, they derive their novelty from the main claim and are not anticipated.

120. To establish lack of novelty of the claimed invention in view of document D1, the Opponent relies on postdated documents of the Applicant in other jurisdictions such as Complaints filed before the US district Court of Delaware in matter of US872874, US9073994, US9067999 (equivalents of D1), Patent term extension filed in JP equivalent of D1, SPC in Europe (equivalents of D1), EP Opposition (equivalents of D1), EP Opposition (equivalents of present application**), which are besides being irrelevant are inadmissible in law to establish anticipation**

121. Without prejudice, even otherwise D1's US, EP and JP equivalents relate to identification of PD-1 receptor as a target for treatment of cancer" D1 covers use of anti-PD1 antibodies for treatment of cancer. Per the laws of said countries, a drug product may be covered by multiple different patents with different priority dates and inventive concepts.

122. Regarding the challenges to US patents US8728474, US9073994, and US9067999 in US District Court, we state the following:

a)The complaints filed in the US, besides being post-published documents, DO NOT assist theOpponent to establish that D1 discloses specific human antihuman PD-1 antibodies.

b) D1 claims the use of anti PD1 human antibody for treatment of cancer. Principle claims of US8728474, US9073994, and US9067999 are reproduced below: -

US8728474	1. A method for treatment of a tumor in a patient, comprising administering to the patient a pharmaceutically effective amount of an anti-PD-1 monoclonal antibody. 1
US9073994	1. A method of treating a metastatic melanoma comprising intravenously administering an effective amount of a composition comprising a human or humanized anti-PD-1 monoclonal antibody and a solubilizer in a solution to a human with the metastatic melanoma, wherein the administration of the composition treats the metastatic melanoma in the human.
US9067999	1. A method of treating a lung cancer comprising administering a composition comprising a human or humanized anti-PD-1 monoclonal antibody to a human with the lung cancer, wherein the administration of the composition treats the lung cancer in the human.

123. In the complaints, the Applicants define the invention claimed in the above US patents as below:

Page 315	**INVENTION OF METHODS FOR TREATING CANCER** 14. On July 7, 2015, the United States Patent & Trademark Office ("USPTO") duly and legally issued United States Patent No. 9,073,994 (the "994 patent" (Exhibit 1)) titled "Immunopotentiative Composition." The inventors of the 994 patent showed for the first time that anti-PD-1 antibodies were useful in methods to treat cancer. Tasuku Honjo is a co-inventor
Page 325	**MERCK'S INFRINGEMENT** 19. Merck is exploiting the invention of the 994 patent with an anti-PD-1 antibody called pembrolizumab. On information and belief, Merck started developing pembrolizumab after Plaintiffs had made and started testing nivolumab. On September 4, 2014, Merck received approval to sell pembrolizumab in the United States for the treatment of certain patients suffering from metastatic melanoma. According to Merck, pembrolizumab is a PD-1 antibody that works by blocking the PD-1 checkpoint to treat cancer.
Page 306	**INVENTION OF METHODS FOR TREATING CANCER** 13. On May 20, 2014, the United States Patent & Trademark Office ("USPTO") duly and legally issued United States Patent No. 8,728,474 (the "474 patent" (Exhibit 1)) titled "Immunopotentiative Composition." The inventors of the 474 patent showed for the first time that anti-PD-1 antibodies were useful in methods to treat cancer. Ono is an assignee of the 474 patent. BMS is an exclusive licensee of the 474 patent. The 474 patent claims methods for treating cancer with an antibody against PD-1.

124. In other words, a third party who uses **any** anti-PD1 human antibody for treatment of cancer will infringe D1's US equivalents.

125. It was in this context the US infringement suit was filed by the Applicants, who are also the patentee of D1 against Merck, as Merck was planning to make, use, sell etc. an anti-PD-1 antibody, **pembrolizumab (and not nivolumab)**. See extracts below:

Page 307	**MERCK'S INFRINGEMENT** 18. Merck is planning to exploit the invention of the 474 patent with an anti-PD-1 antibody called pembrolizumab. On information and belief, Merck started developing pembrolizumab after Plaintiffs had made and started testing nivolumab, and Merck has since been engaged in efforts to meet the FDA regulatory requirements for marketing, distributing, offering for sale, and selling pembrolizumab for the treatment of cancer. According to Merck, pembrolizumab is a PD-1 antibody that works by blocking the PD-1 checkpoint to treat cancer.

Page 317	**MERCK'S INFRINGEMENT** 19. Merck is exploiting the invention of the 994 patent with an anti-PD-1 antibody called pembrolizumab. On information and belief, Merck started developing pembrolizumab after Plaintiffs had made and started testing nivolumab. On September 4, 2014, Merck received approval to sell pembrolizumab in the United States for the treatment of certain patients suffering from metastatic melanoma. According to Merck, pembrolizumab is a PD-1 antibody that works by blocking the PD-1 checkpoint to treat cancer.
Page 327	**MERCK'S FUTURE INFRINGEMENT** 18. Merck is planning to exploit the invention of the 999 patent with an anti-PD-1 antibody called pembrolizumab. On information and belief, Merck started developing pembrolizumab after Plaintiffs had made and started testing nivolumab. Merck has received FDA approval to sell pembrolizumab in the United States for the treatment of melanoma, and has since been engaged in efforts to meet the FDA regulatory requirements for marketing, distributing, offering for sale, and selling pembrolizumab for the treatment of lung cancer. According to Merck, pembrolizumab is a PD-1 antibody that works by blocking the PD-1 checkpoint to treat cancer.

126. **In other words, Merck in the US was sued for infringement of D1 as their anti-PD1 antibody pembrolizuma for treatment of cancer infringed D1 and NOT US equivalent of IN 5057. The Opponent are attempting to misguide the Controller. Further, D1 in the US and all other jurisdictions has not rendered the equivalents of IN 5057 in other jurisdictions as lacking in novelty. Clearly, this is an attempt of the Opponent to mislead the Opponent to serve their vested interest against the well- established principles of law on anticipation.**

127. It may be noted here that "*the rights given by the patent do not include the right to practice the invention, but only to exclude others from doing so."* Reliance is placed on Hindustan Lever Limited Vs., R. Lalit Wadhwa, of the Delhi High Court, :

"The grant of a patent to the defendant gives no immunity or defense in an action for infringement of the plaintiff's patent. Reliance is placed on "Patents For Chemicals, Pharmaceuticals and Bio Technology' (IV Edition) by Phillip W. Grubb on page 4 of the said commentary, the learned author states that:

Exclusionary Right

It is important to realise that the rights given by the patent do not include the right to practice the invention, but only to exclude others from doing so. The patentee's freedom to use his

own invention may be limited by legislation or regulations having nothing to do with patents, or by the existence of other patents. For example, owning a patent for a new drug clearly does not give the right to market the drug without permission from the responsible health authorities, nor does it give the right to infringe an earlier existing patent. In the very common situation where A has a patent for a basic invention and B later obtains a patent for an improvement to this invention, then B is not free to use his invention without the permission of A, and A cannot use the improved version without coming to terms with B. A patent is not a seal of government approval, nor a permit to carry out the invention. We very often hear 'This patent allows Company X' to do something or other. It does not, it only allows them to stop someone else from doing it. The right to prevent others from carrying out the invention claimed in a patent may be enforced in the courts; if the patent is valid and infringed the court can order the infringer to stop his activities, as well as providing other remedies such as damages."

128. Reliance is also placed on the Article, " The relationship between basic and improvement patents", by Arnold B. Silverman, :

"*There is a common misconception that obtaining a patent gives the right to practice the patented invention. A patent grants the patent owner a negative right (i.e., the right to prevent others from making, using, or selling the patented inventions); it does not give the patentee the rights to practice the invention. In many instances, a patented improvement cannot be made, used, or sold without infringing the basic patent.*

A simplistic example: a basic patent is obtained for a chair having three legs. Another may decide that a chair would be more stable if it had four legs and obtains a patent for a chair with four legs. The improvement patent would give the owner the right to keep others from making, using, or selling chairs having four legs. As the original patent claimed a chair with three legs, making, using, or selling the four legged version would infringe the basic patent. The presence of an additional leg permits the inventor of the improvement to obtain a patent, but does not avoid infringement of the basic patent for chair with three legs"

129. Similarly, the reliance on Japanese patent term extension for JP patent equivalent to D1 and EP's supplementary protection certificate in EP Patent equivalent of D1 is misfounded. The D1's US, EP and JP equivalents cover the use of PD-1 antibodies for treatment of cancer. In said documents there is absolute lack of teaching of the 5C4 CDR sequences. The claim 1 of the present invention therefore cannot be anticipated by D1.

130. The Opponent fails to direct the Learned Controller to anything in D1 that discloses the claimed CDR's of 5C4 or an antibody comprising said CDR'S as claimed in the present invention and therefore fails in establishing that D1 enables a person skilled in the art to perform the invention claimed in the present invention without undue experimentation establishing in view of disclosure of D1. The ground of anticipation therefore fails.

131. The Opponent during the hearing also stated that D1 inherently anticipates the present invention. However, even on repeated questioning by the Learned Controller, the Opponent:

a) Failed to show which portion of D1 can be said to be inherently the disclosing present invention;

and

b) Failed to show which antibody referred to in D1 has the sequence of the claimed antibody sequence or of 5C4

132. The Learned Controller also correctly said during the hearing that the inherent disclosure has to be seen in the context the statement has been made in any prior art document or any other document that has been referred to interpret said inherent disclosure. It is respectfully submitted that:-

a) The inherent disclosure may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. The opponent has failed to show where any feature of the presently claimed invention is disclosed in D1.

b) Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. Of course, a person skilled in the art is aware of methods of making an antibody and can make anti-PD-1 antibodies; however, he cannot arrive at 5C4 or the claimed antibodies with such superior properties without any undue experimentation. The possibility of arriving at the claimed anti-PD-1 antibodies is extremely low, as seen by the fact that no prior art anti-PD-1 antibody has a similar sequence or the superior properties.

c) Further the context in which a statement is being made has to be considered. D1 and its US, JP, EP equivalents are for use of anti-PD-1 antibodies for treatment of cancer and any anti-PD-1 antibody when used in cancer would infringe said invention.

133. Thus, the prior art D1 does not teach or disclose the claimed antibody. For at least these reasons, the claimed antibody comprising the six CDRs of the 5C4 antibody would not have been anticipated and the Opponents arguments be dismissed.

1.4 My findings w.r.t the Novelty of the claims of the Present application:

The amended independent claim 1 of the present invention (referred as '5057 hereinafter) is claiming for an isolated monoclonal antibody or an antigen-binding portion thereof that binds specifically to human Programmed Death (PD-1), comprising:

a) a heavy chain CDR1 consisting of the amino acid sequence set forth in SEQ ID NO: 18;

b) a heavy chain CDR2 consisting of the amino acid sequence set forth in SEQ ID NO: 25;

c) a heavy chain CDR3 consisting of the amino acid sequence set forth in SEQ ID NO: 32;

d) a light chain CDR1 consisting of the amino acid sequence set forth in SEQ ID NO: 39;

e) a light chain CDR2 consisting of the amino acid sequence set forth in SEQ ID NO: 46; and

f) a light chain CDR3 consisting of the amino acid sequence set forth in SEQ ID NO: 53.

The amended claim 7 of '5057 is claiming for a composition comprising the monoclonal antibody or antigen-binding portion thereof as claimed in any one claims 1-6 and a pharmaceutically acceptable carrier.

The amended claim 8 of '5057 is claiming for an isolated nucleic acid encoding the monoclonal antibody or antigen-binding portion thereof as claimed in any one claims 1- 7, wherein the nucleic acid sequence encoding the heavy chain comprises sequence defined in Figure 4A and that encoding the light chain comprises sequence defined in figure 4B.

The cited prior art document for lack of novelty in both the oppositions PGO-3 and 4 is EP1537878 B1 [WO 2004004771] [referred as '878 herein after]. The prior art document cited '878 does not disclose the isolated monoclonal antibody or antigen binding portion thereof that specifically binds to human Programmed Death (PD-1), comprising SEQ ID No. 18, 25, 32, 39, 46 and 53 as claimed in claim 1 of the present invention, hence the product claimed in claim 1 of the present invention is held new or novel over the cited prior art '878. The opponents arguments based on the submissions of the applicant during the EP prosecution and also the submissions made by applicant in obtaining regulatory approval for Nivolumab from the US FDA are not tenable as the opponent relied mainly on the prior

document ‘878 and which never discloses the monoclonal antibody as claimed in claim 1 with six CDR sequences. The inherent anticipation by cited document ‘878 as argued by the opponent along with the applicants’ assertion in complaints filed before US courts is also cannot be forming basis for the lack of novelty in the absence of disclosure of the monoclonal antibody as claimed in claim 1 with six CDR sequences in cited document ‘878. **Therefore, the antibody claimed in amended claim 1 is new or novel over the disclosures of cited prior art ‘878. The amended claims 2 to 6 are dependent claims on claim 1 and hence these claims are also said to be new or novel over the disclosures of cited prior art ‘878.**

The composition claimed in amended claim 7 is **also said to be new or novel over the cited prior art ‘878** as the composition is claimed with having the new or novel isolated monoclonal antibody or antigen binding portion thereof that specifically binds to human Programmed Death (PD-1) as claimed in claims 1 to 6 of the present invention in the composition.

The prior art document cited ‘878 does not disclose the isolated nucleic acid encoding the monoclonal antibody or antigen-binding portion thereof as claimed in any one claims 1-6 and having the nucleic acid sequence encoding the heavy chain comprises sequence defined in Figure 4A and that encoding the light chain comprises sequence defined in figure 4B as claimed in claim 1 of the present invention, **therefore the product claimed in claim 8 of the present invention is held new or novel over the disclosures of cited prior art ‘878.**

Thus, I am in agreement with the applicant’s agent that the cited prior art document ‘878 never discloses the SEQ ID’s of the antibody claimed in amended claim 1 and nucleic acid

claimed in amended claim 8 of the '5057 application and also opponents failed to give details of the features anticipated by cited document '878 vis-à-vis amended claims 1 to 8 of the '5057. In my opinion, the disclosures in the document '878 do not anticipate product claimed in amended claims 1 to 8 of the '5057 and hence they meet the criteria of the new (or novel) product as per the provisions of the section 2 (1) (j) of the Patents Act, 1970. Therefore, the opponents clearly failed to establish this ground of opposition u/s 25 (1) (b) of the Patents Act, 1970.

2. OBVIOUSNESS/LACK OF INVENTIVE STEP [Section 25 (1) (e)] –PGO 1, 3 and 4]

2.1 Opponent 1 w.r.t obviousness of Claims stated as following:

Obviousness of Claim 1 in view of D1, D3, D8 and general art

D1 discloses a method for modulating an immune response comprising contacting an immune cell with an agent that modulates signaling via PD-1 to thereby modulate the immune response. It also discusses that PD-1 may be involved in immunoevasion by tumors. It discloses a blocking antibody that recognizes PD-1 and can stimulate the immune response. Example 10 discloses Generation of Human Single Chain Fvs Reactive with B7-4 or PD-1. It is given under example 10 that "*As an alternative to preparing monoclonal antibody-secreting hybridomas, anti B7-4 or anti-PD-1 antibodies (single chain Fv-like portions of antibodies) were identified and isolated by screening a combinatorial library of human immunoglobulin sequences displayed on Ml 3 bacteriophage from Cambridge Antibody Technology"*(Please see page 123, lines 23-27 of D1). It shows that Human Single Chain anti-PD-1 antibodies have been developed at the priority date of the invention of D1 as an alternative of the human antibodies for the purpose of the screening. It means that human antibodies can be produced at the priority of D1 against PD-1 antigen. It also discloses that monoclonal antibody–secreting hybridomas can be prepared at the priority of D1.

Thus, D1 provides teachings for the development of antibody against PD-1 antigen

and preferably development of monoclonal antibody secreting hybridoma. It is clearly mentioned that inventors of D1 had chosen to develop single human anti-PD-1 antibody for the screening purpose only. Otherwise, skilled person at the priority of D1 was well aware of the fact that monoclonal antibody against PD-1 antigen should be developed for targeting PD-1 antigen.

D3 discloses anti-PD-1 antibody produced by the hybridoma strain "J43", which was deposited on May 30, 2001 in International Patent Organism Depositary (0015 of D3). It also discloses divalent or hybrid antibody where it is constructed by bridging anti-PD-1 antibody and anti-BCR or anti-CP3 antibody (Please see para [0011] of D3). D31 discloses antibody produced by hybridoma technology. In addition, D3 discloses bispecific molecule where one of the moieties is anti-PD-1 antibody and another moiety is anti-BCR or anti-CP3 antibody.

D8 discloses human anti- PD-1antibody directed to human PD-1 antigen. D8 also discloses that there are two distinct epitopes on human PD-1 antigen where targeting antibodies bind. Nivolumab is the antibody which is covered under the instant application as per the applicants' assertions. D8 also discloses that human antibody binding to PD-1 antigen increase T-cell proliferation and IC_{50} values. We would like to submit here that there is prior article of 2003 where K_D values of two of the human PD-1 antibody are disclosed (Please see D9; page 713, left hand column, first paragraph below the heading Abs to PD-1 can act as agonists and antagonists of the pathway). Thus, D8 discloses epitopes of Nivolumab, effect of human PD-1 antibodies in terms of T-cell proliferation and IC_{50} values of human antibodies. Further, K_D values of human PD-1 antibodies of D8 are also disclosed in the prior literature. It should be noted that antibodies generated in D8 are by scFv phagemid library method (Please see Example 1 of D8). Subsequently, conversion of scFv to full IgG antibody has been also disclosed in D8 (Please see Example 5 of D8). Thus, human anti-PD-1 antibodies are disclosed in detail with their developmental process in D8. It is different from the human antibody disclosed in the opposed application in terms of its development. In the opposed application human antibody is developed using HuMab mice or KM mice. Here, in D8 human antibodies developed have higher similarity with the germline from which they obtained. Therefore, such antibodies cannot be highly similar with the other human PD-1 antibodies which are developed from the different germline. It should be noted that germline selection for generation of antibody against target antigen is done by the immune system of the

animal which is used for the generation of antibody during somatic mutation, affinity maturation and clonal expansion phenomena.

The opponents would like to draw the kind attention of the Ld. Controller towards Annexure-5. On October 22, 1993, *GenPharm International received the 1993 "**Best Scientific Achiever**" Award at the October Biotech Meeting at Laguna Niguel sponsored by Ernst & Young and Kleiner Perkins Caufield & Byers.* ***The Award was made in recognition of GenPharm's transgenic mouse system for generating*** completely human monoclonal antibodies (HuMAbs) (Please see paragraph 6, page no. 32 of Annexure-5). On April 27, 1994, *GenPharm announced that its researchers had successfully completed development of the HuMAb™ mouse, thus enabling a new, reliable method of generating fully human monoclonal antibodies from transgenic mice (Please see* Paragraph 7, page no. 32 of Annexure-5)." Further, on December 5, 1995, "*GenPharm International announced at the 6th International Conference on Antibody Engineering in La Jolla, California**, the generation of high affinity human IgG antibodies suitable for therapeutic use. These antibodies were produced from GenPharm's HuMAb-Mouse™* **(Please see p**aragraph 9, page no. 32 of Annexure-5)." The USPTO issued on October 31, 1996 to GenPharm International, Inc. two U.S. patents for transgenic mice producing human antibodies. (U.S. Patent 5,545,806 and U.S. Patent 5,569,825; Please see paragraph 10, page no. 32 of Annexure-5). It should be noted that the same references (US patents) are referred in the specification of the opposed application for generation of transgenic mouse. "*On January 8, 1997, GenPharm was awarded a further patent relating to transgenic mouse technology, US Patent 5,591,669, which covered transgenic mice whose antibody genes had been inactivated* (Please see paragraph 12, page no. 32 of Annexure-5). Thus, methods of making such transgenic mouse and human antibodies from such mouse are known in the art since 1996.

It is given in Annexure-6 that *"With the UltiMAb platform, Medarex has assembled a unique family of genetically engineered mice* ***for creating the entire spectrum of high-affinity, fully human antibodies****. Medarex and Kirin combined their technologies, and the* ***unique traits of the HuMAb -Mouse(R) and TC Mouse(TM), to create a new crossbred mouse that retains the capability to produce all human antibody isotypes with a robust immune response*** *previously unseen in any human antibody producing mouse system.* ***Medarex's HuMAb -Mouse has the proven ability***

to generate fully human antibodies with affinities in the picomolar range *(as high as 10^{12}). Developed by Kirin, the TC Mouse utilizes transchromosomic technology to generate human monoclonal antibodies of any isotype* (Please see second paragraph, page 1 of Annexure-6). It shows that the transgenic animals used in the present invention are well explored by the skilled person to have high affinity antibodies against any target antigen. This is for the kind information of the Ld. Controller that one of the applicants-Medarex LLC has numbers of collaborations for generation of antibodies against variety of antigens using transgenic animals used in the present invention. Many evidences are available prior to the opposed application showing above mentioned fact for which Annexure-6 is cited here. These evidences can be reproduced, if required.

Ustekinumab (Annexure-2), anti- IL-12 antibody and Golimumab (Annexure-3, also admitted by the applicants during the hearing that Annexure-3 is a patent for Golimumab), anti-TNF antibody are the examples of such human monoclonal antibodies which are developed using transgenic mice (HuMab mice). Antibody of Annexure-2 which was generated using the same technology as used in the impugned application was analyzed for its binding affinity towards the antigen-IL-12 in Annexure-2. Results obtained of BIAcore analysis revel that several of the human monoclonal antibodies are very high affinity with K_D in the range of 1×10^{-9} to 7×10^{-12} (Please see lines 13-15, page no. 62 of Annexure-2). Antibody of Annexure-3 which was generated using the same technology as used in the impugned application was analyzed for its binding affinity towards the antigen-TNF in Annexure-3. Results obtained of BIAcore analysis reveal that several of the human monoclonal antibodies are very high affinity with K_D in the range of 1×10^{-9} to 7×10^{-12} (Please see lines 10-13, page no. 67 of Annexure-3). Further, Golimumab has average K_D value 18 pM (Please see Table on page 17 of Annexure-9).

In such a situation, where D1 suggests a skilled person to develop monoclonal antibody, skilled person can easily develop an anti-PD-1 antibody which is claimed in the present application at its priority date. Moreover, at the priority date of the impugned application, D8 provides human antibody targeting human PD-1 antigen. Furthermore, such antibodies have higher affinity up to 10^{-10} M (D9). D3 provides bispecific antibody which can target PD-1 antigen and any other antigen simultaneously. Thus, two distinct regions of epitopes of PD-1 antigen where developed or being developed as antibody which should bind to block ligand binding to PD-1 antigen were also available for the person skilled in the art in view of D8.

28 Therefore, at the priority date of the impugned application human antibodies were
29 available along with the binding site of PD-1 to obtain anti-cancer activity. In view of
30 the teachings of D1, D3, and D8, in combination of aforementioned general
31 knowledge (use of transgenic mice for generating antibodies high binding affinity etc)
32 skilled person can easily develop human antibodies using known techniques.

2.2 Opponent 3 w.r.t obviousness of Claims stated as following:

4.3 It is respectfully submitted that the antibodies targeting PD-1 antigen are well known in the art. Reliance is placed on prior art documents D1, D2, D3, D11 and D19.

4.4 Further, human antibody targeting human PD-1 antigen is well known in the art. Reliance is placed on documents D3, D11 and D19.

4.5 It is obvious to prepare the said antibody from the teaching of document D3 and the submissions of the Applicant during the European prosecution of D3. The relevant extracts are reproduced herein below for the ease of reference of the Learned Controller:

> *"…Furthermore, even though the priority application filed on July 3, 2002 might not*
> *disclose an anti-PD-1 antibody, no undue experimentation is required to carry out the*
> *claimed invention. As explained herein above, the priority application provides sufficient information to generate an anti-PD-1 antibody of the invention (see page 9, line 18 to page 12, line 22). The subject of the claims is the use of an anti-PD-1 antibody in the treatment of cancer."*
> (Emphasis Supplied)
>
> (D5, page 438, last paragraph of Opponent's documents)

4.6 Human antibody targeting human PD-1 antigen with high degree of specificity and less cross-reactivity is known and taught in the art. Reliance is placed on documents D3, D11 and D19. In fact, the Applicants' claim that the claimed 5C4 antibodies of the opposed specification have greater degree of specificity for PD-1 antigen as compared to antibodies known in the art is not supported and in fact contradicted by the data provided in the complete specification.

4.7 Figure 14 of the opposed specification provides data showing the binding specificity of the claimed antibodies 5C4 along with other antibodies

as disclosed in the opposed specification for PD-1 family of antigens. The relevant figure is reproduced herein below for the ease of reference of the Learned Controller:

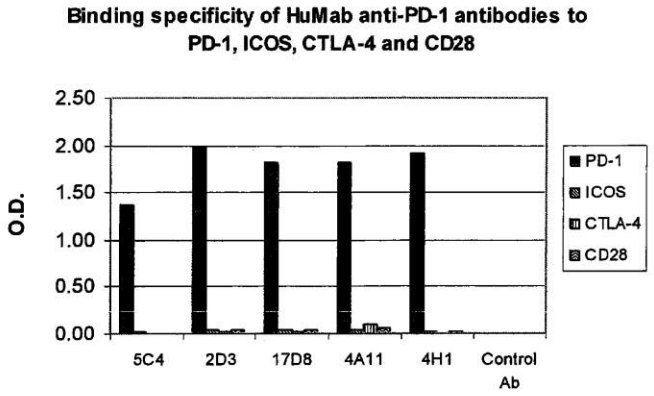

Figure 14

The said data has also been relied upon by the Applicant in the **Reply Statement, paragraph 89** and in the Evidence on behalf of the Applicant filed by Mr Brian T. Fife under cover of letter dated 15 January 2018 (**Please refer paragraphs 15-17 of the Evidence**).

This data clearly demonstrates that other antibodies viz. 2D3, 17D8, 4A11, 4H1 have a higher specificity for PD-1 antigen family over other protein receptor families namely ICOS, CTLA-4 and CD-28 in comparison to 5C4 antibodies. Thus, claimed antibody does not have superior affinity to other antibodies of the specification.

4.8 The Applicants in paragraph 89 of the Reply Statement, referring to Figure 1 and paragraphs 15-16, pages 510-511 of the Applicants' documents, have submitted data to show that claimed antibodies do not cross-react with other antigen families such as ICOS, CTLA-4 and CD-28 while the anti-PD-1 antibodies known in the art react with these antigen families. However, the said data in fact supports the fact that the cross-reactivity of the claimed antibodies is similar to the known anti-PD-1 antibodies in as much as:

(a) different scales have been taken to show the specificity of other anti-PD-1 antibodies of the specification with PD-1 protein and with CTLA-4, CD-28 and ICOS proteins. If the same scales would have been taken, the cross-reactivity of the said anti-PD-1 antibodies would be

comparable with the claimed 5C4 antibodies.

(b) There is no comparative data of the claimed 5C4 antibodies with the known anti-PD-1 antibodies to demonstrate any unexpected, superior specificity of the claimed antibodies as claimed by the Applicant. Neither the Applicants' nor their experts have made any attempt to provide this comparative data which is essential to show superior specificity of the claimed antibodies over the anti-PD-1 antibodies known in the art.

(c) In the Applicant's Reply Statement, it has been clearly stated that 5C4 binds only with PD-1 antigen. It does not cross-react with other CD28 family receptors. [please refer to paragraph 89, 1st row-2nd column of table, page no. xlviii; paragraph 151, 1st row-2nd column of table, page no. lxxxvi; paragraph 175, 1st row-2nd column of table, page no. ciii] However, Applicant's expert has changed the conclusion of the same experiment by admitting in his last affidavit that claimed antibody does not bind to at least CD-28 and CTLA-4.[please refer to expert's affidavit filed by Applicant on 15th January, 2018]. The Applicant's expert has admitted to cross-reactivity of the claimed antibody with other protein families other than PD-1 family.

(d) This admission by the Applicant's expert is a direct result of a review of the Opponent's expert affidavit where Opponent's expert has raised an objection that the claimed antibody binds with ICOS family of proteins. Thus, the Applicant's expert has concurred with the objection of the Opponent's expert and accordingly, admitted to cross-reactivity of the claimed antibody.

Thus, the claimed antibodies are nothing more than obvious alternatives of known anti-PD-1 antibodies.

4.9 The process of making human antibodies against PD-1 is already disclosed, enabled and taught by the prior art documents. As previously submitted, document D3 teaches a process for making human antibodies specifically targeting PD-1 antigen. Document [D34]
– WO 2002/012500; Date of publication- February 14, 2002, document [D35] – WO
2002/012502; Date of publication- February 14, 2002 and document [D36] – WO
2001/014424; Date of publication- March 01, 2001 disclose the same process for a different
target antigen. Thus, when provided with the documents D3, D34, D35

and D36, a person skilled in the art can prepare the antibodies claimed in the opposed specification by routine experimentation. The Applicant has also admitted that the process of preparation of the claimed antibodies is known in the art on pages 42 and 43 of the WIPO publication of the opposed specification.

4.10 The process of preparation of human monoclonal antibodies is also known. Reliance is placed on **page 19** and **Annexure B3, page 99** of the Expert Affidavit of Dr Datta Madamwar filed on behalf of the Opponent.

4.11 The process of preparation of human monoclonal antibodies against PD-1 antigen is routine for the person skilled in the art at the time of priority of document D3 i.e. 03 July 2002. (Please refer **D5, page 438, last paragraph** of the **Opponent's documents**)

4.12 The process used by the Applicant in making human monoclonal antibodies against PD-1 as described in Example 1 on pages 74-75 of WO'168 (corresponding WIPO publication of IN 5057/CHENP/2007) is well known in the art and is in fact the established and preferred process for making human monoclonal antibodies. In this regard, reliance is placed on documents **D20-D24, D27** and **D35-36** of the **Opponent's documents.**

4.13 A human antibody targeting PD-1 antigen with excellent specificity and significant anti- cancer activity is disclosed, enabled and taught by document D3. This is evident from the Applicants' own submission during prosecution of D3 wherein the Applicants' have relied upon Example 18 of the opposed specification to demonstrate inventiveness of D3.

4.14 The affinity for PD-1 of the claimed antibodies of the opposed specification, measured in terms of K_D value, is already known from prior art document D11. In fact, the claims 6 and 7 as originally filed claimed antibodies with K_D values which were already covered in prior art document D11. Thus, by claiming antibodies with known K_D values from the prior art document, the Applicants' have already admitted that affinity of the claimed antibodies is known and thus, there is no inventive feature in the claimed antibody.

4.15 In view of the above submissions, the Applicant has abysmally failed

to demonstrate any inventive technical feature of the claimed monoclonal antibody *vis a vis* the prior art documents including document D3 in as much as the monoclonal antibody:

(a) is produced wholly within the transgenic mouse system;
(b) is produced by natural processes and known methods and techniques within the mouse system;
(c) there is no man-made mutation or alteration or modification carried out in the antibody structure and thus, no human intervention;
(d) is naturally occurring;
(e) has a specificity for PD-1 which is comparable to and in fact already known in the antibodies existing in the art;
(f) has an anti-cancer activity which is already known from document D3;
(g) has an affinity for PD-1, measured in terms of K_D value, which is already known from document D11

Thus, the claimed monoclonal antibody is within the scope of ordinary experimentation for a person skilled in the art and the claims 1-11 of the opposed specification are liable to be refused on the ground of obviousness and lack of inventive step alone.

2.3 Opponent 4 w.r.t obviousness of Claims stated as following:

c. The Opponent submits that the present invention as claimed in obvious in view of D1. As disclosed under technical field, D1 pertains to immune-stimulation characterized by inhibiting immunosuppressive signals induced by PD-1, PD-L1 or PD- L2, compositions for cancer or infection treatment, and therapies that use them. Even though D1 belongs to the applicant and in spite of acknowledging several prior art documents by various authors, the applicant failed to acknowledge its own patent application. The need for developing human antibodies against PD-1 was already recognized and acknowledged in D1. In particular, the Opponent makes reference to the below passages of D1, which are highly relevant to the present invention. D1 at page 302(xii) of Pre-Grant Representation Volume teaches that,

> As an antibody to PD-1, PD-L1 or PD-L2, all antibodies derived from human, mouse, rat, rabbit, or goat which can inhibit the immunosuppressive signals by PD-1, PD-L1, or PDL2, those polyclonal or monoclonal antibodies, complete or shorten (for example, F(ab') 2, Fab', Fab, or Fv fragment) antibodies, chimeric antibodies, humanized antibodies, or completely humanized antibodies will be acceptable.

d. Further at pages 302-(xv), 302-(xvi) and 302-(xvii), D1 teaches that,

When non-human antibody is used to treat for human, it is

indispensable to decrease the antigenicity of the antibody. Since the immune reaction to patient's antibody often shortens an effective treatment period, the process of decreasing the antigenicity of the antibody by making the antibody humanize or completely human type is necessary. The humanized antibody modified to be acceptable for administering to human is the antibody which is modified so that the decrease of antigenicity or the blood movement may improve to extent that can be allowed in pharmacology when the antibody is administered to human.

Human PD-1 antibody or human PD-L1 antibody in specification of the present inventionincludes the humanized or the complete human type antibody, too.

The complete human type antibody can be prepared by using mice (XenoMouse (Chemical Biology (2000), vol. 7, issue 8, p. R185-6.), HuMAb-Mouse (Infection and Immunity (2002), vol. 70, issue 2, p.
612-9.), TC mouse (Biotechnology and Genetics EnginneringRevew (2002), vol. 19, p. 73-82.), and KM mouse (Cloning Stem Cells (2002), vol. 4, issue 1, p. 91-102.)) of which a constant region gene of human immunoglobulin have been transferred, and a target antibody can be mass-produced by making theantibody production lymphocytes separated from mice to hybridomas. It can be prepared by phage display method (FEBS Letter (1998), vol. 441, p. 20-24.). In
this method, by using phages of which the human antibody gene have been incorporated into a cyclic single strand DNA, the human type antibody can be expressed on the surface of the phage as a form fused with coat protein of the phages.

e. D1 also teaches that monoclonal antibodies are more suitable and discloses methods of preparation of monoclonal antibodies at pages 302(xiii) and 302-(xiv) as reproduced hereinbelow.
The monoclonal antibody producing cells can be prepared as
hybridomas to be possible to subculture which produce the monoclonal antibody by selecting the individual of which the antibody titre is confirmed in an antigen immunized animals, gathering the spleen or the lymph node on day 2-5 after the final immunization, and fusing the antibody producing cells included in them with homogeneous or heterozoic myeloma cells. The antigen itself or with the carrier and the diluent is administered to the part in which the antibody production is possible. To improve the antibody producibility, Freund's complete adjuvant or Freund's incomplete adjuvant can be administered with the antigen. According to the method of calling "DNA immunization",

animals are immunized. This method is a method using a phenomenon in which antigen-expressing vectors are introduced into the part and are taken into myocytes on the process of tissue repair, and expresses the antigenic protein (Nature Immunology (2001), vol. 2, issue 3, p. 261-267) after Cardiotoxin (cardiotoxin) is treated to immune animal's tibialis anterior muscle of hind leg.

As an immune animal, mouse, rat, sheep, goat, rabbit, or guinea pig can be used, mouse and rat are suitable. The fusion operation can be executed by the method (Nature (1975), vol. 256, issue 5517, p. 495-
497.) of Kohler and Milstein, and as fusion accelerants, polyethylene glycol (PEG) and Sendai virus, etc. are used. As those myeloma cells, myeloma cells such as P3U1, NS1, SP2/0, and AP1 can be used, P3U1 are often used usually. The monoclonal antibody producing cells can be selected by detecting by ELISA, etc. executed by adding hybridoma culture supernatant to solid phase in which antigenic proteins are adsorbed direct or with carrier perhaps. Hybridoma culture supernatant's antibody titre can be measured by ELISA. The separation and refinement of the monoclonal antibody can be executed according to the separation refining method similar to the separation and refinement of immunoglobulin for the above polyclonal antibody. Concretely, it is anti-mouse PD-L1 antibody producted by hybridomas identified by International Trust Number FERM BP-8396 or anti-human PD-1 antibody producted by a hybridoma identified by International Trust Number FERM BP-8392.

f. Thus, the Opponent submits that D1 clearly taught the necessity of developing human antibodies and even developed human antibodies, as evident from the above passages. D1 teaches that inhibitor(s) of PD-1 and PD-L1 can be selected from PD-1 antibody, PD-L1 antibody, soluble PD-1, and soluble PD-L1. Such PD-1 antibody can in turn be selected from antihuman PD-1 antibody. D1 teaches the preparation of such antibodies using transgenic mice like HuMAb®, TC mouse and KM mouse™ of which a constant region gene of human immunoglobulin have been transferred, and a target antibody can be mass-produced by making the antibody production lymphocytes separated from mice to hybridomas.

g. Without prejudice to its submissions under the ground of lack of novelty, the Opponent submits that it would be evident upon reading the examples, particularly Examples 1 and 2 of the specification, that the applicant merely follow the teachings of D1 in order to arrive at the present invention, i.e. selecting the specific six CDRs of the presently-claimed antibody out of the numerous possibilities of potential CDR sequences which does not involve any undue experimentation. Moreover, there is nothing in the impugned specification which demonstrates that selecting the specific six CDRs of the allegedly

therapeutically superior antibody, out of the numerous possibilities of potential CDR sequences involves an inventive step, whatsoever. In fact, the specification states that the selection of CDRs was carried out using routine and standard techniques.

h. To better understand the "selection of the specific six CDR", reference was made to the detailed description of the impugned specification.

i. In the background section of the impugned specification, the applicant acknowledges and admits various publications teaching that the interaction between PD-I and PD-L1 results in a decrease in tumour infiltrating lymphocytes, a decrease in T-cell receptor mediated proliferation, and immune evasion by the cancerous cells. However, it is imperative to note that the applicant is wholly silent on D1, which is it's own patent application and teaches anti- PD1 antibodies including human antibodies for immunostimulation.

j. The alleged invention as disclosed in the specification relates to isolated monoclonal antibodies, particularly human antibodies, which exhibit the following properties:
(a) binds to human PD-I with a KD of 1 x 10^7 M or less;(b) does not substantially bind to human CD28, CTLA-4 or ICOS;(c) increases T-cell proliferation in an Mixed Lymphocyte Reaction (MLR) assay;(d) increases interferon-gamma production in an MLR assay;(e) increases DL-2 secretion in an MLR assay; (f) binds to human PD-I and cynomolgus monkey PD-I;(g) inhibits the binding of PD-Ll and/or PD-L2 to PD- 1; (h) stimulates antigen-specific memory responses;(i) stimulates antibody responses; and (j) inhibits tumor cell growth in vivo.

k. Further at page 53 of the Pre-grant Representation Volume, the impugned specification discloses that, preferred antibodies of the invention are the human monoclonal antibodies 17D8, 2D3, 4Hl, 5C4, 4Al, 7D3 and 5F4 isolated and structurally characterized as described in Examples 1 and 2.

l. The currently amended claims recite the six-specific CDRs of 5C4, which is a monoclonal, human antibody. In this regard, the Opponent refers to the definitions of human antibodies as found in the impugned specification. [pages 49 & 57 of the Pre-Grant Representation Volume]

> The term "human antibody", as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human

germline immunoglobulin sequences {e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo). However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

The term "recombinant human antibody",

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As used herein, a human antibody comprises heavy or light chain variable regions that is "the product of or "derived from" a particular germline sequence if the variable regions of the antibody are obtained from a system that uses human germline immunoglobulin genes. Such systems include immunizing a transgenic mouse carrying human immunoglobulin genes with the antigen of interest or screening a human immunoglobulin gene library displayed on phage with the antigen of interest. A human antibody that is "the product of or "derived from" a human germline immunoglobulin sequence can be identified as such by comparing the amino acid sequence of the human antibody to the amino acid sequences of human germline immunoglobulins and selecting the human germline immunoglobulin sequence that is closest in sequence (i.e., greatest % identity) to the sequence of the human antibody. A human antibody that is "the product of or "derived from" a particular human germline immunoglobulin sequence may contain amino acid differences as compared to the germline sequence, due to, for example, naturally- occurring somatic mutations or intentional introduction of site- directed mutation. However, a selected human antibody typically is at least 90% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that identify the human antibody as being human when compared to the germline immunoglobulin amino acid sequences of other species (e.g., murine germline sequences). In certain cases, a human antibody may be at least 95%, or even at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the germline immunoglobulin gene. Typically, a human antibody derived from a particular human germline sequence will display no more than 10 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene. In certain cases, the human antibody may display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene.

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Engineered antibodies of the invention include those in which

modifications have been made to framework residues within VH and/or VK, e.g. to improve the properties of the antibody. Typically such framework modifications are made to decrease the immunogenicity of the antibody. For example, one approach is to "backmutate" one or more framework residues to the corresponding germline sequence. More specifically, an antibody that has undergone somatic mutation may contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues can be identified by comparing the antibody framework sequences to the germline sequences from which the antibody is derived.

m. The production of monoclonal antibodies using transgenic mouse has also been described by the applicant. [Pages 72 and 73 of Pre-Grant Representation Volume]. The relevant passage has been reproduced below.

The HuMAb mouse® (Medarex, Inc.) contains human immunoglobulin gene miniloci that encode unrearranged human heavy (μ and γ) and K light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ and K chain loci (see e.g., Lonberg, et al. (1994) Nature 368(6474): 856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or K, and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgGκ monoclonal (Lonberg, N. etal. (1994), supra; reviewed in Lonberg, N. (1994) Handbook of Experimental Pharmacology 113:49-101; Lonberg, N. and Huszar, D. (1995) Intern. Rev. Immunol. 13: 65-93, and Harding, F. and Lonberg, N. (1995) Ann. NY. Acad. Sd. 764:536-546).

n. The Opponent submits that the method of producing the antibodies as claimed by the applicant involved the steps as under (refer to Examples 1 and 2).

i. Immunization: the step of immunization was carried out according to standard techniques using (i) a recombinant fusion protein comprising the extracellular portion of PD-I and (ii) membrane bound full-length PD-I. (page 73 of the opposition Volume).

ii. Commercially available transgenic mice strains like HCo7 strain of HuMab and the KM strain of transgenic transchromosomic mice were used to develop the human antibodies. As acknowledged by the applicant, these transgenic mice express human antibody genes.

iii. These mice were immunized with purified recombinant PD-I fusion protein and PD-1-transfected CHO cells as antigen. The applicant has acknowledged that such techniques are disclosed in General immunization schemes for HuMab mice are described in Lonberg, N. et al (1994) Nature 368(6474): 856-859; Fishwild, D. et al. (1996) Nature Biotechnology 14: 845-851

and PCT Publication WO 98/24884.

iv. The immunization is done when the mice are 6-16 weeks of age upon the first infusion of antigen. A purified recombinant preparation (5-50 μg) of PD-I fusion protein antigen and 5 -10x106 cells were used to immunize the HuMab mice and KM mice™ intraperitonealy, subcutaneously (Sc) or via footpad injection.

v. Several immunizations were carried out followed by ELISA to test antibodies that bound to PD-1. The mice that developed the highest titers of anti-PD-1 antibodies were used to generate the hybridoma, which involved fusing the mouse splenocytes, isolated from the HuMab or KM mice, were fused to a mouse myeloma cell line either using PEG based upon standard protocols or electric field based electrofusion using a CytoPulse large chamber cell fusion electroporator (Cyto Pulse Sciences, Inc., Glen Burnie, MD).

vi. the resulting hybridomas are then screened for the production of antigen- specific antibodies.

vii. Following routine steps and ELISA and further screening stable subclones are cultured in vitro to generate small amounts of antibody in tissue culture medium for further characterization, which led to selecting Hybridoma clones 17D8, 2D3, 4Hl, 5C4,4Al 1, 7D3 and 5F4 for further analysis.

viii. For determining the CDRs of these cloned, the applicant carried out structural characterization using standard DNA sequencing techniques as stated in Example 2.

o. In view of the above, it is evident that all that the applicant has done is immunize transgenic mice like HuMAb mouse® or KM mice™ according to standard techniques. As expected, the PD-1 triggers the process of generation of antibodies which involve class switching and somatic mutation to generate high affinity human antibodies. Further steps of repeated immunization in order to increase the affinity of the antibody and steps of screening to determine the mice producing the highest titer are routine and standard steps, as acknowledged by the applicant. Upon selection of the highest titer producing mice, hybridomas were prepared to generate the monoclonal antibodies. The preferred monoclonal antibodies 17D8, 2D3, 4Hl, 5C4, 4Al 1, 7D3 and 5F4 were isolated and structurally characterized as described Example 2.

p. Thus, the applicant had no knowledge of the six-specific CDRs until the preferred isolated antibodies were structurally characterized using standard techniques. Accordingly, the applicant's averments and assertions that it selected the six-specific CDRs out of the numerous possibilities of potential CDR sequences is wholly misleading.

q. The opponent categorically submits that there was no prior selection of the six-specific CDRs, the sequencing of the antibodies was carried out only upon isolating

the preferred antibodies using standard sequencing techniques. It is submitted that upon immunization, the transgenic mice produced antibodies, which undergoes class switching and somatic mutation to generate high affinity human antibodies. Such preferred antibodies are selected based on the highest titer, followed by isolation and structural characterization using standard PCR and DNA sequencing techniques. Thus, arriving at the claimed antibody by standard methods in view of the disclosure in D1 and the knowledge possessed by a person skilled in the art is wholly devoid of any inventive step. It is reiterated that the preferred antibodies were produced as a result of the naturally occurring somatic mutation in the transgenic mice. In this regard, the Opponent also relies upon the textbook excerpt annexed to the Reply Statement as Exhibit 56, which elucidates the process of generating diversity in immunoglobulin repertoire. It in fact teaches that "in practice, combinatorial diversity is likely to be less than one might expect from the theoretical calculations above." Thus, the applicant's assertion is that the total possibilities of making a germline antibody is 1.9 million, is a theoretical calculation and does not happen in practice. Thus, a person skilled in the art using routine and standard techniques would have arrived at the alleged invention as claimed in view of D1.

r. Moreover, it was already known at the time of the invention that human antibodies have higher specificity (lower cross reactivity) and greater binding, as particularly taught in D4. D4 teaches that transgenic mice containing human heavy and light chain immunoglobulin genes to generate high affinity, completely human, monoclonal antibodies that can be used therapeutically to inhibit the action of TNF for the treatment of one or more TNF mediated disease. It further teaches that such completely human anti-TNF antibodies have affinity somewhere between $lxl0^{-9}$ M and $9x10^{-12}$ M. In fact, anti-TNF antibodies, Golimumab (Transgenic mice HuMab®) has a K_D of 0.018 nM.

s. [page 456 of Opposition]

> As used herein, the term "human antibody" refers to an antibody in which substantially every part of the protein (e.g., CDR, framework, C_L, C_H domains (e.g., C_H1, C_H2, C_H3), hinge, ($V_ , V_H$)) is substantially non-immunogenic in humans, with only minor sequence changes or variations. Similarly, antibodies designated primate (monkey, babboon, chimpanzee, etc.), rodent (mouse, rat, rabbit, guinea pid, hamster, and the like) and other mammals designate such species, sub-genus, genus, sub-family, family specific antibodies. Further, chimeric antibodies include any combination of the above. Such changes or variations optionally and preferably retain or reduce the immunogenicity in humans or other species relative to non- modified antibodies. Thus, a human antibody is distinct from a chimeric or humanized antibody. It is pointed out that a human antibody can be produced by a non-human animal or prokaryotic or eukaryotic cell that is capable of

expressing functionally rearranged human immunoglobulin (e.g., heavy chain and/or light chain) genes. (….) Low or acceptable immunogenicity and/or high affinity, as well as other suitable properties, can contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as raising significant HAHA, HACA or HAMA responses in less than about 75%, or preferably less than about 50% of the patients treated and/or raising low titres in the patient treated (less than about 300, preferably less than about 100 measured with a double antigen enzyme immunoassay) (Elliott et al., Lancet 344:1125-1127 (1994), entirely incorporated herein by reference).

t. [Page 505 of Opposition]

Materials and Methods Animals

Transgenic mice that can express human antibodies are known in the art (and are commecially available (e.g, from GenPharm International, San Jose, CA; Abgenix, Freemont, CA, and others) that express human immunoglobulins but not mouse IgM or Ig . For example, such transgenic mice contain human sequence transgenes that undergo V(D)J joining, heavy-chain class switching, and somatic mutation to generate a repertoire of human sequence immunoglobulins (Lonberg, et al. Nature 368:856-859 (1994)). The light chain transgene can be derived, e.g, in part from a yeast artificial chromosome clone that includes nearly half of the germline human V region. In addition, the heavy-chain transgene can encode both human μ and human l(Fishwild, et al. Nature Biotechnology 14:845-851 (1996)) and/or 3 constant regions. Mice derived from appropriate genotopic lineages can be used in the immunization and fusion processes to generate fully human monoclonal antibodies to TNF.

u. Thus, it was all but expected that human antibodies have higher specificity and binding.

v. In this regard, reference was made to the Expert evidence of Dr. Sateesh Kumar Natarajan. Dr. Sateesh relies on D1 of the opposition. Additionally, he relies on 4 more Annexures as stated at page 1030 of the Opposition Volume, of which WO2002/079499 is of particular relevance.

w. Dr. Sateesh explains the state of the art at the time of the alleged invention of the impugned patent application and all that as known about PD-1 and PD-L1 and states that it is a natural endeavour in this field of research to make the human antibodies for achieving higher efficacy and a safer toxicological profile and methods for producing human antibodies were already well known in the art at the time of the invention. He further states the process of iterative cycles of mutation

and selection of higher specificity antibody from a myriad antibody repertoire ("affinity maturation"), is a natural immune response in any mammal and that transgenic mice, such as HuMAb® and KM mice™, are in fact engineered in the lab to mimic, and take advantage of, this natural process. WO2002/079499 teaches the modulation of immune response by contacting an antibody that modulates signalling via PD-1. In examples 8 and 9, '499 exemplifies the preparation of murine antibodies and human antibodies to B7-4 and PD-1 respectively. The fully human antibodies were prepared using transgenic mice having human germline as exemplified in Example 9.

x. In fact, the method steps followed in Example 9 to produce the fully human antibodies are similar to the present process. It has been set out below for ready reference.

Example 9: Generation of Fully Human Antibodies to B7-4 (pages 1655 & 1656 of the opposition)

In this example, fully human antibodies against B7-4 or PD-1 are made in mice that are transgenic for human immunoglobulin genes. Transgenic mice are made using standard methods, e.g., according to Hogan, et al, "Manipulating the Mouse Embryo: A Laboratory Manual", Cold Spring Harbor Laboratory, which is incoφorated herein by reference, or are purchased commercially. Embryonic stem cells are manipulated according to published procedures (Teratocarcinomas and embryonic stem cells: a practical approach, Robertson, E. J. ed., IRL Press, Washington, D.C.,
1987; Zijlstra et al. (1989) Nature 342:435-438; and Schwartzberg et al. (1989) Science 246:799-803, each of which is incoφorated herein by reference). DNA cloning procedures are carried out according to Sambrook, J. et al. in Molecular Cloning: A Laboratory Manual, 2d ed.,
1989, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., which is incoφorated herein by reference. Oligonucleotides are synthesized, e.g., on an Applied Bio Systems oligonucleotide synthesizer according to specifications provided by the manufacturer or are purchased commercially.

Transgenic mice are immunized using a purified or recombinant B7-4
or
PD-1 or a fusion protein comprising at least an immunogenic portion
of
the extracellular domain of B7-4 or PD-1. Approximately four hundred μg of B7-4 or PD-1 in 100 μL of phosphate buffered saline (PBS) is injected intraperitoneally into each mouse. Serum samples are collected approximately six days later by retro-orbital sinus bleeding.

Antibody reactivity and specificity for B7-4 or PD-1 are assessed using an indirect enzyme-linked immunosorbent assay (ELISA). Several

immunoglobulin superfamily molecules are tested as controls (e.g., CTLA4 and CD28) to analyze the antibody specificity of the antibody for B7-4 or PD-1. Antibodies having human variable regions which bind to B7-4 or PD-1 are detected by enzyme conjugates specific for human IgM and human IgG sub-classes with no cross reactivity to mouse immunoglobulin. Briefly, PNC microtiter plates are coated with B7-4 or PD-1 by coating wells overnight at 37°C with 5 μg/mL B7-4 in PBS. Serum samples are diluted in PBS, 5% serum, 0.5% Tween-20 and are incubated in the wells for 1 hour at room temperature, followed by anti-human IgG Fc and IgG F(ab')- horseradish peroxidase or anti-human IgM Fc-horseradish peroxidase in the same diluent. After lhour at room temperature enzyme activity is assessed by addition of ABTS substrate (Sigma, St. Louis, Mo.) and read after 30 minutes at 415-490 nm. In pre-immunization serum samples from the same mice, titers of human antibodies to the same target antigens are also tested.

Spleen cells isolated from mice having appropriate antibody titers are harvested. The spleen cells are fused to appropriate fusion partners (e.g., myeloma cells) to make hybridomas. Hybridomas and antibodies are manipulated according to "Antibodies: A Laboratory Manual", Ed Harlow and David Lane, Cold Spring Harbor Laboratory (1988), which is incorporated herein by reference.

y. Dr. Sateesh also referred to Exhibit A4, Example 2 (pages1867 & 1868 of the opposition) that disclose that human antibodies (such as those prepared by transgenic mice) will have a high likelihood of arriving at good antibodies.

> Example 2: Generation of High Affinity Human IgG Monoclonal Antibodies Reactive With Human IL-12 Using Transgenic Mice
>
> **Summary**
>
> Transgenic mice have been used that contain human heavy and light chain immunoglobulin genes to generate high affinity, completely human, monoclonal antibodies that can be used therapeutically to inhibit the action of IL-12 for the treatment of one or more IL-12- medıated disease (CBA/J x C57/BL6/J) F, hybrid mice containing human variable and constant region antibody transgenes for both heavy and light chains are immunized with human recombinant IL-12 (Taylor et al., Intl. Immunol. 6.579-591 (1993); Lonberg, et al.,
>
> Nature 368:856-859 (1994); Neuberger, M., Nature Biotech. 14.826 (1996); Fishwild, et al., Nature Biotechnology 14:845-851 (1996)). Several fusions yielded one or more panels of completely human IL-12 reactive IgG monoclonal antibodies. The completely human anti-IL-12 antibodies are further characterized. All are IgGl. Such antibodies are found to have affinity constants somewhere

between $1x10^9$ and $9x10^{12}$. The unexpectedly high affinities of these fully human monoclonal antibodies make them suitable candidates for therapeutic applications in IL-12 related diseases, pathologies or disorders.

z. Based on the above, Dr. Sateesh stated that the claimed invention is a result of routine techniques. Interestingly, even though the applicant relied upon seven evidences from various Experts, none has addressed Dr.Sateesh's evidence, leave alone denying or refuting his opinion.

aa. Due to dearth of time, the Opponent could not discuss and make submissions at length on the other documents which were relied upon in its representation. Accordingly, it wholly adopts its submissions made in the representation with respect to the D2 to D4.

bb. Turning to the applicant's reply under the ground of obvious, its only contention is that none of the cited references teach or suggest the six-specific CDRs of 5C4. It is stated that even the applicant was unaware of the six-specific CDRs until it structurally characterized the antibodies using standard PCR and DNA sequencing techniques. Insofar as the production of the antibodies are considered, as elaborated in the preceding paragraphs, the production process is standard and routine and is wholly devoid of an inventive step, whatsoever. Therefore, the claims of the impugned application are obvious to a person skilled in the art and lacks an inventive step.

cc. Expected properties of the claimed antibody, 5C4 Alleged tighter binding

The Opponent would deal with the contentions and assertions of the applicant as provided in its Reply Statement. As stated in paragraphs 24 to 30, the applicant has stated that, no antibody with a similar sequence (leave apart identical) was known. It further states that the person skilled in the art would not be able to arrive at the six-specific CDRs by modifying the antibodies disclosed in D1 or D2. It is submitted that the applicant chose a method of production of the antibodies wherein the transgenic mice by itself produced high affinity antibodies as a result of the naturally occurring somatic mutation. The applicant itself acknowledges such class switching and somatic mutation to generate high affinity human antibodies, which is naturally occurring in the mouse. Therefore, the changes in the sequences were bound to happen when the transgenic mice are immunized, particularly repeatedly.

It has further relied upon the tighter binding affinity of 5C4. To substantiate it, the applicant has relied upon Roques affidavit which puts forth the

comparison with the human antibodies taught in D2. The K_D value of 5C4 as provided in the impugned specification is 0.73 nM, while in Roques affidavit it is 0.336nM and in the FDA dossier it is 3.06 nM. The Opponent submitted that such disparate and inconsistent figures are highly unreliable and lacks credibility. The applicant has merely responded by stating that such difference is a mere variance. It was submitted that a difference or 4 to 9 fold is not regarded as mere variance in scientific experiments as stated by Dr Novak. The concluding paragraph of her evidence is reproduced below.

> Beyond this discrepancy is the difference between the K_D listed in the referenced FDA review document on the molecule, where a K_D of 3.06 nM is listed. This value is 9.1 times higher than the recalculated value from the above table, or 4.2 times higher than the original value claimed. Though variations in Biacore values are known to exist between experiments, the variation within the applicants claims in different documents undermines the validity of claiming a significantly lower K_D than the originally licensed molecule. The difference in K_D from that listed in the FDA review document (EXHIBIT C) for the very same molecule (5C4/Nivolumab) adds further ambiguity to the underlying data relied upon in this patent. This leaves the 5C4 molecule as a molecule claimed to be Nivolumab, whose affinity across a range of less than 1 order of magnitude but their exact value is experimentally uncertain, rendering it unreliable.

dd. Therefore, the tighter affinity as indicated by the K_D value does not establish any inventive step. Moreover, as manifest from the above submissions, the K_D value is inherent of the antibody and is expected in view of the method of production of the claimed antibodies, specifically in light of D4 which clearly teaches that human antibodies are expected to have better binding. In fact, anti-TNF antibodies, Golimumab (obtained from Transgenic mice HuMab®), has a K_D of 0.018 nM. Alleged higher binding specificity

The applicant relied upon the first Fife affidavit to establish the allegedly superior specificity of the 5C4 antibody. The Opponent submitted that Dr. Fife has compared data from different experiments which not only vary in scale but lacks proper control to conclusively infer that 5C4 has higher specificity. The Opponent relies upon its expert, Dr. Kumar's evidence, which reads as under.

> Thus, Dr. Fife compares data from different experiments, performed at different occasions, by different persons (viz. the inventors and Dr. Fife), that also vary in scale, and with no proper control, to infer that 5C4 / nivolumab

possesses high specificity to PD-1, and/or lack cross-reactivity to other members of CD28, when compared with prior-art antibodies. This is an inappropriate way of making comparisons, and hence the conclusions cannot be considered reliable.

It is stated that on one hand Dr. Fife emphasizes the importance of 'direct comparison' of data obtained from a single experiment, for the comparison of binding affinities of nivolumab with prior-art antibodies, and thereby chooses to brush aside the variations in KD values. On the other hand, the Applicant, and Dr. Fife in particular, pivot to different standards, while comparing the specificity of nivolumab with prior-art antibodies.

In fact, when Dr. Madamwar (expert of previous Opponent) pointed out this scientifically inconsistent approach, i.e., comparing different experimental data to infer specificity, Dr. Fife's response was, "Dr.Madamwar's critique of my analysis for the "absence of comparison of 5C4 with the four antibodies of the prior art in a single experiment" is meritless. It is not necessary to test 5C4 in the same experiment as the prior art antibodies to determine that the prior art antibodies cross react but 5C4 does not" [Dr. Fife's statement, paragraph no.18 in Exhibit 60-Third Affidavit of Applicant]. This not only goes to show the wholly contradictory stances taken by the expert, but also results in inferences/conclusions made from application of inappropriate scientific methodology

ee.The Opponent submits based on Dr.Kumar's affidavit dated 12th September 2018 filed with the Rejoinder of the Opponent regarding Fife'sAffidavits as follows –

At the outset, Dr. Fife himself in paragraph 10 of his Fourth Affidavit at page 907 of the Reply statement himself states that –

> ''A good way to compare affinity of different antibodies for a given antigen is to test the compared antibodies in the same experiment using the same conditions. This allows comparison of relative affinity – which is a better comparison than examining numerical values measured in different experiments.''

However he does exactly to the contrary. This has been pointed out by Dr. Vikas Kumar in paragraph 15 of his Affidavit.

i. Dr. Kumar also points out that –

14. I say that Dr. Fife in his affidavit describes the 10-fold difference between the various binding affinity values of 5C4 reported by the Applicants (0.336 nM or 0.47 nM and 3.06 nM) as 'small' and within the "normal range" of variation. I disagree with Dr. Fife's statement that an order of magnitude variation in affinity is "small", and reiterate Dr. Novak's (Dr. Reddy's expert) conclusion that affinity values displaying such magnitude of variations cannot be considered accurate and reliable, especially so when the antibody concerned is of therapeutic importance.

ii. Dr. Kumar points out the following with respect to Experiments that compare the specificity with other anti-PD1 antibodies – Exhibit 38 to Reply Statement-

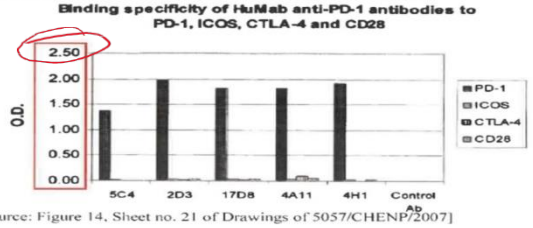
8. I say that Dr. Fife in his Affidavit (Experiments that compare the specificity of 5C4 antibody with other anti-PD1 antibodies - Exhibit 38 of Applicants) concludes that 5C4 antibody exhibits high specificity to PD-1, while not binding to other CD28 family members, ICOS, CTLA-4, or CD28. On the other hand, prior art anti-PD1 antibodies (PD1-17, PD1-28, PD1-33 and PD1-35) are alleged to exhibit greater cross-reactivity, since they bind to at least one of the other CD28 family members as well. He arrives at these conclusions by comparing the binding studies performed by him in 2015, with the experimental results reported in Example 3 and Figure 14 of the patent application specification, filed in 2005.

In paragraph 9 of his affidavit Dr. Kumar further points about the data that the Dr. Fife does not conduct the experiment again for 5C4 but uses the data shown in the specification against data of the prior art fully human anti-PD1 antibodies done in a different set of experiments in 2015 –

9. At the outset I say that such comparisons are scientifically inappropriate and hence unacceptable. Comparisons of properties of molecules, especially those exceedingly sensitive to experimental conditions and variations, (such as, binding affinity, cross-reactivity etc.) must be performed in a single set of experiments to ensure identical assay conditions and reduced variability (due to person, process etc.). This was clearly not done by Dr. Fife. Experiments performed by him in 2015 were only with anti-PD1 antibodies other than the 5C4 antibody. He then proceeds to compare the binding results of these antibodies with the 5C4 results reported in the application specification of 2005. Thus, Dr. Fife's conclusions cannot be considered reliable.

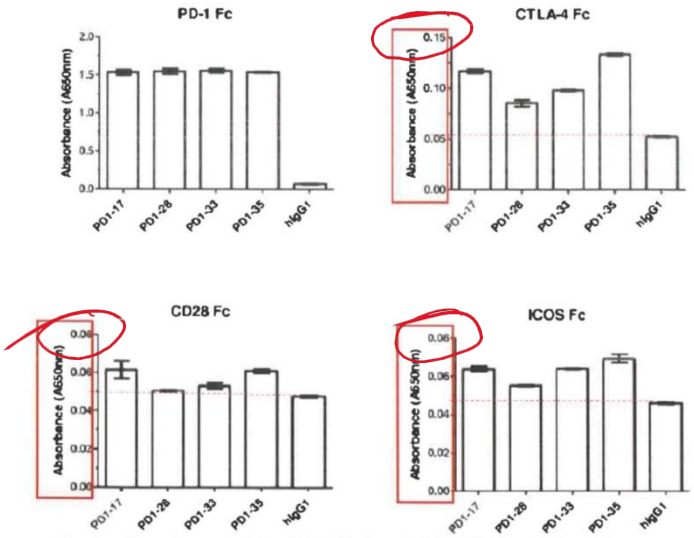
iii. With respect to Binding specificities and in respect of which a question fell from the Ld. Controller as to whether the comparison shows better binding specificities for 5C4, it is pointed out that the Figure 14 of 5C4 is from the specification–

Figure 14 of the patent specification representing 5C4 data



[Source: Figure 14, Sheet no. 21 of Drawings of 5057/CHENP/2007]

While the data of the prior art fully human anti-PD1 antibodies (from D2) are different conditions where even the control hIgG1 shows binding of high value unlike the control used in Figure 14 for 5C4. The same is evident from the date of Fife i.e.



[Source: Figure 1, page 6 of Dr. Fife Affidavit and Exhibit 38 of the Applicants]

The said charts do not have 5C4 mentioned in them and the said data is to be compared with the Figure 14 of the specification where in additionally the chart in Figure 14 conveniently is silent on the error range in the statistical representation and thus is unreliable apart from the scale being different.

Dr. Kumar IMPORTANTLY further specifically points out that -

11. Be that as it may, Dr. Fife's experiments suggest that the prior-art antibodies, PD1-17, PD1-28, PD1-33 and PD1-35 have significant binding to PD1, with 1.5 absorbance units (AU) when compared to the negative control, hG1. On the other hand, the binding of these prior-art antibodies to CTLA4 are in the range of 0.08 to 0.13 AU, and to CD28 and ICOS in the range of 0.05 to 0.06 AU. However, and important to note, **these values are in the same range as the binding value reported for the negative control (hG1), 0.05AU**. Hence, one cannot infer this as 'binding'.

But based on these data, Dr. Fife makes the claim that the prior art antibodies exhibit less specificity (viz. greater cross-reactivity) than 5C4. Dr. Fife arrives at this conclusion by reporting these values on a scale of 0.0 to 0.1 or 0.0 to 0.06 AU in the accompanying figures, to show significance that is not apparent. Dr. Fife then proceeds to use the values presented on these scales to compare with that reported for 5C4 in Figure 14 of the specification, **which is plotted on a scale of 0.0 to 2.5 AU**, in which any absorbance units of less than 0.1, would either not show, or would appear very insignificant (the respective figures are reproduced below wherein the scales of the axis are highlighted in red rectangles and dashed lines point to the 0.05 AU obtained for negative control. It should also be noted that in the Figure 14, the 5C4 binding to PD1 appears to be less than 1.5 AU). Were the scales of comparison same, the prior art antibodies may have been shown to exhibit same/similar levels of specificity, and cross-reactivity, as 5C4.

12. Thus, using the 5C4 data in Figure 14 of the specification and relating it to a different set of experiments (performed by Dr. Fife), that were not designed to be comparative, leads to misleading and unreliable comparisons and conclusions.

iv. With respect to data in the fifth Affidavit of Dr. Fife, Dr. Kumar categorically points out –

> 16. Dr. Fife's 5th Affidavit includes a series of experiments in which the 5C4 antibody was compared with the prior-art antibodies on their a) binding affinity b) ability to block binding of PD1 ligands to PD1, and c) cytokine production and cell proliferation in human PBMCs.
>
> 17. First and foremost, I say that all data appear to be obtained from a single measurement, and none of them include any replicates to demonstrate statistical significance of the data, which is required to derive any meaningful conclusion. Hence I question the accuracy and scientific reliability of such data. Nevertheless, I proceed with the analysis of the data and infer the following;

Interestingly, the data goes to show that there is in fact no improvement in 5C4 over prior art i.e.

> **A. Binding of the anti-PD1 antibodies to PD1 expressed on CHO cells:**
>
> 18. I say that in the experiment performed to compare the binding of prior-art antibodies and 5C4 antibody to PD1 expressed by CHO cells, the binding levels of all the antibodies, especially those between 5C4 and PD1-28 and PD1-33 were comparable [Figure 4.1]. This has been acknowledged by Dr. Fife.
>
> 19. As a result, in the experiment performed to assess the blocking of ligand binding to PD1 by the PD1 antibodies, all the five antibodies (PD1-17, PD1-28, PD1-33, PD1-35 and 5C4), seem to be effective in blocking the binding of ligands, PDL1 and PDL2, to PD1. The minor difference in the mean fluorescence intensity (a measure of effectiveness of blocking) between the antibodies, for example as seen in Figure 6.1, can fall within a typical experimental variability, and cannot be relied upon to make any inference. Especially in the absence of error bars or standard deviation represented in the data (a point I allude in earlier paragraphs/section as well), one cannot establish that there exists a true or significant difference between the effectiveness of the antibodies.
>
> 20. Hence, from the data one cannot conclude that 5C4 (or any other antibody tested) is superior to other PD1 antibodies tested in the experiment.

Thus even the data in FIGURE 4.1 and 6.1 as mentioned above is not relevant.

v. Similarly the supposed data on

> **B. Effect of the antibodies on cell proliferation and cytokine production (studies that correlate to T-cell function):**

Actually shows no improvement over prior art i.e. Dr. Kumar in paragraph 21 of his affidavit has stated that -

In the MLR assay performed by Dr. Fife to compare the ability of 5C4 and prior-art antibodies to induce cytokine production, the 5C4 antibody is seen to increase cytokine production relative to the control (hG4) and prior-art antibodies. However, in the case of another MLR assay performed to check yet another function of the antibodies, the ability to induce T-cell proliferation, at least one of the prior-art antibody, PD1-35, is concluded to have a similar effect as 5C4. This was noted by Dr. Fife himself [Example 5, Point 9 of 5th Affidavit].

Thus, while 5C4 appears to show superior effect in one of the functional assays, it does not show any superiority over at least one of the prior-art antibodies in another assay. That is, the results of the two MLR functional assays does not augment or corroborate each other. Hence it is difficult to conclude that 5C4 is functionally superior over the prior-art antibodies.

In fact in the 5th Affidavit of Dr. Fife (at Pages 1035 to 1051 of the Reply Statement Volume), Dr. Fife makes a categorical admission (on page 1037 of the Reply Statement Volume) at Point 9 under the heading Example 5 which highlights the fact that PD1-35 of D2 (WO2004/056875) has similar level of proliferation as that of Antibody 5C4 i.e.

9. Antibody 5C4 also demonstrably enhanced proliferation of PBMCs in the MLR (data not shown). One of the other antibodies tested (PD1-35) produced similar levels of proliferation at an antibody dose of 1µg/mL. However, it was noticeable that the second best performing antibody from Example 4 (PD1-28) produced levels of proliferation that were considerably lower than 5C4 at a dose of 100µg/mL.

vi. With respect to the data of Dr. Fife on

C. Effect of the antibodies on the release of cytokines in blood:

same shows that –

22. In the experiments performed to determine whether the anti-PD1 antibodies (the 4 prior-art antibodies and 5C4) provoked the release of certain cytokines from unstimulated human blood cells (tested as a measure of negative response, and hence low side effects), the results, presented in Tables 7.1 and 7.2 of the Affidavit, depict high variability, making the derivation of any a meaningful inference difficult.

To illustrate:

- Non-specific cytokine stimulation by an antibody is generally measured by adding the antibody into a human blood sample, incubating it for a period of time and measuring the levels of cytokine post the incubation period. In case of cytokine stimulation by a particular antibody, one would normally expect an *increase* in cytokine level (or at least maintain an equivalent value) upon increase in concentration of antibody, at a particular incubation time.
- However, on the one hand, at a particular incubation time, 10 µg/ml of an antibody (PD1-28 and 5C4) released 36 pg/ml cytokines. But the same antibodies, in 100 µg/ml concentration, did not seem to stimulate any cytokine release [the incongruity in values are pointed out in the figure reproduced below]. If the response has reached to a saturation level with low concentration, then it should at least be maintained at a similar level with higher concentration at the same incubation time.
- Also, and surprisingly, the incongruent values obtained for a particular antibody gets repeated again for a different antibody, with the same level of precision, i.e., up to two decimal points [highlighted by rectangles in the Tabulated data]. PD1-28 and 5C4 increase the human IL-17A levels to the same extent, albeit at different incubation time. Similarly, PD1-35 and 5C4 increase human IL-6 levels to the same extent, again at different incubation time.

TABLE 7.1 Cytokine production following 6 hour incubation with blood

	Human IL-17A (pg/mL)	Human IFN-γ (pg/mL)	Human TNF (pg/mL)	Human IL-10 (pg/mL)	Human IL-6 (pg/mL)	Human IL-4 (pg/mL)	Human IL-2 (pg/mL)
PD1-17 (10µg/mL)	**0.00**	0.00	3.64	0.00	2.16	0.24	0.00
PD1-17 (100µg/mL)	**0.00**	0.00	2.10	**0.44**	6.74	0.24	0.90
PD1-28 (10µg/mL)	**36.11**	0.00	15.65	**0.93**	58.75	0.24	0.00
PD1-28 (100µg/mL)	0.00	0.00	90.01	**3.66**	433.07	0.61	0.00
PD1-33 (10µg/mL)	0.00	0.00	2.10	**1.10**	4.76	0.00	0.00
PD1-33 (100µg/mL)	0.00	0.00	20.18	1.10	**74.63**	0.24	1.30
PD1-35 (10µg/mL)	0.00	0.00	0.00	0.00	2.81	0.00	0.00
PD1-35 (100µg/mL)	0.00	0.00	3.64	0.00	0.54	0.24	0.00
SC4 (10µg/mL)	0.00	0.00	3.64	0.77	3.13	0.00	0.00
SC4 (100µg/mL)	0.00	0.00	4.40	0.12	3.46	0.00	0.10
hIgG1 (10µg/mL)	0.00	0.00	5.15	1.10	18.28	0.00	0.00
hIgG1 (100µg/mL)	36.11	0.00	3.64	0.00	6.74	0.00	0.00
hIgG4 (10µg/mL)	176.63	0.00	4.40	0.00	0.54	0.00	0.00
hIgG4 **(100µg/mL)**	115.91	0.00	2.68	1.10	4.76	0.24	0.00
control **(blood only)**	66.26	0.00	0.00	0.00	0.00	0.00	0.00
control (blood only)	107.16	0.00	0.00	0.12	1.84	0.00	0.00
anti-CD3 (10µg/mL)	0.00	329.87	641.13	64.99	327.28	0.00	369.35
anti-CD3 (100µg/mL)	180.53	774.21	1490.50	130.25	1542.22	22.23	730.84

TABLE 7.2 Cytokine production following 24 hour incubation with blood

	Human IL-17A (pg/mL)	Human IFN-γ (pg/mL)	Human TNF (pg/mL)	Human IL-10 (pg/mL)	Human IL-6 (pg/mL)	Human IL-4 (pg/mL)	Human IL-2 (pg/mL)
PD1-17 (10µg/mL)	0.00	0.00	0.00	0.00	1.51	0.00	0.00
PD1-17 (100µg/mL)	**0.00**	**0.00**	1.31	0.44	0.54	0.00	0.00
PD1-28 (10µg/mL)	0.00	5.71	0.00	0.12	21.40	0.00	0.00
PD1-28 (100µg/mL)	66.26	0.00	5.15	4.24	475.85	0.00	0.00
PD1-33 (10µg/mL)	0.00	5.71	0.00	0.44	**0.54**	0.00	0.00
PD1-33 (100µg/mL)	0.00	0.00	11.15	9.67	2142.74	0.00	0.00
PD1-35 (10µg/mL)	**0.00**	**3.11**	1.31	0.00	1.51	0.00	0.00
PD1-35 (100µg/mL)	**0.00**	0.00	0.00	0.00	0.00	0.00	0.00
SC4 (10µg/mL)	36.11	5.71	0.00	0.00	2.81	0.61	0.00
SC4 (100µg/mL)	0.00	5.71	0.00	0.00	0.54	2.11	0.00
hIgG1 (10µg/mL)	**0.00**	0.00	6.65	0.93	**29.79**	0.00	1.30
hIgG1 (100µg/mL)	0.00	0.00	1.31	1.10	8.40	0.00	**0.00**
hIgG4 (10µg/mL)	97.98	0.00	0.50	0.00	1.19	0.61	**0.00**
hIgG4 (100µg/mL)	0.00	0.00	0.00	0.00	0.86	0.00	0.00
control (blood only)	0.00	0.00	3.64	0.00	1.19	0.24	0.00
control (blood only)	0.00	0.00	0.00	**0.12**	**0.86**	0.00	0.50
anti-CD3 **(10µg/mL)**	0.00	1514.24	**2489.87**	341.21	10399.05	34.30	2641.14
anti-CD3 (100µg/mL)	0.00	**1393.90**	**1172.90**	396.41	**17321.36**	**16.33**	1825.46

the

In any case, the data does not show superiority and in fact contradict the case of the Applicant i.e.

24. However, assuming that the values are accurate, comparison between the various antibodies reveal that three of the five tested antibodies (5C4, PD1-17 and PD1-35) show the same levels of cytokine release, i.e., they do not stimulate any significant cytokine release compared to their respective control. In particular, PD1-35 shows a uniformly lower response, i.e., minimal stimulation of cytokines in all of the human cytokines tested, compared to 5C4 or any other antibody.

25. While PD1-28 and PD1-33 antibodies show an increased IFN-γ release in the unstimulated blood, 5C4 has also demonstrated the same effect. Also the increase in cytokine (IL-6) release, relative to the control, observed for PD1-28 and PD1-33, is also seen for 5C4 (albeit, only slight).

26. I thus say that at any particular time of incubation (6h or 24h) all the tested antibodies appear to show reduced release of one cytokine and increased release of another (although PD1-35 is an exception and depicted an uniformly much lower response). Hence, picking one particular cytokine, and deducing an antibody response/non-response is not possible with the kind of data presented.

On the whole, these results do not demonstrate any superiority, in 5C4's functional effect or lower side effects, *vis-à-vis* other anti-PD1 antibodies.

The aforesaid paragraphs of the affidavit of Dr. Kumar clearly highlight the admissions of Dr. Fife in his 5th affidavit at page 1038 of the Reply Statement Volume in points 13 to 14 regarding Example 7 wherein Dr. Fife in facts highlights that there is no demonstration of superiority by the antibody 5C4 over all the antibodies of D2 (WO2004/056875) and in fact the same are comparable i.e.

Example 7 - Effect of human anti-PD-1 antibodies on the release of cytokines in human blood

13. The aim of this experiment was to compare the four different anti-PD-1 antibodies from WO 2004/056875 (PD1-17, PD1-28, PD1-33, PD1-35) with the antibody 5C4 from European Patent No. 2,161,336 for the effect of each antibody on the release of certain cytokines from unstimulated cells in human blood. The protocol used is set out in Annex 4.

14. The results are shown in Tables 7.1 and 7.2. In general, at both 6 hours and 24 hours following administration of the antibodies to human blood, the response provoked by three of the five tested antibodies (5C4, PD1-17, and PD1-35) was comparable to or lower than the corresponding isotype negative control, that is the results are effectively negative. The only exceptions are antibodies PD1-28 and PD1-33. At both time-points after administration of these antibodies, levels of the pro-inflammatory cytokine IL-6 were produced that were considerably in excess of the corresponding isotype negative control.

Thus, the data of Dr. Fife relied upon by the applicant fails to show any superiority of 5c4 over fully human anti-PD1 antibodies of the prior art and more often than not the comparison shows that some of the prior art antibodies are as good as 5C4. It is thus stated that the applicant's data on tighter binding and higher specificity is not only inconclusive but also expected in view of the teachings of the cited documents. Therefore, the data fails to establish the inventiveness of the alleged invention as claimed.

2.4 APPLICANTS SUBMISSIONS ON INVENTIVE STEP OF THE AMENDED CLAIMS:

2.4.1 Applicants submissions on Inventive Step in PGO-1:

b. The Presently Claimed Invention is Not Obvious

33. The claimed antibody comprising the six CDRs of the 5C4 antibody or the present application would not have been obvious to a person or ordinary skilled in the art (POSA) at the time of filing the application in view or any combination of the references cited hy the Opponent. None or the cited rcrcrcnccs would have motivated a POSA to arrive at the claimed antibody with a JTasonahlc expectation or success. Furthermore, the claimed antibody had superior properties that would not have been expected in view of the cited rcJCrcnccs.)-·0r at least these reasons. the claimed antibody comprisinthe six CI)Js oftlw l("4 .1111ihndy \Vf.lU]d JW1 h:IVC bC:Cll obviou ; at the time or the rrcscnt invention. and the Opponent's clain1 of obviousncs-> should be dismissed.

40. An obviousness enqutry thus requtres that the Opponent show that the claimed subject matter was naturally suggested by the alleged prior art or predictable from the alleged prior art, and that a POSA would have been motivated, with a reasonable expectation of success, to arrive at the claimed invention in view of the alleged prior art. Because no combination of the references cited by the Opponent motivates a POSA to arrive at the claimed antibody comprising the six CDRs ofthe 5C4 antibody with a reasonable expectation of success, the claimed antibody would not have been obvious at the time of the invention. And, even if *arguendo* the Learned Controller accepts the Opponent's arguments that the claims are *prima facie* obvious, objective indicia weigh in favor of non-obviousness. Accordingly, Applicants request that the Opponent's arguments of obviousness be dismissed.

D1 TO D7

41. In the notice of Opposition. PCT claims 1-7 and 43-56 were said to be lacking an inventive step over (i) D 1-D3 (4.1 of the Opposition) and D4 and D5 in view of D6 and D7 (4.2 of the Opposition). Not in acquiescence to the allegation. hut solely In

expedite the representation proceeding, Applicants canceled the above claims, rendering the allegation moot.

D4, D8, D9, DIO, D11, D12, and D13 and Anncxnrcs l to 10

42. The Opponent asserted in the notice of Opposition that the "subject matter" of the application "lacks inventive step" over the "prior art teachings" or D4, D 8, D 9, D10, D11,D12, and D13

43. The Opponent alleges that human and non-human anti-PD-1 antibodies were known in the art at the time of the filing date of the present invention, as well as methods or producing the same.

44. The Opponent contended that the present invention merely provides "an alternative antibody to the antibodies taught in the prior art," concluding that the "Sub_ject matter" of this application is obvious.

45. During the hearing, the Opponent relied on the newly cited documents (i.e., Anncxures 1 to 10) and even Dl and D2 to allege that the claimed antibody comprising the six CDRs of the 5C4 antibody was prepared by known methods, and thus the claimed antibody would have been an obvious alternative to other antibodies a11cgccl1y known in the art, e.g,, anti-1L12 antibody (Annexure 2), anti-1L-CIJ-25 (Annexure 3), anti-TNf antibody (Annexure 4), and anti-TNf'-a antibody (Annexure 9). (The Opponent did not deal \Vith any of these newly cited documents in detail and just passed a general statement)

-1-(L App!icanh do not agree \Vith the above and submit the following:

i) A POSA would not have been motivated to arriYe at the claimed antibody

-1-7. 0Jonc of rcfCrcnccs D4, 08, D(J, D I0. D I L D !2_ anJ D)) or Annexure::, I to I0. or anv other document (l1ke U1 or U2) or combm llion thereof. teachcor suggests an anti-PD-1 mtibody or nn antigen binding portion thereof comprising the six CDRs of

the 5C4 antibody. In fact, the antibodies disclosed by the cited references are completely different n·om the claimed antibody:

a. D1 and D2 do not disclose any particular nnti-PDl antibody, leave apart antibody with the claimed CDR sequences and only disclose a method for modulating an immune response with an agent thatmoduh1tes signaling via PD-1 or a method !Or screening compounds that modulate such signaling

b. The six CDRs of the antibodies disclosed in D8 and D9, i.e., PDI-17, PDI-28, PDI-33, PDI-35, and PDI-F2, hove very little to no homology to the six CIJRs of the 5C4 antibody. *See* Exhibit 36.

c. Eoch or the six CDRs of the .143 antibody in DIO and Dll has 0% to 50% homology to the corresponding CDR of the 5C4 antibody. *See* Exhibit 36.

48. rurthcnnore, none of the antibodies disclosed by D12, 013, and 04 are derived from human. Rather, Dl2 discloses a hamster anti-mouse PD-1 antibody, D11 discloses a rat anti-mouse PD-1 antibody, and D4 discloses five mouse PD-1 antibodies. One skilled in the art would have clearly known that the six CDRs in each or the non-human antibodies disclosed by D 12, 013, and D4 would have had no mcaninglllli homology to the six CDRs of the human 5C4 antibody. J\t the time or filing of the prcsLnt application, a POSA V.'otlid have known that antibodies derived rrom a mouse genome or another non-human organism's genome would have different CDR sequences from the six CDR sequences of the 5C4 antibody. *S'ee, e.g.,* Riechmann *e! a/., Na!ure 332:323-327* (1988) (Exhibil32 oflhc Reply sllitcrncnt): and 012, page l 090. left hand column, second paragraph (noting that "G4 mAB ... docnot bind ht11m1n PD-! ").

49. Newly cited Annexurcs 1-10 also t iil to overcome tilL ddlcicncics of D1-Dl:1. /\nnexures 1-6 and 9 do not even disclose PD-1 or antibodic.'i directed to JlD-1. kt alone the specific CDR:-. or the 5('; antibody. Thus none of/\nnc.'\Urcs l-6 and i.J.nor any combination or Anncxures 1-6 and 0 \vith the previously cited rc/Crcnccs. would

have motiv8tcd a POSA \Vith a reasonable expect<1tion of succcsslldly arriving at the claimed anti-PD-1 antibody cornprising the six CDRs or the 5C4 antibody. Annexures 7, 8, and 10 are post-filing rc/Crenccs, which provide no evidence or obviousness at the time of the filing date of' the application.

50. Due to the lack of disclosure in the rcfCrcnces cited by the Opponent and the stark ditTerenccs in the CDR sequences between the reference antibodies in the cited references and the 5C4 antibody, a person skilled **in** the art *would not have been motivated to modj/.)' the ('DRs disclosed in the reference antibodies to arrive a/ the six CDRs of the 5C4 antibody.*

ii) There would have been no reasonable expectation of success

51. Without prejudice to the above, even if one were motivated to modify the CDR sequences of the rcJCrence antibodies, which Applicants dispute, it would have been essentially impossible to modify them in such a way as to arrive at the six CDRs of the 5C4 antibody, considering the vast Jif!'erences between these sequences.

52. Furthermore, the person *lrOidd no/ have had a reasontJh!c expectation lhot modif}inx the nf(•rcnce antibodies \Fotdd bring uhout the superior, therapeutic antibodies qfthe claimed invent inn described herein. See* Rudikoff e/ *a/., PN;JS* 79: 1979-19X3 (1982) (Exhibit 33 of Reply Statement).

53. Applicants further disagree with the Opponent's assertion thut the claimed antibody is no more than "an alternative antibody". The mere existence of other human antibodies against PlJ-1 prior to the filing of' this upplication does not render the presently-claimed anti-PD-1 antibody comprising the six CDRs or the 5C4 antibody obvious. Selecting the specific six CDRs or the presently-claimed. thcn1pcutic8lly superior antibody. out of the numerous possibilities of potential CDR sequences is neither trivial nor routine.

54. ThcreJ<H·c. Applicants rcspcctrully submit that the pending claims arc not obvious.

iii) Objective Indicia show that the pending claims are not obvious

SS. Even iJ: *orguendo,* the Lcurncd Controller believes that Opponent-cited reJ'erences render the clclimcd untibody *phma fCtcie* obvious, the objective indicia support a finding of non-obviousness. For example, evidence of unexpectedly superior properties, grant in other jurisdictions, regulatory expedited approvals, unmet need being ruJJlleJ, and commercial success weigh in favor of non-obviousness.

56. It is submitted that nivolumClb represents an important advance in the search for effective treatment or prevention of cancer. In this regard reliance is placed *Roche v. Cipla, 2012 (52) PTC I (Del),* in which it was held in paragraph 87:

> *87. Another reason which persuades me to il?fer to the conlrmJ' in !he absence qf the evidence is that there is a commercial success of the medicine "vorldwide which has been widely recognized and the some ;„„ proven to he swxes4it! medicine. This ;s clearjl-um the depw·itions rfPW 3 Nick Thatcher. it i.r.: true thai the said commercial success pr!r se is not delerminative (I the foe! that there i,)' a non obviousness. hut it at feast somehow ocls as an olfending circumstance to shOH' that there could have existed the purposefltl research on !he existing stale of' the ar! hy the person who is skilled in the art. who has made ceriain experiments and by narrmving down the compounds resulting in a single compound which has heen widely szu:ces. fitl ond ef/icacious.*

unexpcctedly superior properties

57. The 5C4 antibody has an unexpected!) superior binding affinity [lnd specificity ns compared to the antibodies in the cited references. The superior binding atlinity is disclosed in the PCT application os filed.

58. The direct comp<mson of !he reference antibodies 1nd the 5C'il :unihmh w:l.c. submitted during the representntion proceeding in the corresponding f·P patent b) an Oppo11t:11L EJ..hiUit *39* (H.oques Affidavit enclosed with the H.cply statement).

59. The binding aftlnity between the 5C4 antibody and the PDI-28, PDI-33, and PDI-35 nntibodies was tested in Biacorc kinetics assay for their affinity to rhPD-1 ΓC (R&D). *See* Exhibit 35. The *Ku* of the 5C4 antibody is 0.47 X 10·' M while the *Kn* of the rciCrcnce antibodies is higher than 3.23 *X* 10-^{9} **M.** The comparison table shown in Exhibit :35 is reproduced belov.,r.

60. The 5C4 antibody also has a high binding specillcity lr1r PD-1. Example 3 of the PCT speciJication (f'igure 14) teaches that the 5C4 antibody bound to PD-1 with high specilkity, but not to other CD28 family members (ICOS, CTLA-4, CD28).

61. In controst, the PDI-17, PDI-28, PDI-33 and PDI-35 antibodies bind to human PD-1, but also bind to at least one of CTLAA. CD28 and ICOS. *Sec* fife Aftldavit at Figure I and I 0-17. As shown by Dr. Fife's af1idavit, the superior specificity of the 5C4 antibody to the reference antibodies "would not have been expected."

64. The 5C4 antibody (nivolumab) is shown to have unexpectedly superior therapeutic efficacy to standard chemotherapy. Dr. Feltquate has explained the details in his evidence, a summary of which is also enclosed herewith. In particular:

a. Nivolumab has repeatedly shown "'[u]nprecedented' responses in comparison to standard-of-care treatments and in various tumor types. As evidence of the unprecedented response, Dr. Feltquate cites multiple reports and scientific articles showing "the transformative nature that nivolumab [the 5C4 antibody] is expected to have on cancer treatments."
b. Dr. Feltquate quotes a statement of Professor Weber who conducted the first phase Ill clinical trial of the 5C4 antibody indicating that "[t]he impressive data on duration or response suggest that there will be significant prolongation of progression-free and overall survival when the analysis ofthose data is mature."
c. Nivolumab has been investigated in more than l 00 human clinical trials both as a monotherapy and in combination \Vith other therapies.

Meets long felt need

65. In addition to the unexpectedly superior results shown by nivolumab, Dr. 1-'eltquate recognizes that nivolumab J'ulfills a long-felt need:

a. by providing cancer patients vvith further treatment options that prolong their overall survival, and

b. by providing more effective and less toxic alternatives to standard of care chemotherapeutic treatments.

Grant in other jurisdictions

66. It is respectl'ully submitted that corresponding patents have been granted in US, EP, AU, CN, I-lK, IL, JP, KR, MX, NZ, RlJ, SG, TW, and ZA,

67. In conclusion, the references cited by the Opponent, alone or in combination, fail to teach or suggest each and every element of the claims. Due to the lack ol' disclosure in the cited rciCrcno.:s, a skilkd person would not have been motivated to make the claimed anti-PD-1 antibody comprising the six CDRs ol' the 5C4 antibody and would not have had a reasonable expectation that such an antibody would \Vork as intended. h1rthermore, even if one skilled in the arl would have been motivated to make a human anti-PD-1 antibody, which Applicants dispute, the numerous unexpectedly superior properties and other objective indicia provided herein overcome any *prima facie* case or obviousness.

68, Accordingly, the prcscntly-cluimcd antibody is not obvious. Applicants respectfully request that the grounds of non-obviousness be dismisst:d.

2.4.2 Applicants submissions on Inventive Step in PGO-3:

4. INVENTIVE STEP

xv1. The only document from the plethora of documents cited by the Opponent that discloses any kind of human anti-human PD-l antibody is **Dll.** Few others like **D3** disclose mouse anti PO-l, hamster anti-PO-l antibodies etc. The other prior arts either do not disclose antibodies to PO-l, or disclose antibodies to other antigens, or disclose method of production of antibodies, or are state of the art documents about PO-l and its biological effect. The closest prior art for the present invention therefore can only be **!III**(WO 2004/056875),

XVII. The Applicant here deals with **D3 and Dll** (which were also the documents relied by the Opponent during the hearing) for remaining documents reply statement may be referred to. The present invention is inventive in view of 03 and OII because:

a. Selecting the specific six CORs of the presently-claimed, antibody out of the numerous possibilities is not routine. The probability of having a germline antibody with a particular VH and VL is one out of about 1.9 x 10^6, which can further have 1 to 15 amino acid mutations per antibody, further increasing the number of possibilities.

b. The six CDRs of the antibodies disclosed in D3 (.143), D11 (PD 1-17, PD1-28, PD1-33, PD1-35, and PD l-F2), have very low to no homology to the six CDRs of the 5C4 antibody.

Antibody of prior art	**Heavy Chain**			**Light Chain**		
	CDRI	**CDR2**	**CDR3**	**CDRI**	**CDR2**	**CDR3**
PDJ-17	40	35	50	36	29	33
PDJ-28,	20	24	50	18	29	33
PDJ-33,	20	29	50	18	43	33
PDJ-35,	20	35	50	27	14	33
PDJ-F2,	20	59	50	73	29	56
143	20	47	50	27	29	0

c. The differences are so enormous that a person skilled in the art would not have been motivated to start from the antibodies disclosed in the references and modify the CDRs to arrive at the exact six CDRs of the 5C4 antibody with a reasonable expectation of success.

d. Further, the claimed unique antibodies show unexpectedly superior properties over the reference antibodies which could not have been predicted by a person skilled in the ati:

e. !IH;IH:R BI\Ili\C; .\FH\IT\: The 5C4 antibody has an unexpectedly superior binding affinity compared to the human antibodies to human **PD-1** in D II. The direct comparison of the reference antibodies and the 5C4 antibody done by a 3'd party, an opponent in Europe,' is below:

Ab	KD (M)
5C4	0.47E-09
PDI-28	3.23E-09
PDI-33	6.29E-09
PDI-35	4.71E-09

f. !!CIliR m D \L PH i(I!\: 5C4 antibody also has a better binding specificity for PD-1. Example 3 of the PCT specification (Figure 14) teaches that the 5C4 antibody bound to PD-1 with high specificity, but not to other CD28 family members (!COS, CTLA-4, CD28). In contrast, antibody ofDll, the PDI-17, PDI-28, PDI-33 and PDI-35 antibodies bind to human PO-l, but also bind to at least one of CTLA-4, CD28 and !COS. *See* Fife Affidavit. Scale of below graph does not matter as no cross-reactivity is always better than some cross -reactivity and the result no-cross reactivity will not change even if the tests are done simultaneously in a direct comparison or not

g. I\(11'11O\.\i. 11111<\Fit ::C !!H \(\:the 5C4 antibody is shown to have unexpectedly superior therapeutic efficacy to standard chemotherapy. *See* Feltquate Affidavit.

h. LONG-FELT Ln: Nivolumab fulfills a long-felt need by providing cancer patients with further treatment options that prolong their overall survival and providing more effective and less toxic alternatives to standard of care chemotherapeutic treatments. Feltquate Affidavit at.

i. O\f\1 HI Sl. < *CI'1:,,:* The importance of the claimed invention is seen in the commercial success of Opdivo<!D, which has sales totaling more than $3.77 billion dollars (US) during the 2016 calendar year.

xviii. It is not obvious for a person skilled in the art to arrive at the claimed antibodies with unique sequence and such unexpected properties with reasonable expectation of success from the teachings of prior art. (D3, Dll or any of the other documents) even ifthe method of manufacture of antibodies is known. The same has been known for a long time, still patents have been granted to antibodies if they cannot be arrived by a person skilled in the ati during normal course of action.

2.4.3 Applicants submissions on Inventive Step in PGO-4::

219. **Inventive step:** D1 at the outset cannot be considered as the closest prior art. The closest prior art is generally that which corresponds to a similar use and requires the minimum of structural and functional modifications to arrive at the claimed invention. D1 does not disclose any human-anti-human PD-1 antibody and is based on the concept to block the target receptor PD-1 which provides for an inhibition of tumor growth. Examples of D1 showed that tumor growth was completely inhibited in mice deficient in PD-1, which means that the inhibition of PD-1 is effective in the treatment of cancer.

220. The present invention provides new and improved human anti human PD-1 antibodies that specifically bind to human PD-1 with higher affinity and increased specificity relative to previous anti-PD-1 antibodies. The only close prior art could be the one disclosing human anti-human PD-1 antibodies, like D2.

221. Even in EP, where the patent was granted, contested in Opposition and thereafter maintained, the document that disclosed human anti-human PD-1 antibodies (D2 in the present proceedings) was considered closest and not D1 (which was also one of the cited documents).

222. Drug products are frequently the result of multiple inventions, each of which may be separately patented. The disclosure of D1 or any of its corresponding US/JP applications is not relevant to the novelty and inventive step of the present application As D1 dos not disclose any human anti-human PD-1 antibody, leave apart the specific antibodies presently claimed.

223. The mere existence and disclosure of other antibodies, the disclosure of different methods of production of antibodies, antibodies against PD-1, or antibodies against human PD-1 prior to the filing of this application does not render the presently-claimed anti-PD-1 antibody comprising the six CDRs of the 5C4 antibody obvious.

224. Selecting the specific six CDRs of the presently-claimed, therapeutically superior antibody out of thenumerous possibilities of potential CDR sequences is neither trivial nor routine.

225. The cited document that disclose antibody sequences of HUMAN anti-HUMAN PD-1 antibodies is D2.

However, the six CDRs of the antibodies disclosed D2 (PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2), have very low to no homology to the six CDRs of the 5C4 antibody. Furthermore, the person would not have had a reasonable expectation that modifying the reference antibodies would bring about the superior, therapeutic antibodies of the claimed invention described herein as it was well known before filing of this application that a single amino acid change in the CDR regions could change the binding of the antibody to the antigen.

226. FURTHER, THE CLAIMED ANTIBODIES SHOW UNEXPECTEDLY SUPERIOR PROPERTIES OVER THE REFERENCE ANTIBODIES OF D2/3 (WHICH IS THE ONLY DOCUMENT THAT PROVIDES HUMAN ANTI-HUMAN PD-1 ANTIBODIES): (I) TIGHTER BINDING AFFINITY, (II) HIGHER BINDING SPECIFICITY, AND (III) EXCEPTIONAL THERAPEUTIC EFFICACY. SEE SECTION “ABOUT THE INVENTION” ABOVE.

2.5 <u>My findings w.r.t the Inventive Step of the claims of the Present application:</u>

All the Opponent’s [PGO 1, 3 and 4] allegations are that the alleged invention claimed in amended claims 1 to 8 in the application ‘5057 do not involve inventive step as required u/s 2(1) (ja) of the Patents Act, 1970 as these claimed products are obvious to a person skilled in the art in view of the following prior art cited documents:

PGO-1 Cited Documents For lack of Inventive Step	PGO-3 Cited Documents For lack of Inventive Step	PGO-4 Cited Documents For lack of Inventive Step
D1-WO 2001/014557 D2- WO 2002/079499 D3-EP 1445264 B1 D4- Immunology letters 2002, 83(3), 215-220 D5- WO2004/072286 OR EP1591527 D6- Nature 1994, 368 (6474), 856-859 D7- WO1997/007671 OR EP0843961 D8- WO 2004/056875 D9- Frann Bennett, J Immunol 2003; 170:711-718 D10- Int. Immunology 1996, 8(5), 765-772 D11- WO2003/011911 D12- Cancer Res 2005; 65: (3). February 1, 2005. D13- PNAS, 2002, 99(19_ 12293-12297 D14- J. Exp. Med. 198:39. D17- WO2002/078731 Annexure-1: WO98/24884 Annexure-4: WO2004/045512	D1-WO 2001/014557 D2- EP 1445264 B1 D3- EP 1537878 B1 D11- WO 2004/056875 D19- Frann Bennett, J Immunol 2003; 170:711-718 D34- WO 2002/012500 D35- WO 2002/012502 D36- WO 2001/014424	D1- EP 1537878 B1 D2- WO 2004/056875 D4- WO 2002/012502 A2-WO 2002/079499 A4- WO 2002/012500

COMBINED CITATION INDEX FOR CITED DOCUMENTS FOR LACK OF INVENTIVE STEP by PGO-1, 3 & 4

CD1- EP 1537878 B1 [D3 of PGO-3 and D1 of PGO-4]

CD2-WO 2004/056875 [D8 of PGO-1, D11 of PGO-3 and D2 of PGO-4]

CD3-WO 2002/012502 [D35 of PGO-3 and D4 of PGO-4]

CD4-WO 2002/079499 [D2 of PGO-1 and A2 of PGO-4]

CD5-WO 2002/012500 [D34 of PGO-3 and A4 of PGO-4]

CD6-WO 2001/014557 [D1 of PGO-1 and PGO-3]

CD7- EP 1445264 B1 [D3 of PGO-1 and D2 of PGO-3]

CD8- WO 2004/056875 [D8 of PGO-1 and D11 of PGO-3]

CD9- Frann Bennett, J Immunol 2003; 170:711-718 [D9 of PGO-1 and D19 of PGO-3]

CD10-Immunology letters 2002, 83(3), 215-220 [D4 of PGO-1]

CD11-WO2004/072286 OR EP1591527 [D5 of PGO-1]

CD12- Nature 1994, 368 (6474), 856-859 [D6 of PGO-1]

CD13- WO1997/007671 OR EP0843961 [D7 of PGO-1]

CD14- Int. Immunology 1996, 8(5), 765-772 [D10 of PGO-1]

CD15-WO2003/011911 [D11 of PGO-1]

CD16-Cancer Res 2005; 65: (3). February 1, 2005	[D12 of PGO-1]
CD17-PNAS, 2002, 99(19_ 12293-12297	[D13 of PGO-1]
CD18- J. Exp. Med. 198:39	[D14 of PGO-1]
CD19- WO2002/078731	[D17 of PGO-1]
CD20-WO98/24884	[Annexure-1 of PGO-1]
CD21-WO2004/045512	[Annexure-2 of PGO-1]
CD22- WO 2001/014424	[D36 of PGO-3]

The independent claim 1 of the present invention is claiming for an isolated monoclonal antibody or an antigen-binding portion thereof that binds specifically to human Programmed Death (PD-1), comprising:

a) a heavy chain CDR1 consisting of the amino acid sequence set forth in SEQ ID NO: 18;

b) a heavy chain CDR2 consisting of the amino acid sequence set forth in SEQ ID NO: 25;

c) a heavy chain CDR3 consisting of the amino acid sequence set forth in SEQ ID NO: 32;

d) a light chain CDR1 consisting of the amino acid sequence set forth in SEQ ID NO: 39;

e) a light chain CDR2 consisting of the amino acid sequence set forth in SEQ ID NO: 46; and

f) a light chain CDR3 consisting of the amino acid sequence set forth in SEQ ID NO: 53.

On perusal of the disclosures and teachings in cited documents CD1 to CD22 with the submissions by all the Opponents and applicant along with all the affidavits submitted as expert evidences, case laws submitted and also considering the arguments during the hearing by all the parties attended hearing, it is clear that none of the cited documents CD1 to CD22 either alone or in combination with each other make the isolated monoclonal antibody or an antigen-binding portion thereof that binds specifically to human Programmed Death (PD-1) claimed in amended claim 1 of the ‘5057 is obvious to a person skilled in the art. The cited prior art documents though they are disclosing the antibody against the human PD-1 protein but there is no disclosure or teaching to achieve for the human antibody having SIX specific

CDR sequences of 5C4 as claimed in amended claim 1.

The opponents argument that the generation of monoclonal antibody against PD-1 protein is known in the art by hybridoma technology in transgenic mice and hence the monoclonal antibody claimed in claim 1 of the present invention is obvious to a person skilled in the art is not tenable as there are no specific disclosures or teachings in any of the cited documents CD1 to CD22 for obtaining the specific monoclonal antibody as claimed in amended claim 1 with SIX CDR sequences.

The opponents arguments for obviousness of the claimed antibody based on the comparative data given by applicant and K_D value are also not proving the antibody claimed in amended claim 1 with SIX CDR sequences is obvious to a person skilled in the art in view of the disclosures in any of the cited documents CD1 to CD22.

The opponent-4 argued that "the applicant had no knowledge of the six-specific CDRs until the preferred isolated antibodies were structurally characterized using standard techniques. Accordingly, the applicant's averments and assertions that it selected the six-specific CDRs out of the numerous possibilities of potential CDR sequences is wholly misleading". Also, "It is submitted that upon immunization, the transgenic mice produced antibodies, which undergoes class switching and somatic mutation to generate high affinity human antibodies. Such preferred antibodies are selected based on the highest titer, followed by isolation and structural characterization using standard PCR and DNA sequencing techniques. Thus, arriving at the claimed antibody by standard methods in view of the disclosure in D1 and the knowledge possessed by a person skilled in the art is wholly devoid of any inventive step". These statements are not clearly providing basis for the obviousness of the claimed antibody which is clearly defined with sequences as artificial (in the amended SEQ ID) and hence the opponent's arguments cannot be agreed upon to state that the claimed antibody in amended

claim 1 with SIX specific CDR sequences is obvious to a person skilled in the art in view of the disclosures in any of the cited documents CD1 to CD22 either alone or in combination.

The applicant's argument that "it is not obvious for a person skilled in the art to arrive at the claimed antibodies with unique sequence and such unexpected properties with reasonable expectation of success from the teachings of prior art even if the method of manufacture of antibodies is known. The same has been known for a long time, still patents have been granted to antibodies if they cannot be arrived by a person skilled in the art during normal course of action. Considering the unexpected superior properties of 5C4 over the reference antibodies in tighter binding activity, higher binding specificity along with the therapeutic efficacy the claimed antibody 5C4 in claims is said to involve inventive step vis-à-vis the cited documents".

Therefore, in my opinion, the disclosures in these documents CD1 to CD22 either alone or in combination do not make the claimed antibody 5C4 in amended claim 1 in the '5057 obvious to a person skilled in the art and hence meets the criteria of the inventive step as per the provisions of the section 2 (1) (ja) of the Patents Act, 1970. The amended claims 2 to 6 are dependent claims on amended claim 1 and hence they also involve inventive step as required under section 2 (1) (ja) of the Patents Act, 1970.

The amended claim 7 is claiming for a composition comprising the monoclonal antibody or antigen-binding portion thereof as claimed in any one claims 1-6 and a pharmaceutically acceptable carrier. As the composition is claimed with the novel and inventive antibody 5C4 of claim 1 and hence this claim also involve inventive step as required under section 2 (1) (ja) of the Patents Act, 1970.

The amended claim 8 is claiming for an isolated nucleic acid encoding the monoclonal antibody or antigen-binding portion thereof as claimed in any one claims 1- 7, wherein the

nucleic acid sequence encoding the heavy chain comprises sequence defined in Figure 4A and that encoding the light chain comprises sequence defined in figure 4B. The isolated nucleic acid claimed in claim 8 is encoding the novel and inventive antibody 5C4 of claim 1 and hence this claim also involve inventive step as required under section 2 (1) (ja) of the Patents Act, 1970.

Hence, the amended claims 1 to 8 are involving the inventive step as required under section 2(1)(ja) of the Patents Act, 1970.Therefore, all the opponents clearly failed to establish this ground of opposition u/s 25 (1) (e) of the Patents Act, 1970.

3.NOT PATENTABLE/NOT AN INVENTION [Section 25(1)(f)] [PGO 1, 3 and 4-Section 3(c), (d) and (e)]

3.1 SECTION 3(c):

All the Opponent's alleged that the instant invention is not patentable under section 3 (c) of the Patents Act, 1970.

3.1.1 Opponent-1 submissions for non-patentability of the Claims 1 to 6 and 8 under Section 3(c) of the Patents Act, 1970.

Section 3(c)

According to Section 3(c) of The Patents Act, 1970 as amended by The Patents (Amendment) Act, 2005, "*the mere discovery of a scientific principle or the formulation of an abstract theory or discovery of any living thing or non-living substance occurring in nature*" is not patentable.

As far as non-patentability of the claimed subject matter u/s 3(c) is concerned, the opponents submit the following.

The applicants' submissions on page XXVII & XXVIII in paras 90-96 are denied in their entirety. The opponents respectfully disagree with the applicants' submissions made therein.

Non-Patentability of the alleged antibody u/s 3(c)

Regarding non-patentability of the amended Claim 1 of the impugned application, the opponents would like to submit that the applicants of the impugned application have limited the claimed subject matter to the six CDRs of the monoclonal antibody *viz.* 5C4. The opponents respectfully submit that the claimed antibody is not patentable under Section 3(c) of the Act for the reasons detailed herein below.

The language of Section 3(c) of the Indian Patent Act has been reproduced herein above. According to Section 3(c), discovery of any living thing or non-living substance occurring in nature is not patentable. In reply to the opponent's objection of the non-patentability of the claimed antibody under Section 3(c), the applicants have submitted that, "The claimed antibody or antigen binding portions are novel and have been created after substantial research and human interference and therefore are not mere discoveries" (Please see para 92; page XXVII of the Applicant's Reply).

The applicants further submitted that, "The claimed antibodies are novel because the claimed CDR sequences are not disclosed in any prior art and were not known before the priority date of the present invention. A novel substance, not known before the priority date cannot be considered as a discovery." (Please see para 93, page XXVIII of the Applicant's Reply)

The applicants also submitted that, "In addition, the specification of the present application clearly indicates that the 5C4 antibody was prepared by ***using transgenic mice***, hybridoma cell lines, and recombinant DNA technology. The inventors generated the anti-PD-1 monoclonal antibodies including 5C4 ***from the HCo7 strain of HuMab transgenic mice*** ("HuMab mice") or the ***KM strain of transgenic transchromosomic mice*** ("KM mice") after immunization with human PD-1. See Example 1 at page 74. The hybridoma cell lines obtained by fusing the mouse splenocytes to a myeloma cell line were screened for anti-PD-1 monoclonal antibodies. *See id*. The selected anti-PD-1 monoclonal antibodies were further sequenced and characterized as shown in Example 2". (Please see para 94, page XXVIII of the Applicant's Reply)

In the present instance the opponents would like to invite the kind attention of the Ld.

Controller towards Example 1 of the impugned application. Example 1 is titled as "**Generation of Human Monoclonal Antibodies Against PD-1**" The opponents would like to reproduce the text of Example 1 for the Ld. Controller's ready reference.

Antigen used in Example 1:

Immunization protocols utilized as antigen both,

1. a recombinant fusion protein comprising the extracellular portion of PD-1 and,
2. membrane bound full-length PD-1.

Both antigens were generated by recombinant transfection methods in a CHO cell line.

Transgenic HuMab and KM mice™ used in Example 1:

Fully human monoclonal antibodies to PD-1 were prepared,

1. Using the HCo7 strain of HuMab transgenic mice and the KM strain of transgenic transchromosomic mice, each of which express human antibody genes.
2. In each of these mouse strains, the endogenous mouse kappa light chain gene has been homozygously disrupted as described in Chen et al (1993) EMBO J. 12:811-820 and the endogenous mouse heavy chain gene has been homozygously disrupted as described in Example 1 of PCT Publication WO 01/09187.
3. Each of these mouse strains carry a human kappa light chain transgene, KCo5, as described in Fishwild et al (1996) Nature Biotechnology 14:845-851.
4. The HCo7 strain carries the HCo7 human heavy chain transgene as described in U.S. Patent Nos. 5545806, 5625825 and 5545807.
5. The KM strain contains the SC20 transchromosome as described in PCT Publication WO 02/43478.

HuMab and KM Immunizations:

To generate fully human monoclonal antibodies to PD-1,

1. HuMab mice and KM mice™ were immunized with purified recombinant PD-1 fusion protein and PD-1 transfected CHO cells as antigen.
2. General immunization schemes for HuMab mice are described in Lonberg, N. et al (1994) Nature 368 (6474): 856-859; Fishwild, D. et al (1996) Nature Biotechnology 14:845-851 and PCT Publication WO 98/24884.
3. The mice were 6-16 weeks of age upon the first infusion of antigen. A purified recombinant preparation (5-50μg) of PD-1 fusion protein antigen and 5-$10x10^6$ cells were used to immunize the HuMab mice and KM mice™ intraperitonealy, subcutaneously (Sc) or via footpad injection.
4. Transgenic mice were immunized twice with antigen in complete Freund's adjuvant or Ribi adjuvant IP, followed by 3-21 days IP (up to a total of 11 immunizations) with the antigen in incomplete Freund's or Ribi adjuvant. The immune response was monitored by retroorbital bleeds.
5. The plasma was screened by ELISA (as described below), and mice with sufficient titers of anti-PD-1 human immunogolobulin were used for fusions.
6. Mice were boosted intravenously with antigen 3 days before sacrifice and removal of the spleen. Typically, 10-35 fusions for each antigen were performed. Several dozen mice were immunized for each antigen.

Selection of HuMab or KM Mice™ Producing Anti-PD-1 Antibodies:

To select HuMab or KM mice™ producing antibodies that bound PD-1

1. Sera from immunized mice were tested by ELISA as described by Fishwild, D. et al. (1996).
2. Microtiter plates were coated with purified recombinant PD-1 fusion protein from transfected CHO cells at 1-2 μg/ml in PBS, 100 μl/wells incubated 4°C overnight then blocked with 200 μl/well of 5% fetal bovine serum in PBS/Tween (0.05%).
3. Dilutions of sera from PD-I- immunized mice were added to each well and incubated for 1-2 hours at ambient temperature.
4. The plates were washed with PBS/Tween and then incubated with a goat-anti-human IgG polyclonal antibody conjugated with horseradish peroxidase (HRP) for 1 hour at room temperature.

5. After washing, the plates were developed with ABTS substrate (Sigma, A-1888, 0.22 mg/ml) and analyzed by spectrophotometer at OD 415-495.
6. Mice that developed the highest titers of anti-PD-1 antibodies were used for fusions.
7. Fusions were performed as described below and hybridoma supernatants were tested for anti-PD-1 activity by ELISA.

Generation of Hybridomas Producing Human Monoclonal Antibodies to PD-1:

1. The mouse splenocytes, isolated from the HuMab or KM mice, were fused to a mouse myeloma cell line either using PEG based upon standard protocols or electric field based electrofusion using a Cyto Pulse large chamber cell fusion electroporator (Cyto Pulse Sciences, Inc., Glen Burnie, MD).
2. The resulting hybridomas were then screened for the production of antigen-specific antibodies.
3. Single cell suspensions of splenocytes from immunized mice were fused to one-fourth the number of SP2/0 nonsecreting mouse myeloma cells (ATCC, CRL 1581) with 50% PEG (Sigma).
4. Cells were plated at approximately $1x10^{5}$/well in flat bottom microtiter plate, followed by about two week incubation in selective medium containing 10% fetal bovine serum, 10% P388D1 (ATCC, CRL TIB-63) conditioned medium, 3-5% origen (IGEN) in DMEM (Mediatech, CRL 10013, with high glucose, L-glutamine and sodium pyruvate) plus 5 mM HEPES, 0.055 mM 2-mercaptoethanol, 50 mg/ml gentamycin and 1 x HAT (Sigma, CRL P-7185).
5. After 1-2 weeks, cells were cultured in medium in which the HAT was replaced with HT.
6. Individual wells were then screened by ELISA (described above) for human anti-PD-1 monoclonal IgG antibodies.
7. Once extensive hybridoma growth occurred medium was monitored usually after 10-14 days.
8. The antibody-secreting hybridomas were replated, screened again and, if still positive for human IgG, anti-PD-1 monoclonal antibodies were subcloned at least twice by limiting dilution.
9. The stable subclones were then cultured *in vitro* to generate small amounts of

antibody in tissue culture medium for further characterization.

10. Hybridoma clones 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 and 5F4 were selected for further analysis.

From above it can be seen that the monoclonal anti-PD-1 antibody of the impugned invention was generated using HuMab or KM mice™. In view of the process illustrated above it can be concluded that the antibody of the impugned invention, i.e. 5C4 was generated using HuMab or KM mice™ and the inventors of the impugned application have just ***isolated*** different antibodies and then after screened them with an aim to select suitable candidate for further development. If we look at the Example-1 of the specification, only methods for screening antibodies involve human intervention. From Example-1 of the specification, it is well understood that the process of isolating antibody *per se* does not include any kind of human intervention other than screening of the isolated antibodies (which are generated by the transgenic mouse) includes human intervention.

The applicants further identified the suitable hybridomas which produce desired antibodies that can be isolated using techniques known in the art. Here, the opponents would like to submit that what the applicants claim as a human intervention in generation of the claimed antibody is **limited to the process** for isolation of the claimed antibody, identification of the claimed antibody for its suitability for further development and identification of the hybridoma which produces claimed antibody only. No human intervention is involved as far as **generation of the claimed antibody** is concerned. The claimed antibody is generated by the HuMab or KM mice™ using its own physiological mechanism which produces antibodies. One skilled in the art upon looking at the above mentioned Example-1, at very first instance can certainly say that the process illustrated in Example-1 either relates to the isolation of the monoclonal antibodies or identification thereof. No human ingenuity is involved in the generation of the claimed antibody.

Here, it should be noted that the applicants have just immunized the HuMab or KM mice™ with target antigen (i.e. human PD-1) so that these mice can produce antibodies against human PD-1. Because the used transgenic mice carries human heavy and light chain transgenes (HCo7 and KCo5) and immunized with the human

PD-1 antigen, it produces fully human monoclonal antibodies.

The opponents would like to mention that the technology for the preparation of human monoclonal antibodies against target antigen using transgenic mice (HuMab or KM mice^{TM}) is a very well known and is in extensive use (for instance please see submissions below on pages 49-54 and Table-1 & Table-2). Therefore, what the applicants have done as far as the impugned invention is concerned does not involve any inventive merit and belongs to very well studied, drafted, taught, developed and routine methodologies using which human monoclonal antibodies against target antigens are prepared.

While analyzing the impugned invention, one thing which is essential to keep in mind is that the applicants have merely isolated the **antibodies generated by the transgenic mice**. The applicants have routinely identified the suitable antibody for further development using mouse hybridoma which falls within the scope of the standard techniques known in the relevant field (for instance please see submissions below on pages 49-54 and Table-1 & Table-2). Therefore, the applicants cannot have claim for the antibody which is generated by the transgenic mouse. The **claimed antibody is prepared by the transgenic mouse and therefore occurred in nature** and is therefore not patentable within the premises of Section 3(c) of the Patents Act.

Without prejudice to what has been submitted above, the opponents would like to invite the kind attention of the Ld. Controller towards some of the Controller's Decisions where the Ld. Controllers have straight away rejected the patent applications covering antibodies as products which have been produced by similar techniques under Section 3(c) of the Patents Act.

Controller's Decision in the matter of IPA # 4718/CHENP/2007 (Annexure-15)

It is humbly submitted that refused Indian Patent Application 4718/CHENP/2007 was covering commercially successful product Daratumumab being sold as Darzalex®.

The opponents would like to invite the kind attention of the Ld. Controller towards Controller's Decision pronounced in the matter of Indian Patent Application bearing number 4718/CHENP/2007 (hereinafter referred as '4718 application). The '4718 application has been refused by the Ld. Controller for the reasons detailed herein

below.

Claims of the '4718 application were directed to the antibodies against CD38 for treatment of multiple myeloma. The last amended Claim 1 of the '4718 application was for an antibody binding to human CD38 comprising six (6) CDRs and human light chain and human heavy chain nucleic acids sequences. The Ld. Controller had raised an objection against patentability of the claimed invention covered in the '4718 application under Section 3(c) of the Patents Act and communicated to the applicants of the '4718 application through First Examination Report.

During the hearing held on 03.11.2016 the Ld. Controller also raised an objection that all the sequence IDs claimed namely SEQ ID 18, 25, 32, 39, 46 and 53 refers to the protein (PRT) from Homo sapiens. Thus, it is clear that all the sequences are of natural origin and hence, claimed antibody binding to human PD-1 is a discovery of non-living substance occurring in nature.

In the present instance, the opponents would like to draw the kind attention of the Ld. Controller towards the objections raised in the matter of IPA # 4718/CHENP/2007 which is mentioned below. Upon careful perusal of the submissions of the applicants on Section 3(c), the Ld. Controller held that, "*The objection 12 of hearing notice is not met as the amended claims 1 to 24 claiming for the antibody binding to human CD38… and claim 25 for nucleic acid comprising the SEQ ID No. 11 or 16…. are not patentable as per the provisions of clause (c) of section 3 of the Patents Act, 1970. The claimed subject matter in these claims is the* ***discovery of the naturally existing antibody*** *binding to human CD38 and nucleic acid comprising the SEQ ID No. 11 or 16,* ***which are isolated and claimed as a product of their invention***. *The claimed biomolecule antibody i.e. protein can only be characterized with the structural features as it's sequence IDs and all the sequence IDs claimed namely Seq ID 13, 14, 15, 18, 19 and 20 which are detailed as above in SEQUENCE IDs* ***refers to the protein (PRT) from Homo sapiens***. *Thus, it is clear that* ***all the sequences are of natural origin*** *and hence,* ***claimed antibody*** *binding to human CD38* ***is a discovery of non-living substance occurring in nature***. *Further, the claim 1 also characterizes that the claimed antibody binding to human CD38 light and heavy chain is encoded by nucleic acids in their variable regions as set forth in SEQ ID No. 11 and 16*

respectively, these claimed sequences SEQ ID No. 11 and 16 are also of human origin as detailed in SEQUENCE IDs (above) which refers to the DNA from Homo sapiens."
(Please see paragraph 3 on page 28 of Annexure-15)

Here, the opponents would like to draw the kind attention of the Ld. Controller towards the claimed sequences for characterizing human monoclonal antibody allegedly claimed in amended Claim 1 of the impugned application. The claimed antibody 5C4 has been characterized by six (6) CDRs having Sequence Id Nos. 18 (heavy chain CDR1), 25 (heavy chain CDR2), 32 (heavy chain CDR3), 39 (light chain CDR1), 46 (light chain CDR2), 53 (light chain CDR3). The amino acid sequences of these six (6) CDRs of 5C4 have been reproduced below for the ready reference of the Ld. Controller.

<210> 18
<211> 5
<212> PRT
<213> Homo sapiens

<400> 18
Asn Ser Gly Met His
1 5

<210> 25
<211> 17
<212> PRT
<213> Homo sapiens

<400> 25
Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15
Gly

<210> 32
<211> 4
<212> PRT
<213> Homo sapiens

<400> 32
Asn Asp Asp Tyr
1

<210> 39
<211> 11
<212> PRT
<213> Homo sapiens

<400> 39
Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1 5 10

<210> 46
<211> 7
<212> PRT
<213> Homo sapiens

<400> 46
Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 53
<211> 9
<212> PRT
<213> Homo sapiens

<400> 53
Gln Gln Ser Ser Asn Trp Pro Arg Thr
1 5

From above it is amply clear that the amino acid sequences bearing IDs 18, 25, 32, 39, 46 and 53 refer to the protein (PRT) from *Homo sapiens* and therefore all the sequences are of natural origin. Hence, the claimed antibody having six (6) CDRs as claimed binding to human Programmed Death (PD-1) is a discovery of non-living substance occurring in nature.

Further, a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO : 4 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO : 11 also refer to the protein (PRT) from *Homo sapiens* and are therefore of natural origin. Hence, the claimed antibody comprising a heavy chain variable region comprising the amino acid sequence set forth in SEQ ID NO : 4 and a light chain variable region comprising the amino acid sequence set forth in SEQ ID NO : 11 binding to human Programmed Death (PD-1) is a discovery of non-living substance occurring in nature. These amino acid sequences are reproduced below for the Ld. Controller's ready reference.

<210> 4
<211> 113
<212> PRT
<213> Homo sapiens

<400> 4
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110
Ser

<210> 11
<211> 107
<212> PRT
<213> Homo sapiens

<400> 11
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ser Asn Trp Pro Arg
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

In the matter of the '4718 application, the Ld. Controller further held that, "*[....] claims 1 to 25* ***does not specify any particular recombination or alteration*** ***<u>in the structure of the antibody or nucleic acid sequence claimed</u>*** *and in the absence of that the antibody claimed in claims 1 to 24 and nucleic acid claimed in claim 25 is treated as discovery of the naturally existing molecule/substance and are not patentable u/s 3(c) of the Patents Act, 1970.*" (Please see page 32 of Annexure-15)

In order to overcome the objections raised by the Ld. Controller regarding non-patentability of the invention covered in the '4718 application under Section 3(c) of the Act, the first argument of the agent for the applicants was that the antibody of the invention is generated by immunization of a transgenic mouse (Example 2 of the

present application) comprising human heavy and light chain transgenes. Second argument was that, the antibody of the invention was not generated by any naturally occurring process, thus it was not identified by the "pure isolation" or identification of an already existing antibody. The agent's other arguments were that "further it may be noted that the genome encoding antibodies does not encode for each and every possible antibody binding region which an individual, e.g. mouse or human, is able to raise against a particular antigen" and "furthermore, subsequent to the generation of antibodies a selection process takes place in which different functionalities of the generated antibodies are tested and based on that a suitable antibody is selected. Again, this process is also not a naturally occurring process but one that takes place in the laboratories by highly skilled scientists" (Please see page 32 of Annexure-15).

With respect to the agent's above arguments, Ld. Controller held that, "*The above arguments of agent* ***only quote about the process of generation of claimed antibodies while the objected claim is for the products*** *which are antibody claimed in claims 1 to 24 and nucleic acid claimed in claim 25. As stated above the claimed SEQ ID No. 11, 13, 14, 15, 16, 18, 19 and 20 which are detailed as above in SEQUENCE IDs* ***refers to the DNA and protein (PRT) from Homo sapiens****. Hence, the argument of agent falls short to explain that* ***when the claim is for all natural sequences and where is the non-natural nature of the claimed antibody or DNA****?* ***Though performing the artificial or non-natural process for generation of naturally existing molecules does not prove product claimed is out of discovery and hence does not escape the clutches of section 3(c) of the Patents Act, 1970.***" (Please see page 32 & 33 of Annexure-15)

The Ld. Controller further held that, "*Though the agent uses the word recombinant in the argument but the same is not true with the claims and description of the instant case. The complete specification does not detail the recombination of CD38 antigen with complete details done and also the claims 1 to 24 do not give any clue about the antibody generated from the recombinant CD38 antigen rather the claim 1 states these variable sequences are encoded by the SEQ ID No. 11 and 16. There are also no recombination details of SEQ ID No. 11 and 16 are provided in the complete specification. Further,* ***if any recombinant molecule is claimed than the sequence listing should refer it has artificial or synthetic or non-natural and not from Homo***

sapiens as stated in the complete specification. *Therefore, the agent's argument that they are* ***claiming the recombinant antibody or DNA is not tenable and without doubt they are claiming the antibody and DNA which is of natural origin as evidenced by their sequence listings*** *and hence the alleged claims 1 to 25 of the instant application are not patentable as per the provisions of section 3(c) of the Patents Act, 1970.*" (Please see page 33 & 34 of Annexure-15)

In the present case, the Ld. Controller may please note that the applicants of the impugned application have also placed similar arguments while replying to the objections raised by the Ld. Controller as well as the opponents regarding non-patentability of the claimed invention under Section 3(c) of the Patents Act. In the present instance the opponents would like to point out that the invention allegedly claimed in the amended set of claims are directed to ***isolated*** **human monoclonal antibody or an antigen binding portion thereof (*product*)** that binds to human PD-1 comprising six (6) CDRs as mentioned in amended Claim 1 and not the process for the isolation or identification of the claimed antibody.

The Ld. Controller may also note that what the applicants have given in Example-1 of the impugned application is single line disclosure only regarding recombinant PD-1 antigen. No reference to specific recombinant anti-PD-1 antibody or experimental details of how it is to be prepared is present in the specification. Except this single lined disclosure the applicants have not provided any working example for the preparation of anti-PD-1 antibody using recombination techniques. Therefore, claim to recombinant anti-PD-1 antibody is not enabled in the specification. Further, the applicants themselves did not find it mandatory to provide working example for the recombination of PD-1 rendering it so well known in the art that any person who is reasonably skilled in the art does not require specific teachings for the recombination of PD-1. Further, the Ld. Controller may also note that this disclosure is so general that one may reasonably think that no special skills are required for recombination of PD-1 and it can easily be done by any recombinant transfection method known in the art. This is further clear from the applicant's own submissions under the heading

"***Immunization of Human Ig Mice***" on page 43 of the specification of the impugned application.

On page 43 of the specification of the impugned application the applicants have submitted that "*When human Ig mice are used to raise human antibodies of the invention, such mice can be immunized with a purified or enriched preparation of PD-1 antigen and/or recombinant PD-1, or an PD-1 fusion protein, as described by Lonberg, N. et al. (1994) Nature 368 (6474):856-859; Fishwild, D. et al. (1996) Nature Biotechnology 14:845-851; and PCT Publication WO 98/24884 and WO 01/14424*". Thus the applicants have used known methods for the preparation of recombinant PD-1 and therefore no invention lies in either preparation of the recombinant PD-1 or immunizing the transgenic mice with the recombinant antigen.

Further, the term "***isolated***" used in the independent amended Claim 1 itself suggests that the claimed monoclonal antibody has been isolated using processes known in the art and not prepared by the applicants of the impugned application.

The opponents therefore humbly submit that the claimed antibody falls within the purview of Section 3(c) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 and is therefore not patentable. The impugned application is therefore liable to get rejected *ab intio* and *in toto* on this ground alone for the reasons stated hereinabove.

Controller's Decision in the matter of IPA # 2098/CHENP/2010 (Annexure-16)

In the matter of the Indian Patent Application No. 2098/CHENP/2010 (hereinafter referred as '2098 application) the Ld. Controller held that, "*the* ***claimed antibody has been generated (naturally) by subcutaneous injection*** *(of RON extracellular domain fragment, RE7 cells and MDCK cells overexpressing the human RON receptor in complete Freund's adjuvant)* ***into HuMab mice."***

The Ld. Controller further held that, "***Except for the injection (and subsequent selection) part there is no human intervention and the antibody as claimed is indeed a natural antibody; and amended claims 1-3 still fall u/s 3(c) of the act for claiming non-living substances occurring in nature. Mere generation and selection of the hybridoma/antibody produced from them, does not make the antibody non-natural.*** *Hence the arguments are not tenable and the objection 04 of the FER is not met.*"

Here, the opponents would once again like to state that the alleged monoclonal antibody, 5C4 claimed in amended Claim 1 of the impugned application has also been generated ***naturally*** by subcutaneous injection of the target antigen (i.e. human PD-1) ***from HuMab mice*** and therefore except for the injection and subsequent selection part there is no human intervention and the antibody as claimed is indeed a naturally occurring antibody. The opponents humbly submit that the claimed antibody therefore can certainly not escape from the clutches of Section 3(c) of the Patents Act, 1970 rendering it not patentable.

Controller's Decision in the matter of IPA # 3349/CHENP/2005 (Annexure-17)

In the matter of the Indian Patent Application bearing number 3349/CHENP/2005 (hereinafter referred as '3349 application), the Ld. Controller held that, "*[….] the claims does not specify any particular* ***recombination or alteration in the structure of the antibody*** *and in the absence of that the antibody claimed in claims 1 to 24 and 34 can be treated as discovery of the naturally existing molecule/substance and are not patentable u/s 3(c) of the Patents Act, 1970.*" The Ld. Controller further held that, "*Just by amending the claims by* ***word "isolated" does not make the product claimed as patentable u/s 3(c)*** *of the Patents Act, 1970.*" (Please see page 10; first paragraph of Annexure-17)

In the matter of the '3349 application, the applicants argued that isolated monoclonal anti-human MASP-2 antibodies are produced by human intervention, either by generating antibody-synthesizing hybridoma cells or through the use of recombinant techniques such as protein engineering, or by selection from synthetic libraries. With respect to the applicant's above argument, the Ld. Controller held that "*The production method argument by human intervention cannot sustain as mere producing the naturally existing protein in any of the system will never make them patentable under section 3(c) of the Patents Act, 1970 and that will be treated as discovery of non-living thing existing in nature*." (Please see page 11; first paragraph of Annexure-17)

The Ld. Controller further held that, "*the sequence referred in claims 1, 12 and 13 as SEQ ID 1 is the natural protein of Homo sapiens. [….] No recombinant/altered sequences are defined in the complete specification. Therefore in my opinion, the antibody claimed in claims 1 to 24 and 34 is a discovery of the naturally existing*

protein and is not patentable under section 3(c) of the Patents Act, 1970." (Please see page 11; second paragraph of Annexure-17)

#the said patent application 3349/CHENP/2005 was summarily rejected by the Ld. Controller.

In the present instance the opponents would like to invite the kind attention of the Ld. Controller towards following facts of the case,

1. Except the preparation of target antigen, i.e. human PD-1 fusion protein the applicants have not provided any process which can clearly show that the human intervention is involved in the generation of the claimed antibody.
2. As discussed above on page 15 in lines 3-24 that recombination of the target antigen human PD-1 is well within the scope and skills of the person skilled in the art.
3. Upon looking at the process illustrated in Example-1 of the impugned application, it is very much clear that the human intervention is involved in the processes called either screening or isolation of the antibodies once generated within the transgenic mice. This is further clear from the second step after screening where the applicants had to isolate mouse splenocytes for the generation of hybridoma because the desired antibody has been generated by the transgenic mouse therein the splenocytes.
4. Here, the opponents would like to point out that if the applicants would have not used the recombinant antigen (i.e. PD-1) and would have used natural human PD-1, the same antibody, i.e. 5C4 would have been generated by the transgenic mouse because it is the transgenic mouse which generates antibody.
5. The transgenic mouse has nothing to do with whether it is immunized with the recombinant human PD-1 or natural human PD-1. The transgenic mouse will generate the antibody against the antigen (i.e. PD-1). Therefore even if it is accepted for the sake of arguments that the applicants have used recombinant PD-1 antigen, it does not account to any human intervention or add any significant difference in the generation (by transgenic mouse) of the claimed antibody. Because the only human intervention lies in the generation of the human PD-1 fusion protein (i.e. target antigen) and not in the antibody

allegedly claimed in the amended Claim 1, the claimed antibody of the impugned application is indeed a naturally occurring antibody.

6. Further, even if it is accepted for the sake of argument, that the human intervention lies in the generation of the claimed antibody (which clearly is not the case and the opponents not at all concede with that) the same is not clearly taught and reflected in Example-1 of the impugned application. Here, the opponents would once again like to reiterate that being the only example in the entire specification for the generation of the antibodies of the claimed invention, Example-1 teaches only screening of the antibodies generated by the transgenic mice and isolation thereof. Example-1 is absolutely mute regarding what changes in the amino acid sequences of the antibody has been made by the applicants, after it is generated in the transgenic mouse. Also nothing is provided regarding how those changes have been carried out and at what position in the sequences of the complementary determining regions (CDRs-heavy as well as light chains).

7. It is pertinent and also interesting to note that the applicants have provided only one line for the disclosure of recombinant human PD-1 fusion protein in the impugned specification. The said line reads as "*Both antigens were generated by recombinant transfection methods in a CHO cell line*" (Please see Example-1; "*Antigen*"). Except this single lined disclosure, the applicants have not provided any specific process for the recombination of the human PD-1 antigen in any of the examples of the impugned application. This means according to the applicants of the impugned specification no specific and explicit teachings are required for the preparation of recombinant PD-1 antigen and the recombinant PD-1 antigen can be prepared by any process known to the person skilled in the art (in fact the applicants have also admitted the same on page 43 of the specification of the impugned application; please see the paragraph below the title-"**Immunization of Human Ig Mice**"). Therefore the human ingenuity is also not required for the preparation of recombinant PD-1 antigen and it can be prepared by any process known in the art (mentioned by the applicants on page 43 of the specification) and therefore falls within the premises of a common general knowledge as well as teachings available to the skilled artisan. As per the disclosure of the applicants, it can

certainly be said that no special or inventive skills are required for the recombination of the target antigen, i.e. human PD-1.

Furthermore, the opponents would also like to invite kind attention of the Ld. Controller towards following points,

1. The applicants have immunized several dozen HuMab mice or KM mice™ with each antigen, i.e. (i) a recombinant fusion protein comprising the extracellular portion of PD-1 and (ii) membrane bound full-length PD-1.
2. Since Example-1 describes general immunization protocol it is believed that the immunization protocol followed for immunizing these several dozen mice is exactly the same for each mouse used. No difference can be seen from the Example-1 of the impugned application to indicate that different protocols for immunization of transgenic mice have been followed.
3. No changes in the immunizing conditions or parameters for immunization of these several dozen mice have also been provided in the Example-1 of the impugned application.
4. It should also be noted that all these several dozen HuMab mice or KM mice™ used for the generation of monoclonal antibodies carries HCo7 and KCo5 strains which means even there is no difference in the transgenic mice.
5. In view of above, the opponents would like to point out that when everything is exactly the same then why and how, the antibodies isolated from the transgenic mice, are different from each other in terms of structural characteristics, binding affinity, binding specificity and cross reactivity?
6. The applicants have disclosed and initially had claimed seven (7) anti-PD-1 antibodies in their specification of the impugned application *viz*. 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 and 5F4. All these antibodies are different from each other in terms of structural characteristics (amino acid sequences) as well as properties inherent to them (e.g. binding affinity, binding specificity, cross reactivity etc).
7. Here, the opponents would like to argue that,
    1. why these transgenic mice (which have been used in the generation of the anti-PD-1 antibodies of the invention) generated structurally different antibodies when,

    (a) Immunogen (i.e. target antigen, human PD-1) is same

(b) Immunization protocol is same

(c) Immunizing conditions and parameters are same

(d) HCo7 and KCo5 strains-HuMab mice or KM mice^{TM} are same?

Therefore it is clear that there is no human intervention involved in the generation of the anti-PD-1 antibodies of the impugned invention since the applicants could not control which antibodies will be provided by which mice and when. Therefore, these antibodies have been generated naturally within the transgenic mice and the applicants have merely isolated them.

The fact is that these antibodies have been generated ***naturally*** by the transgenic mice and the differences in these antibodies are because once the amino acid sequence (antibody) is generated, it undergoes iterative cycles of somatic hypermutation, the clonal expansion and thus the process of affinity maturation. As a result of which the transgenic mice themselves produce antibodies having high binding affinity. The support for the opponents' above contention can be found in the introductory paragraphs of Exhibit-43 filed by the applicants.

The diversity in the amino acid sequences of these antibodies is because the transgenic mice themselves generate antibody against the target antigen (in this case human PD-1) which further undergo the processes of affinity maturation through iterative cycles of somatic hypermutation. This process of affinity maturation typically results in the introduction of 1 to 15 amino acid mutations per antibody increasing affinity for antigen up to 10^5-fold.Thus there is no human intervention in either of the abovementioned processes and all these processes take place ***naturally*** within the transgenic mice. The person skilled in the art cannot predict which mouse will prepare which antibody and that is why the applicants have obtained seven different antibodies.

Even if for the sake of arguments the opponents accept that there is human intervention, then how following the same immunization protocol and immunizing with the same antigen with same conditions and parameters, the applicants obtained different anti-PD-1 antibodies is not clear.

There is no apparent change seen in the process for immunization of the transgenic mice and common general protocol for immunization is illustrated in Example-1 for generating all the seven (7) antibodies.

Actually the working of Example-1 should result into only one antibody but the fact is seven different antibodies have been isolated. This means that the applicants have done nothing in the generation of the antibodies and all seven (7) antibodies have originally and naturally been generated by the transgenic mice.

If the applicants themselves have done anything which resulted into generation of the different antibodies then it is not even illustrated in the Example-1 of the impugned application. Non disclosure of these important and critical features of the process for the generation of claimed antibody does not enable a person skilled in the art to reproduce the invention as claimed.

Further, as illustrated by the applicants in their reply (Please see page XXII, paragraph 73) there are numbers of human heavy and light chain germlines. Now, which human germ line the transgenic mice should use to produce claimed monoclonal antibody as well as other disclosed antibodies is also something which the skilled person cannot decide. What only the skilled person can do is that after isolating the antibody generated by the mice, he can align those isolated antibody sequences with human germline sequences in order to find out using which human germline the transgenic mice have prepared that particular antibody.

For example the transgenic mice used VH 3-33 and VK L6 human germlines for generating 17D8, 2D3, 4H1, 5C4 and 7D3 monoclonal antibodies while transgenic mice used VH 4-39 and VK L15 human germlines for generating 4A11 and 5F4 monoclonal antibodies. The transgenic mice used different germlines for preparing different antibodies because it is a natural process and no human intervention is involved in selecting the human germline. If a skilled person can decide which germline to use then why the applicants did not use VH 3-33 and VK L6 for all the seven antibodies or VH 4-39 and VK L15 for all the seven antibodies?

Therefore the complexity in the generation of the claimed monoclonal antibody 5C4 shown by the applicants in terms of arguments for establishing inventive step and patentability becomes mute and irrelevant because the applicants have not done

anything either in selecting the human germlines from which the antibody has been generated or in selecting the six (6) CDRs of the monoclonal antibody 5C4 as allegedly claimed in the impugned application. All these have been decided by the transgenic mice while generating the antibody against human PD-1 and all these processes up to generation of the monoclonal antibody 5C4 have taken place ***naturally*** within the transgenic mice. The skilled person cannot intervene during the processes of the generation of the antibodies and only after completion of all the processes for preparing the antibody by the mice, he can merely isolate the antibody from the transgenic mice using standard methods.

Non-Patentability of the claimed nucleic acid u/s 3(c)

It is respectfully submitted that the nucleic acid allegedly claimed in amended Claim 22 of the opposed application is not patentable under Section 3(c) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 for following reasons.

In view of above submissions the opponents would like to point out that, in the matter of the Indian Patent Application bearing number 4718/CHENP/2007 (hereinafter referred as '4718 application), the Ld. Controller held that, "*The objection 12 of hearing notice is not met as the amended claims 1 to 24 claiming for the antibody binding to human CD38… and claim 25 for* ***nucleic acid comprising the SEQ ID No. 11 or 16…. are not patentable as per the provisions of clause (c) of section 3 of the Patents Act, 1970****. The claimed subject matter in these claims is the discovery of the naturally existing antibody binding to human CD38 and* ***nucleic acid comprising the SEQ ID No. 11 or 16****,* ***which are isolated and claimed as a product of their invention****. The claimed biomolecule antibody i.e. protein can only be characterized with the structural features as it's sequence IDs and all the sequence IDs claimed namely Seq ID 13, 14, 15, 18, 19 and 20 which are detailed as above in SEQUENCE IDs refers to the protein (PRT) from Homo sapiens. Thus, it is clear that all the sequences are of natural origin and hence, claimed antibody binding to human CD38 is a discovery of non-living substance occurring in nature. Further, the claim 1 also characterizes that the claimed antibody binding to human CD38 light and heavy chain is encoded by nucleic acids in their variable regions as set forth in SEQ ID No. 11 and 16 respectively,* ***these claimed sequences SEQ ID No. 11 and 16 are also of***

1 ***human origin as detailed in SEQUENCE IDs (above) which refers to the DNA***

2 ***from Homo sapiens***." (Please see paragraph 3 on page 28 of Annexure-15)

3 DNA sequences encoding the V_H sequence of 5C4 is shown in SEQ ID NO: 60. DNA

4 sequence encoding the V_L sequence of 5C4 is shown in SEQ ID NO: 67. SEQ ID NO:

5 60 and SEQ ID NO: 67 have been listed below for the ready reference of the Ld.

6 Controller.

<210> 60
<211> 339
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(339)

<400> 60

```
cag gtg cag ctg gtg gag tct ggg gga ggc gtg gtc cag cct ggg agg      48
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                  10                  15

tcc ctg aga ctc gac tgt aaa gcg tct gga atc acc ttc agt aac tct      96
Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser
            20                  25                  30

ggc atg cac tgg gtc cgc cag gct cca ggc aag ggg ctg gag tgg gtg     144
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

gca gtt att tgg tat gat gga agt aaa aga tac tat gca gac tcc gtg     192
Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
    50                  55                  60

aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac acg ctg ttt     240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65                  70                  75                  80

ctg caa atg aac agc ctg aga gcc gag gac acg gct gtg tat tac tgt     288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aca aac gac gac tac tgg ggc cag gga acc ctg gtc acc gtc tcc     336
Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100                 105                 110

tca                                                                 339
Ser
```

7

8

<210> 67
<211> 321
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(321)

<400> 67

```
gaa att gtg ttg aca cag tct cca gcc acc ctg tct ttg tct cca ggg      48
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                  10                  15

gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt gtt agt agt tac      96
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30

tta gcc tgg tac caa cag aaa cct ggc cag gct ccc agg ctc ctc atc     144
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

tat gat gca tcc aac agg gcc act ggc atc cca gcc agg ttc agt ggc     192
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

agt ggg tct ggg aca gac ttc act ctc acc atc agc agc cta gag cct     240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

gaa gat ttt gca gtt tat tac tgt cag cag agt agc aac tgg cct cgg     288
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ser Asn Trp Pro Arg
                85                  90                  95

acg ttc ggc caa ggg acc aag gtg gaa atc aaa                        321
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

From above it is amply clear that the amino acid sequences bearing IDs 60 and 67 refer to the DNA from *Homo sapiens* and therefore both the sequences are of natural origin. Hence, the claimed nucleic acid having above mentioned DNA sequences as claimed in Claim 22 of the impugned application is a discovery of non-living substance occurring in nature.

In the matter of the '4718 application, the Ld. Controller further held that, "*[....] claims 1 to 25* ***does not specify any particular recombination or alteration in the structure of the antibody or nucleic acid sequence claimed and in the absence of that*** *the antibody claimed in claims 1 to 24 and* ***nucleic acid claimed in claim 25 is treated as discovery of the naturally existing molecule/substance and are not patentable u/s 3(c) of the Patents Act, 1970.***" (Please see page 32 of Annexure-15)

In view of above it can be concluded that the nucleic acid claimed in amended Claim 22 of the impugned application is indeed a naturally occurring nucleic acid and therefore cannot be patented under Section 3(c) of the Patents Act, 1970.

Therefore it is humbly submitted that the invention as claimed in the amended claims (Claims 1-22) of the impugned application is not patentable under the provisions of Section 3(c) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005.

3.1.2 Opponent-3 submissions for non-patentability of the claims 1 to 6 and 8 under Section 3(c) of the Patents Act, 1970.

2. **CLAIMED ANTIBODY IS NATURALLY OCCURRING**
Section 25(1)(f)- The claimed subject matter is naturally occurring and thus, non- patentable under Section 3(c) of the Act.

2.1 It is respectfully submitted that claims 1-11, as presently on record, of the opposed application **5057/CHENP/2007** (hereinafter also referred to as "*opposed application*" and **5057/CHENP/2007**) are directed to a monoclonal antibody which is **naturally occurring** and therefore the claims are not patentable under Section 3(c) of the Act.

2.2 Section 3(c) of the Act precludes from patentability *inter alia* the discovery of any living thing or non-living substances occurring in nature. For an Applicant to overcome this statutory bar, it must demonstrate human intervention. The human intervention must be to such an extent such that it should not only be novel and inventive, the claimed subject matter should no longer be capable of being classified as falling within the purview of ***"naturally occurring"*** under Section 3(c). In other words, even if there is a human intervention, for example in a purification step, such human intervention should be novel and inventive.

2.3 The Applicants' alleged invention resides in a 5C4 antibody. The said antibody is prepared by a transgenic mouse after undergoing natural processes such as somatic hypermutation, affinity maturation and clonal expansion. Thus, the natural processes result in the claimed antibodies having the 6 CDR amino acid sequences and there is no

human intervention in producing the claim antibody. Reliance is placed on paragraphs 10.4.i (a)-(l), pages 116-124 of the Opposition and paragraphs 8 and 17 of the Evidence Affidavit filed by Dr. Datta Madamwar on behalf of the Opponent.

2.4 It is respectfully submitted that even if the original transgenic mouse may have been man- made, the offsprings of such mouse are no longer man-made. In any event, the claimed antibody is made by a natural biological process within the mouse and is thus, not man- made.

2.5 It is also pertinent to note that something which is man-made at the time of creation need not necessarily continue to be man-made forever. Even assuming for the sake of argument that the very transgenic mouse was man-made at the time of its creation (which was several decades ago), that does not mean that everything produced by the mouse will be man- made even today almost five decades after its creation. For example seedless bananas, seedless grapes, hybrid plants may once be considered man-made but today, having been produced and used for many years, are part of the known body of substances which occur naturally and cannot be held to be '*non-naturally occurring'*. The transgenic mice used in the impugned invention, breed and reproduce by natural processes. Therefore, they are deemed to be naturally occurring even if they are kept in captivity.

2.6 It is also a necessary corollary of the above that merely because a plant, fruit or any other substance doesn't grow in the wild does not render that plant, fruit or other substance as '*non-naturally occurring*'.

2.7 In support of the above submissions, the Opponent relies upon the following decisions of the Chennai Patent Office under Section 15 of the Act:

(A) Decision dated **31 January 2018** in **Application No. 5808/CHENP/2007**

The said **application was filed** on **17/12/2007** and related to "RECEPTOR ANTAGONISTS FOR TREATMENT OF METASTATIC BONE CANCER". A recombinant antibody for human PDGFRa comprising specific CDR sequences of heavy chain variable region and light chain variable region was claimed in the said application. The relevant portion of the Learned Controller's decision is reproduced herein below:

> *"….The applicant's argument regarding objection no 3 of the FER has been considered. The applicant has amended the claim by the addition of the word recombinant, which is not supported by the specification.* ***Just by amending the claims by word***

"re combinant" does not make the product claimed as patentable u/s 3 (c) of the Patents Act, 1970. The antibodies of the instant application are produced by standard methods and known techniques. Neither the claims nor the specification specify any particular recombination or alteration in the structure of the antibody and in the absence of that, the antibody claimed in claims 1 to 4 and can be treated as discovery of the naturally existing molecule/substance and are not patentable u/s 3 (c) of the Patents Act, 1970."

(emphasis supplied) (please refer to last page, third paragraph of the decision)

The said decision is annexed herewith as **Annexure A**.

(B) Decision dated **29 December 2017** in **Application No. 5542/CHENP/2010**

The said application was filed on 03/09/2010 and related to "ANTIBODY CAPABLE OF BINDING SPECIFICALLY TO AB-OLIGOMER, AND USE THEREOF". The antibody claimed had specific sequences in the heavy and the light chain regions. The relevant portion of the Learned Controller's decision is reproduced herein below:

"…In the reply the applicant has stated that the claimed 6E4 which is a mouse anti-human Aβ oligomer antibody is an antibody that can be produced only when mice are immunized with a sufficient amount of human Aβ oligomer prepared by copolymerizing the modified Aβ and the synthetic Aβ, but cannot be present in the body of a mouse without immunization at all. **Here the claimed antibody with specific amino acid H or L chain sequence are the inherent features and do not distinguish the claimed antibody, H chain or L chain from those which occur in nature. Hence the antibodies produced are natural nonliving substance which is not patentable u/s 3 (c) of the Patents Act 1970**……"

(emphasis supplied) (please refer to last page, third paragraph of the decision)

The said decision is annexed herewith as **Annexure B.**

(C) Decision dated **27 December 2017** in **Application No. 3327/CHENP/2010**

The said **application was filed** on **03/06/2010** and related to "ANTIBODIES THAT BIND HUMAN DENDRITIC AND EPITHELIAL CELL (DEC-205)". The relevant portion of the Learned Controller's decision is reproduced herein below:

"….1. In view of objection no 1 of the hearing notice is not met as the amended claims 1 to 6 claiming for the antibody binding to human Dendritic and Epithelial Cell 205 receptor (Dec-205) are not patentable as per the provisions of sec 3(c) of The Patents Act 1970. ***The claims does not specify any particular recombination or alteration in the structure of the antibody and in the absence of that, the antibody claimed in claims 1 to 6 can be treated as discovery of the naturally existing molecule/substance and are not patentable u/s 3 (c) of the Patents Act, 1970. Just by amending the claims by deleting the word "isolated" does not make the product claimed as patentable u/s 3 (c) of the Patents Act, 1970. The antibodies of the instant application are produced by standard methods and known techniques. The applicant's argument regarding the class switching and somatic mutation cannot be considered, since these processes are inherent in hybridoma technology. The human intervention to make such changes in the instant invention is not clear from the specification. No technical evidences are provided to show that there is a modifications in the processes result in other products which are distinct with regard to their properties over the products known in the prior art****. Also the claims to an antibody raised against a known protein as immunizing an animal with an antigen is a routine procedure. The claimed biomolecule antibody characterizied with the structural features as its sequence ids and all these sequence ids claimed namely Seq Id 29,30,31,35,36 and 37 which are refers to protein (PRT) from Homo sapiens. Thus , it is clear that all the sequences are of natural origin and hence, the claimed antibody binding to Human (Dec-205) is encoded by nucleic acids in their variable regions as set forth in seq id no 26 and 32 are of human orgin as detailed in Sequence IDs which refers to the DNA from Homo sapiens. Further, if any recombinant molecule is claimed then the sequence listing should refer it has artificial or synthetic or non-natural and not from Homo sapiens as stated in the complete specification. Hence the explanation give for objection no 1 has not found to be persuasive…"*

(emphasis supplied) (please refer to serial no.1, second last page of the decision) The said decision is annexed herewith as **Annexure C.**

Thus, it is evident from the above decisions that the position of the Learned Controller and the Indian Patent Office *qua* monoclonal antibodies is as below:

(1) a claimed monoclonal antibody which is naturally occurring in pith and substance will not become non-naturally occurring merely by claim drafting or use/non-use of certain

expressions such as "*recombinant*" or "*isolated*", what needs to be considered is the pith and marrow of the alleged invention and not the claim language;

(2) use of standard methods and known techniques to produce the claimed monoclonal antibodies, even though the same may be used in a known recombinant animal model such as transgenic mouse, is not sufficient to overcome an objection under Section 3(c);

(3) mere use of hybridoma technology, including processes and features which are inherent to the technology, does not render the claimed monoclonal antibodies as *non-naturally occurring*;

(4) the precise human intervention to arrive at the claimed monoclonal antibody must be demonstrated in the specification;

(5) the said human intervention must show how the claimed monoclonal antibodies are different from the antibodies that occur in nature; particularly from antibodies produced by mouse after immunization, and not from the germlines which are the source of any naturally occurring antibody;

(6) the technical differences such as modifications, mutations if any, allegedly carried out in the natural antibody sequences to arrive at the claimed monoclonal antibody must be demonstrated in the specification. The specification must clearly specify any particular recombination or alteration in the structure of the antibody as claimed;

(7) the particular recombination or alteration in the structure of the antibody as claimed should be as a result of human ingenuity and should be reproducible.

2.8 It is respectfully submitted that in the present case, mere use of transgenic mouse is not sufficient to overcome the hurdle of Section 3(c). It is evident that whatever happens inside the transgenic mouse is a result of known methods and techniques. Reference is placed on the textbook ***Kuby's Immunology, Page 99, Annexure B3 of the Expert Affidavit*** filed on behalf of the Opponent which describes the process of preparation of monoclonal antibodies known in the art. The process is reproduced hereunder for the ease of reference of the Learned Controller:

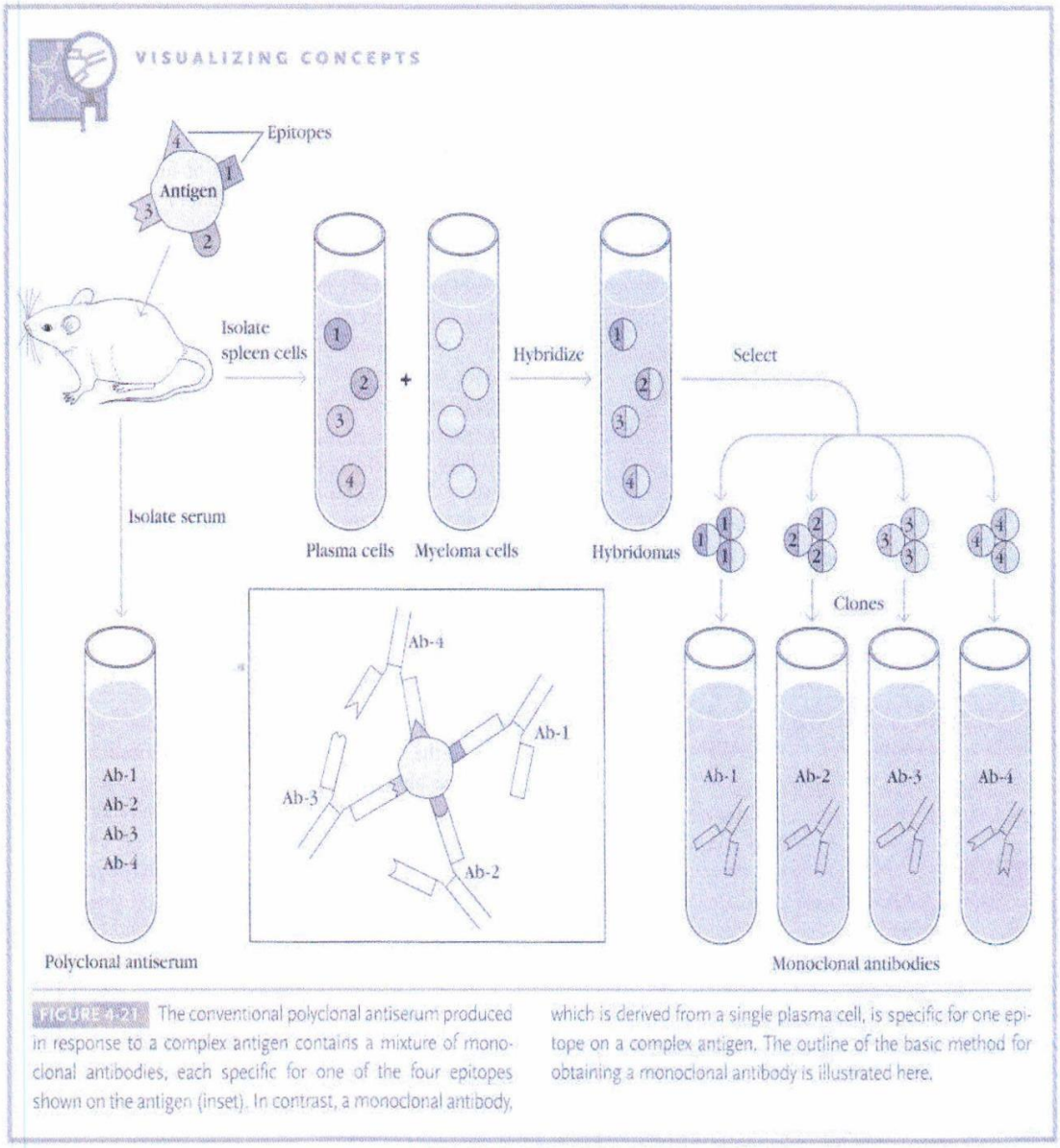


FIGURE 4-21 The conventional polyclonal antiserum produced in response to a complex antigen contains a mixture of monoclonal antibodies, each specific for one of the four epitopes shown on the antigen (inset). In contrast, a monoclonal antibody, which is derived from a single plasma cell, is specific for one epitope on a complex antigen. The outline of the basic method for obtaining a monoclonal antibody is illustrated here.

The process disclosed herein above anticipates the process of preparation of the claimed antibodies disclosed in ***Example 1, page 74 of the specification***. Reference is also made to ***Figures 8 and 9 of the Specification*** which compare the claimed 5C4 antibodies with the germline antibodies which are the known antibodies occurring in nature.

Thus, the mutations, if any, produced in the natural antibody sequence inside the mouse is a result of well-known natural processes such as somatic

hypermutation, affinity maturation and clonal expansion. Therefore, it is evident that there is no human induced mutation caused in the antibody sequence and rather it is the mouse which causes any mutations, if at all, in the germline resulting in the naturally occurring antibody sequence.

2.9 It is the Applicants' case that the claimed antibody with the 6 CDR sequences is prepared by transgenic mouse. Assuming arguendo that the claimed antibodies involve human intervention, then the Applicants' should be able to reproduce the antibodies. However, the Applicants' have admitted at the hearing that there is no way to ensure that the transgenic mouse shall undergo the same mutations and thus, produce the claimed antibodies with the 6 CDR sequences on every single occasion. This admission clearly points out to the fact that there has been no mutation/modification carried out by human intervention and rather, the mouse system solely and exclusively produces the claimed antibodies. In this regard, the Opponents submit a chart annexed herewith as **Annexure D**. The highlighted portion of the chart shows (a) step in the synthesis of the Antibodies where human intervention may take place and a mutation/modification may be performed, (b) expected result if any human intervention had taken place and (c) compares it with the actual result in the absence of human intervention. Since there has been no human intervention, therefore the antibodies produced only have the mutations generated by natural processes within the mice and there is no other modification/mutation in the antibodies.

2.10 Thus, the claims on the opposed application relate to naturally occurring monoclonal antibodies which are not patentable under Section 3(c) of the Act. In addition, the Applicant's admission that the claimed antibodies cannot be reproduced by the transgenic mouse also establishes that the claimed alleged invention lacks industrial applicability.

2.11 In view of the above submissions, the Learned Controller is respectfully requested to reject the opposed application on the ground of Section 3(c) alone.

3.1.3 Opponent-4 submissions for non-patentability of the Claims 1 to 6 and 8 under Section 3(c) of the Patents Act, 1970.

b. At the hearing, it made submissions with respect to Section 3(c). It was submitted that Section 3(c) bars patenting of any living thing or non-living substances occurring in nature. Even the Indian Patent Office in its Guidelines for Examination of Pharmaceutical Patents, Oct 2014 [Page 27, Unit 10.2], clearly states;

> Section 3 (c) of the Act, excludes the mere discovery of a scientific principle or the formulation of an abstract theory or discovery of any living thing or non-living substance occurring in nature from the scope of patentability. Compounds which are isolated from nature are not patentable subject-matter. However, processes of isolation of these compounds can be considered subject to requirements of Section 2 (1) (j) of the Act''.

c. The Indian Patent Office in its Guidelines for Examination of Biotech [Page 11], clearly states;

> 11. SECTION 3(C): SCIENTIFIC PRINCIPLES OR ABSTRACT THEORY OR DISCOVERY OF LIVING THINGS OR NON-LIVING SUBSTANCES According to Section 3 (c) of the Act, the mere discovery of a scientific principle or the formulation of an abstract theory or discovery of any living thing or non-living substance occurring in nature is not a patentable invention. Products such as microorganisms, nucleic acid sequences, proteins, enzymes, compounds, etc., which are directly isolated from nature, are not patentable subject-matter. However, processes of isolation of these products can be considered subject to requirements of Section 2 (1) (j) of the Act.

d. As described elaborately the 5C4 has been generated by the HuMab™ transgenic mice upon injection with human PD-1 antigen. Applicants have injected the transgenic mice with standard procedure of obtaining antibody, isolated antibodies from mice, madehybridomas from the isolated antibodies and screened them using techniques known in the art [Examples 1 and 2 of the specification].

e. Reference is made to page 57 of Opposition

> As used herein, a human antibody comprises heavy or light chain variable regions that is "the product of or "derived from" a particular germline sequence if the variable regions of the antibody are obtained from a system that uses human germline immunoglobulin genes. Such systems include immunizing a transgenic mouse carrying human immunoglobulin genes with the antigen of interest or screening a human immunoglobulin gene library displayed on phage with the antigen of interest. A human antibody that is "the product of or "derived from" a human germline immunoglobulin sequence can be identified as such by comparing the amino acid sequence of the human antibody to the amino acid sequences of human germlineimmunoglobulins and selecting the human germline immunoglobulin sequence that is closest in sequence (i.e., greatest %

identity) to the sequence of the human antibody. A human antibody that is "the product of or "derived from" a particular human germline immunoglobulin sequence may contain amino acid differences as compared to the germline sequence, due to, for example, naturally- occurring somatic mutations or intentional introduction of site- directed mutation. However, a selected human antibody typically is at least 90% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that identify the human antibody as being human when compared to the germline immunoglobulin amino acid sequences of other species (e.g., murine germline sequences). In certain cases, a human antibody may be at least 95%, or even at least
96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the germline immunoglobulin gene. Typically, a human antibody derived from a particular human germline sequence will display no more than 10 amino acid differences from the amino acid sequence encoded by the human

germline immunoglobulin gene. In certain cases, the human antibody may display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene.

Example 1: Generation of Human Monoclonal Antibodies Against PD-I [page 73 of Opposition]

Antigen

Immunization protocols utilized as antigen both (i) a recombinant fusion protein comprising the extracellular portion of PD-I and (ii) membrane bound full-length PD-I. Both antigens were generated by recombinant transfection methods in a CHO cell line. Transgenic HuMab and KM mice™

Fully human monoclonal antibodies to PD-I were prepared using the HCo7 strain of HuMab transgenic mice and the KM strain of transgenic transchromosomic mice, each of which express human antibody genes. In each of these mouse strains, the endogenous mouse kappa light chain gene has been homozygously disrupted as described in Chen et al. (1993) EMBO J. 12:811-820 and the endogenous mouse heavy chain gene has been homozygously disrupted as described in Example 1 of PCT Publication WO 01/09187. Each of these mouse strains carries a human kappa light chain transgene, KCo5, as described in Fishwild et al. (1996) Nature Biotechnology 14:845-851. The HCo7 strain carries the HCo7 human heavy chain transgene as described in U.S. Patent Nos. 5,545,806; 5,625,825; and 5,545,807. The KM strain contains the

SC20 transchromosome as described in PCT Publication WO 02/43478. HuMab and KM

Immunizations:

To generate fully human monoclonal antibodies to PD-I, HuMab mice and KM mice™ were immunized with purified recombinant PD-I fusion protein and PD-1-transfected CHO cells as antigen. General immunization schemes for HuMab mice are described in Lonberg, N. et al (1994) Nature 368(6474): 856-859; Fishwild, D. et al. (1996) Nature Biotechnology 14: 845-851 and PCT Publication WO
98/24884. The mice were 6-16 weeks of age upon the first infusion of antigen. A purified recombinant preparation (5-50 μg) of PD-I fusion protein antigen and 5 -10x106 cells were used to immunize the HuMab mice and KM mice™ intraperitonealy, subcutaneously (Sc) or via footpad injection.

Transgenic mice were immunized twice with antigen in complete Freund's adjuvant or Ribi adjuvant IP, followed by 3-21 days IP (up to a total of 11 immunizations) with the antigen in incomplete Freund's or Ribi adjuvant. The immune response was monitored by retroorbital bleeds. The plasma was screened by ELISA (as described below), and mice with sufficient titers of anti-PD-1 human immunogolobulin were used for fusions. Mice were boosted intravenously with antigen 3 days before sacrifice and removal of the spleen. Typically, 10-35 fusions for each antigen were performed. Several dozen mice were immunized for each antigen. Selection of HuMab or KM Mice™ Producing Anti-PD-1 Antibodies:

To select HuMab or KM mice™ producing antibodies that bound PD- I, sera from immunized mice were tested by ELISA as described by Fishwild, D. et al. (1996). Briefly, microtiter plates were coated with purified recombinant PD-I fusion protein from transfected CHO cells at 1-2 μg /ml in PBS, 100 μl/wells incubated 4 0C overnight then blocked with 200 μl/well of 5% fetal bovine serum in PBS/Tween (0.05%). Dilutions of sera from PD-I- immunized mice were added to each well and incubated for 1-2 hours at ambient temperature. The plates were washed with PBS/Tween and then incubated with a goat- anti-human IgG polyclonal antibody conjugated with horseradish peroxidase (HRP) for 1 hour at room temperature. After washing, the plates were developed with ABTS substrate (Sigma, A-1888, 0.22 mg/ml) and analyzed by spectrophotometer at OD 415-495. Mice that developed the highest titers of anti-PD-1 antibodies were used for fusions. Fusions were performed as described below and hybridoma supernatants were tested for anti-PD-1 activity by ELISA.

Generation of Hybridomas Producing Human Monoclonal Antibodies to PD-I:

(page 71 of REP)

The mouse splenocytes, isolated from the HuMab or KM mice, were fused to a mouse myeloma cell line either using PEG based upon standard protocols or electric field based electrofusion using a Cyto Pulse large chamber cell fusion electroporator (Cyto Pulse Sciences, Inc., Glen Burnie, MD). The resulting hybridomas were then screened for the production of antigen-specific antibodies. Single cell suspensions of splenocytes from immunized mice were fused to one- fourth the number of SP2/0 nonsecreting mouse myeloma cells (ATCC, CRL 1581) with 50% PEG (Sigma). Cells were plated at approximately 1x10 5/well in flat bottom microtiter plate, followed by about two week incubation in selective medium ~ containing 10% fetal bovine serum, 10% P388D1 (ATCC, CRL TIB-63) conditioned medium, 3-5% origen (IGEN) in DMEM (Mediatech, CRL 10013, with high glucose, L-glutamine and sodium pyruvate) plus 5 mM HEPES,

0.055 mM 2-mercaptoethanol, 50 mg/ml gentamycin and Ix HAT (Sigma, CRL P-7185). After 1-2 weeks, cells were cultured in medium in which the HAT was replaced with HT. Individual wells were then screened by ELISA (described above) for human anti-PD-1 monoclonal IgG antibodies. Once extensive hybridoma growth occurred, medium was monitored usually after 10-14 days. The antibody-secreting hybridomas were replated, screened again and, if still positive for human IgG, anti-PD-1 monoclonal antibodies were subcloned at least twice by limiting dilution. The stable subclones were then cultured in vitro to generate small amounts of antibody in tissue culture medium for further characterization.

Hybridoma clones 17D8, 2D3, 4Hl, 5C4, 4Al 1, 7D3 and 5F4 were selected for further analysis.

Example 2: Structural Characterization of Human Monoclonal Antibodies 17D8, 2D3, 4Hl, 5C4, 4A11, 7D3 and 5F4

The cDNA sequences encoding the heavy and light chain variable regions of the 17D8, 2D3, 4Hl, 5C4, 4Al 1, 7D3 and 5F4 monoclonal antibodies were obtained from the 17D8, 2D3, 4Hl, 5C4, 4Al 1, 7D3 and 5F4 hybridomas, respectively, using standard PCR techniques and were sequenced using standard DNA sequencing techniques.

f. The applicant has placed substantive reliance on the fact that sequence of 5C4 differs from that of the germline sequence. The Opponent submitted that these modifications are a result of the naturally-occurring somatic mutations and thus lacks any human intervention,

whatsoever. Moreover, in the detailed description the applicant states that typically, a human antibody derived from a particular human germline sequence will display no more than 10 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene.

g. The applicant in its reply and at the hearing argued that the present claims do not fall under Section 3(c) as they employed recombinant technology using recombinant mouse. In page OO of Reply Statement (para i), the applicant states as under.

> Furthermore, to generate the 5C4 antibody, several steps with human intervention areinvolved, the recombinant mouse strains were immunized multiple times with humanPD-1 antigen. As described in Example 1, 6-16 week old mice were first immunized with 5-50 μg of PD-l fusion protein antigen and 5-10 x 106 cells were used to immunizetheHuMab mice and KM miceTMintraperitoneally, subcutaneously (Sc), or via footpadinjection. Transgenic mice were then immunized twice with antigen in completeFreund's adjuvant or Ribi adjuvant IP, followed by 3-21 days IP (up to a total of' 11immunizations) with the antigen in incomplete Freund's or Ribi adjuvant. The immuneresponse was monitored by retro orbital bleeds. The plasma was screened by ELISA,and mice with sufficient titres of anti-PD-1 human immunoglobulin were used forfusions. Mice were boosted intravenously with antigen 3 days before sacrifice andremoval of the spleen. Therefore, the at least twelve immunization steps described above, in addition to the recombinantly generated mouse strains, are not naturally occurring steps. Accordingly, the recombinant mouse strains used to generate the 5C4antibody would not have naturally produced an antibody that specifically binds tohuman PD-1.

h. As evident from the disclosure of the impugned specification, there has been no particular recombination or alteration in the structure of the antibody or nucleic acid sequence claimed and the antibody produced in the transgenic mice underwent naturally occurring process of somatic mutation. Moreover, the above para from the Reply Statement only discuss the process of generation of claimed antibodies while the objected claim is for 5C4 which is a product. It is therefore submitted that the steps of immunization; monitoring; and screening of plasma by ELISA, using a recombinant mouse, which is commercially available, are routine steps and does not tantamount to human intervention and therefore fails to render 5C4 patentable under Section 3(c).

3.1.4 APPLICANTS SUBMISSIONS FOR PATENTABILITY OF CLAIMS 1 TO 6 AND 8 UNDER SECTION 3(c)

3.1.4.1 Applicants submissions for patentability of claims 1 to 6 and 8 under section 3(c) in PGO-1:

a. Patentability under Section 3 (c) of the Indian Patents Act

26. An anti-PO-l monoclonal antibody or an antigen-binding portion thereof in pending claim I is not a discovery or a product of nature.

27. Section 3(c) considers mere discovery of a scientific principle or the f'ormul;Jtion 0r an abstract theory Dr discovery or any living thi11g or 11011-living substances occurring lll nature as not being patentable.

a. Not a discovery: Oxford dictionary defines "discovery" as "the action or em act of finding or becoming aware or f'or the first time. csp.. the first bringing to light or ɑ scientific phenomenon". !'he claimed antibodies m-e novel us udmittcJ lw the Opponent because the ch imcd CDR sequences arc not disclosed in any of the prior art documents, were not known before the priority date of the present invention, and are di !Terent n·om the human germ line sequences. Therefore, the claimed antibody cannot be considered at the outset as a discovery.

b. Not occurring in nature/ made by human intervention: The antibodies recited in the pending claims arc not occurring in nature and arc not merely isolated from nature.

c. The Opponent failed to point out any naturally-occurring anti-PD-1 antibody containing the six CDR sequences recited in the pending claims. No references cikd by the Opponent show an anti body or antigen-binding portion thereof that comprises the six CDRs recited in the pending claims.

d. Indeed, Figure 8 and Figure 9 show that the six CDRs or· the 5C4 antibody recited in the pending claims *arc* diffCrcnt !l·om the six CDRs or the germ line sequences. In particular, the VI l sequence or the 5C4 antibody is a combination of the

VII J-33 germ! inc sequence and the VH .IH4h germline sequence; therefore, the VI-I CDR l and VH CDR2 sequences of the 5C4 antibody arc derived li·01n but e1rc not the same as-the VH 3-33 germ tine sequence, white the VI l CDRJ sequence of the 5C4 antibody was derived from btll is not the same as-the VH .IH4h germline sequence. *See* Figure 8. The Opponent fl1iled to show that the particular combination of the two VH gcrmlinc sequences (VI-/ 1-33 rtnd VL Jll4b) is natur<. lly-occurring. let alone shm-ving a naturally-occurring antibody or antigen-binding portion thereof that conwins the VI I CDR sequences recited in the pending claims. Therefore. <111 antibodv or cmtigen-binding portion thereof' which comprises the VI-I CDR I. VH ('1)/{2_ and/or VII C:DR3 o/" the 5C4 antibody is not a naturally-occurring antibody or <llltigt:n-binding portion thereof.

c. !n addition. **Figure** 9 shows th<lt the VI :,cquencc or the 5C4 antibody is a combination of the VL L6 germ lint: sequence nml the VL .11<4 germ line ::::,cqucncc. d he scqUL'IICC alignment or the germ line sequence <lild the VL sequence or lhc *SC4* antibody shows that the VL CDR l and VL CDR2 are derived from-but not the same as-the VL L6 germline sequence, and the VL CDR3 is derived from a combination of the VL L6 germline sequence and the VL JK4 germline sequence-but is not the same as either the VL L6 sequence or the VL JK4 germline sequence. Again, the Opponent failed to show that the particular combination of the two VL germ line sequences or the three VL CDRs recited in the pending claims are naturally-occurring. Therefore, an antibody or antigen- binding portion thereof which comprises the VL CDR 1, VL CDR2, and/or VL CDR3 of the 5C4 antibody is not a naturally-occurring antibody or antigen- binding portion thereof.

f. In summary, an antibody or antigen-binding portion thereof comprising the three VH CDRs ofthe 5C4 antibody and the three VL CDRs of the 5C4 antibody is not naturally-occurring.

g. In addition, the sequence alignment ofthe human germline sequences and the VH and VL sequences of the 5C4 antibody in Figures 8 and 9, respectively, clearly show that the six CDRs and the VH and VL sequences of the 5C4 antibody are not naturally-occurring. The 5C4 VH and VL sequences are clearly different from the germline sequences. *See* Figures 8 and 9. Moreover, there has been no showing that even each of the CDR sequences or VH or VL sequences occurs naturally, let alone the combination of the CDRs or the VH and VL. Therefore, the combination ofthe six CDRs ofthe 5C4 antibody is not a product of nature.

h. Recombinant technology using recombinant mouse strains: Moreover. an antibody comprising the six CDRs of the 5C4 antibody is not naturally-occurring because the 5C4 antibody comprising the six CDRs was generated by several steps of recombinant techniques. The 5C4 antibody ofthe present application was prepared by immunizing recombinantly-prepared mice strains. *See* Example I. The recombinantly-prepared mice strains arc the 11Co7 strain of HuMab transgenic mice and the KM strain of transgenic transchromosomic mice. Example I shows:

> *In each o.lthese mouse strains, the endogenous mouse kappa light chain gene has been homozygously disrupted as described in Chen et al. (1993) EMBO J 12:811-820, and the endogenous mouse heavy chain gene has been homozygously disrupted as described in Example I of' PCT Publication WO 01/09187. Each of' these mouse strains carries a human kappa light chain transgene, KCo5, as described in Fishwild et a!. (1996) Nature Biotechnology 14:845-*
> *851. The HCo7 strain carries the HCo7 human heavy chain transgene as described in U.S. Patent Nos. 5,545,806; 5,625,825; and 5,545,807. The KM strain contains the SC20 transchromosome as described in PCT Publication WO 02/:13478.*

Therefore, the mouse strains used to generate the 5C4 antibody of the present application are not naturally-occurring, but were generated recombinantly.

1. Furthermore, to generate the 5C4 antibody, the recombinant mouse strains were immunized multiple times with human **PO-l** antigen. As described in Example **1,** 6-16 weeks old mice were first immunized with 5-50 tg of PO-l fusion protein antigen and 5-10 x $l0^6$ cells were used to immunize the 1-luMab mice and KM miceTM intraperitoneally, subcutaneously (Sc), or via footpad injection. Transgenic mice were then immunized twice with antigen in complete Freund's adjuvant or Ribi adjuvant **lP,** followed by 3-21 days **lP** *(up to a total of' //immunizations)* \Vith the antigen in incomplete Freund's or Ribi adjuvant. The immune response was monitored by retro orbital bleeds. The plasma was screened by ELISA. and mice with sufficient titres of anti-PD-1 human immunoglobulin were used for fusions. Mice were boosted intravenously with antigen 3 days before sacrifice and removal of the spleen. Therefore, the immunization steps described above, in addition to the recombinantly generated mouse strains, are not naturally-occurring steps.

.1· Applicants also remind the Learned Controller that human PD-1 is a naturally-occurring protein in the human body. The claimed antibodies specifically bind human PD-1. A skilled artisan would have known that a human would not naturally produce an antibody against a self-antigen, PD-1. The Opponent failed to submit any evidence that a human can naturally produce an antibody specifically binding to human PD-1.

k. Moreover, the recombinant mouse strains used to generate the 5C4 antibody would not have naturally produced an antibody that specifically binds to human PD-1, but otherwise required at least twelve rounds of immunization as described above, because human PD-1 is not naturally present in mice.

l. Nonetheless, solely to expedite this opposition process, but not in acquiescence to the

Opponent's argument or the Learned Controller's objection, Applicants are ready to amend the preamble of claim 1 to recite "a recombinant monoclonal antibody."

28. Applicants also request the Learned Controller to consider the fact that the antibodies disclosed in this application, including the 5C4 antibody, and their uses have been patented in the United States (US Patent 8,008,449; US Patent 8,779,1 05; US Patent 9,358,289; US Patent 9,387,247; US Patent 9,492,539; US Patent 9,492,540; and US Patent 9,084,776), Australia (AU Patent No. 2006244885 and AU Patent No. 2011203119), China (CN Patent CN 1012132978 and CN Patent ZL20121 0554886.5), Europe (EP Patent 2161336), Hong Kong (HK Patent 1140793), Israel (IL Patent 187108 and IL Patent 208642), Japan (JP Patent 4361545, JP Patent 5028700, and JP Patent 5028700), South Korea (KR Patent 1318469, KR Patent 1014988340000, and KR Patent 1339628). Mexico (MX Patent 305803), New Zealand (NZ Patent 563193), Russia (RU Patent 2406760, RU Patent 2494107, and RU Patent 2599417), Singapore (SG Patent 137162), Taiwan ('T'W Patent 1379898), and South Africa (ZA Patent 200709631).

29. Even following the strict United States recent case law and the USPTO Eligibility Guidelines tor examination or nature-based products. the antibodies comprising the six CDRs of the 5C4 antibody have been deemed patent eligible. The U.S. case law and the USPTO guidelines expressly requ1re an evidence that such an antibody is naturally-occurring. In particular, example 8 of the USPTO Eligibility explicitly indicates:

> *Some murine antibodies to Protein S occur in nature, and it is possible that nature might randomly create a murine antibody having the CDR sequences of SEQ ID NOs: 7-12. But unless the examiner can show that this particular murine antibody exists in nature, this mere possibili(v does not bar the eligibili(v of this claim. See, e.g., Myriad, 133 S. Ct. at 2119 n.8 ("The possibility that an unusual and rare phenomenon might randomly create a molecule similar to one created .synthetically through human ingenuity does not render a composition of matter non-patentable"*

(emphasis in original)). Because the claimed antibodies have different CDRs than ·what exists in nature, they have dfffferent structural (e.g., d[fferent amino acid sequences and three-dimensional structures) and functional (e.g., bind to different antigem) characteristics. These differences rise to the level of a marked d[fference, and so the claimed antibodies are not "product of nature" exceptions. Thus, the claim is not directed to an exception (,_)tep 2A: NO). and qualifies as eligible subject matter.

The Guideline can also be accessed at:

https://www .uspto.gov/patents/law/exam/mdc examples nature-based products. pdf.

29. It is respectfully submitted that corresponding patents have been granted in US, EP, AU, CN, HK, IL, JP, KR, MX, NZ, RU, SG, TW, and ZA. The granted claims of US, EP, AU, IL, NZ, RU

30. Applicants, without prejudice to the above, submit that human monoclonal antibodies have been considered as being patentable by the Indian Patent Office, even under section 3(c). A list or approximately 50 patents in which the granted claims arc directed to human monoclonal antibodies is enclosed herewith as Annexure-D. The antibodies disclosed in those patents were generated by the two most common methods of antibody generation: library-based methods and transgenic mouse-based methods. The other list enclosed as Annexure E contains approximately 800 patents granted in the field or antibodies. These two li.-;ts clearly show that the Indian Patent Officc has taken the posit ion that human monoclonal anti bod ics arc patentab lc under section 3(c) ofthe Indian Patents act.

31. In lite!, the Indian equivalents of various prior art documents cited by the Opponent. which also prepare antibodies bssccl on similar techniques of preparing human monoclonal antibodies, have also been granted:-

Annexure	Number	**lndian Patent**
Annexure 1	WO 2004/056875	239794
Annexure 2	WO 2002/12500	236195
Annexure 3	WO 2004/ 045512	219996
Annexure 4	WO 2002/ 12502	225434

32. In view of the above, there can be no reason /'or the present Applicants being deprived of the right to obtain a patent for human monoclonal antibodies, when others in the field have been granted patents for human monoclonal antibodies, even after meeting n higher standard or showing that the antibodies are not only prepared by recombinant means and human ingenuity, but in addition, and above this, also have mutations in the sequences vis- 1-vis the human germ line,

3.1.4.2 Applicants submissions for patentability of claims 1 to 6 and 8 under section 3(c) in PGO-3:

PATENTABILITY UNDER SECTION 3 (C) OF THE INDIAN PATENTS ACT

33. Section 3(c) considers mere discovery of a scientific principle or the formulation of an abstract theory or discovery of any living thing or non-living substances occurring in nature (–product of nature‖) as not being patentable. An anti-PD-1 monoclonal antibody or an antigen-binding portion thereof in pending claim 1, or any of the claims dependent thereon is not a discovery or a product of nature:

a. Not a discovery: Oxford dictionary defines "discovery" as "the action or an act of finding or becoming aware of for the first time, esp., the first bringing to light of a scientific phenomenon". The claimed antibodies are novel as admitted by the Opponent because the claimed CDR sequences are not disclosed in any of the prior art documents, were not known before the priority date of the present invention, and are different from the human germline sequences.–Therefore, the claimed antibody cannot be considered at the outset as merely a discovery of a natural or scientific phenomenon..

b. Not occurring in nature/ not "product of nature"/ made by human intervention: The antibodies recited in the pending claims are not occurring in nature and are not merely isolated from nature.

c. As stated in the **Biotech Guidelines (relevant page enclosed herewith)** issued in March 2013, for Section 3(c), –products such as microorganisms, nucleic acid sequences, proteins, enzymes, compounds, etc., which are **directly isolated** from nature, are not

patentable subject-matter‖. However, the Opponents have failed to establish that the claimed antibody is –**directly isolated**‖ from nature.

d. The Opponent failed to point out any naturally-occurring anti-PD-1 antibody containing the six CDR sequences recited in the pending claims. No references cited by the Opponent show an antibody or antigen-binding portion thereof that comprises the six CDRs recited in the pending claims.

e. Applicants also remind the Learned Controller that human PD-1 is a naturally-occurring protein in the human body. The claimed antibodies specifically bind human PD-1. A skilled artisan would have known that a human would not naturally produce an antibody against a self-antigen, PD-1. Said antibodies can only be created in an artificial system with human intervention.

f. In fact, contrary to the assertions of the Opponent, **Figure 8** and **Figure 9** show that the CDRs of the 5C4 antibody recited in the pending claims are different from the CDRs of the germline sequence. In particular, the VH sequence of the 5C4 antibody is a combination of the VH 3-33 germline sequence and the VH JH4b germline sequence; therefore, the VH CDR1 and VH CDR2 sequences of the 5C4 antibody are derived from—but are not the same as—the VH 3-33 germline sequence, while the VH CDR3 sequence of the 5C4 antibody was derived from—but is not the same as—the VH JH4b germline sequence. *See* Figure 8. The Opponent failed to show that the particular combination of the two VH germline sequences (VH 3-33 and VL JH4b) is naturally-occurring, let alone showing a naturally-occurring antibody or antigen-binding portion thereof that contains the VH CDR sequences recited in the pending claims with specific mutations. Therefore, an antibody or antigen-binding portion thereof which comprises the VH CDR1, VH CDR2, and/or VH CDR3 of the 5C4 antibody is not a naturally-occurring antibody or antigen-binding portion thereof.

g. In addition, **Figure 9** shows that the VL sequence of the 5C4 antibody is a combination of the VL L6 germline sequence and the VL JK4 germline sequence. The sequence alignment of the germline sequence and the VL sequence of the 5C4 antibody shows that the VL CDR1 and VL CDR2 are derived from—but not the same as—the VL L6 germline sequence, and the VL CDR3 is derived from a combination of the VL L6 germline sequence and the VL JK4 germline sequence—but is not the same as either the VL L6 sequence or the VL JK4 germline sequence. Again, the Opponent failed to show that the particular combination of the two VL germline sequences or the three VL CDRs recited in the pending claims (with specific mutation) are naturally-occurring. Therefore, an antibody or antigen-binding portion thereof which comprises the VL CDR1, VL CDR2, and/or VL CDR3 of the 5C4 antibody is not a naturally-occurring antibody or antigen-binding portion thereof.

h. In summary, an antibody or antigen-binding portion thereof comprising the three VH CDRs of the 5C4 antibody and the three VL CDRs of the 5C4 antibody is not naturally- occurring.

i. In addition, the sequence alignment of the human germline sequences and the VH and VL sequences of the 5C4 antibody in Figures 8 and 9, respectively, clearly show that the six CDRs and the VH and VL sequences of the 5C4 antibody are not naturally-occurring. The 5C4 VH and VL sequences are clearly different from the germline sequences. *See* Figures 8 and 9. Moreover, there has been no showing that even each of the CDR sequences or VH or VL sequences occurs naturally, let alone the combination of the CDRs or the VH and VL. Therefore, the combination of the six CDRs of the 5C4 antibody is not a product of nature.

j. Recombinant technology using recombinant mouse strains: Moreover, an antibody comprising the six CDRs of the 5C4 antibody is not naturally-occurring because the 5C4 antibody comprising the six CDRs was generated by several steps of recombinant techniques. The 5C4 antibody of the present application was prepared by immunizing recombinantly-prepared mice strains. *See* Example 1. The recombinantly-prepared mice strains are the HCo7 strain of HuMab transgenic mice and the KM strain of transgenic transchromosomic mice. Example 1 shows:

In each of these mouse strains, the endogenous mouse kappa light chain gene has been homozygously disrupted as described in Chen et al. (1993) EMBO J. 12:811-820, and the endogenous mouse heavy chain gene has been homozygously disrupted as described in Example 1 of PCT Publication WO 01/09187. Each of these mouse strains carries a human kappa light chain transgene, KCo5, as described in Fishwild et al. (1996) Nature Biotechnology 14:845-851. The HCo7 strain carries the HCo7 human heavy chain transgene as described in U.S. Patent Nos.
5,545,806; 5,625,825; and 5,545,807. The KM strain contains the SC20 transchromosome as described in PCT Publication WO 02/43478.

Therefore, the mouse strains used to generate the 5C4 antibody of the present application are not naturally-occurring, but were generated recombinantly.

k. Furthermore, to generate the 5C4 antibody, the recombinant mouse strains were immunized multiple times with human PD-1 antigen. As described in Example 1, 6-16 weeks old mice were first immunized with 5-50 μg of PD-1 fusion protein antigen and 5-
10 x 10^6 cells were used to immunize the HuMab mice and KM mice™ intraperitoneally,
subcutaneously (Sc), or via footpad injection. Transgenic mice were then immunized twice with antigen in complete Freund's adjuvant or Ribi adjuvant IP, followed by 3-21 days IP (*up to a total of 11 immunizations*) with the antigen in incomplete Freund's or Ribi adjuvant. The immune response was monitored by retro orbital bleeds. The plasma was screened by ELISA, and mice with sufficient titres of anti-PD-1 human immunoglobulin were used for fusions. Mice were boosted intravenously with antigen 3 days before sacrifice and removal of the spleen. Therefore, the immunization steps described above, in addition to the recombinantly generated mouse strains, are not naturally-occurring steps.

l. Applicants also remind the Learned Controller that human PD-1 is a naturally-occurring protein in the human body. The claimed antibodies specifically bind human PD-1**.** A skilled artisan would have known that a human would not naturally produce an

antibody against a self-antigen, PD-1. The Opponent failed to submit any evidence that a human can naturally produce an antibody specifically binding to human PD-1.

m. Moreover, the recombinant mouse strains used to generate the 5C4 antibody would not have naturally produced an antibody that specifically binds to human PD-1, but otherwise required at least twelve rounds of immunization as described above, because human PD-1 is not naturally present in mice.

n. Nonetheless, solely to expedite this opposition process, but not in acquiescence to the Opponent's argument or the Learned Controller's objection, Applicants are ready to amend the preamble of claim 1 to recite "a recombinant monoclonal antibody."

34. Applicants also request the Learned Controller to consider the fact that the antibodies disclosed in this application, including the 5C4 antibody, and their uses have been patented in the United States (US Patent 8,008,449; US Patent 8,779,105; US Patent 9,358,289; US Patent 9,387,247; US Patent 9,492,539; US Patent 9,492,540; and US Patent 9,084,776), Australia (AU Patent No. 2006244885 and AU Patent No. 2011203119), China (CN Patent CN101213297B and CN Patent ZL201210554886.5), Europe (EP Patent 2161336), Hong Kong (HK Patent 1140793), Israel (IL Patent 187108 and IL Patent 208642), Japan (JP Patent

4361545, JP Patent 5028700, and JP Patent 5028700), South Korea (KR Patent 1318469, KR Patent 1014988340000, and KR Patent 1339628), Mexico (MX Patent 305803), New Zealand (NZ Patent 563193), Russia (RU Patent 2406760, RU Patent 2494107, and RU Patent

2599417), Singapore (SG Patent 137162), Taiwan (TW Patent I379898), and South Africa

(ZA Patent 200709631).

35. Even following the strict United States recent case law and the USPTO Eligibility Guidelines

for examination of nature-based products (issued after the strict interpretation of the US supreme Court in relation to ‒products of nature‖ in USA: Association for Molecular Pathology v. Myriad Genetics (2013) **relevant section enclosed herewith**), the antibodies comprising the six CDRs of the 5C4 antibody have been deemed patent eligible. The U.S. case law and the USPTO guidelines expressly require an evidence that such an antibody is naturally-occurring. In particular, example 8 of the USPTO Eligibility explicitly indicates:

Some murine antibodies to Protein S occur in nature, and it is possible that nature might randomly create a murine antibody having the CDR sequences of SEQ ID NOs: 7-12. ***But unless the examiner can show that this particular murine antibody exists in nature, this mere possibility does not bar the eligibility of this claim****. See, e.g., Myriad, 133 S. Ct. at*

2119 n.8 ("The possibility that an unusual and rare phenomenon might randomly create a molecule similar to one created synthetically through human ingenuity does not render a composition of matter non-patentable" (emphasis in original)). Because the claimed antibodies have different CDRs than what exists in nature, they have different structural (e.g., different amino acid sequences and three-dimensional structures) and functional (e.g., bind to different antigens) characteristics. These differences rise to the level of a marked difference, and so the claimed antibodies are not "product of nature" exceptions. Thus, the claim is not directed to an exception (Step 2A: NO), and qualifies as eligible subject matter.

The Guideline can also be accessed at:

https://www.uspto.gov/patents/law/exam/mdc_examples_nature-based_products.pdf.

36. Applicants, without prejudice to the above, submit that human monoclonal antibodies have been considered as being patentable by the Indian Patent Office, even under section 3(c). A list of patents in which the granted claims are directed to monoclonal antibodies is enclosed herewith as **Annexure-G.** The antibodies disclosed in most of those patents were generated by the two most common methods of antibody generation: library-based methods and transgenic mouse-based methods. These lists clearly show that the Indian Patent Office has taken the position that human monoclonal antibodies are patentable under section 3(c) of the Indian Patents act.

37. In fact, the Indian equivalents of various prior art documents cited by the Opponent, which

Number	**Indian Patent**
WO 2004/056875	239794
WO 2002/12500	236195
WO 2002/ 12502	225434

38. In view of the above, there can be no reason for the present Applicants being deprived of the right to obtain a patent for human monoclonal antibodies, when others in the field have been granted patents for human monoclonal antibodies, even after meeting a higher standard of showing that the antibodies are not only prepared by recombinant means and human ingenuity, but in addition, and above this, also have mutations in the sequences vis-à-vis the human germline.

3.1.4.3 Applicants submissions for patentability of claims 1 to 6 and 8 under section 3(c) in PGO-4

PATENTABILITY UNDER SECTION 3 (C) OF THE INDIAN PATENTS ACT

103. Section 3(c) considers mere discovery of a scientific principle or the formulation of an abstract theory or discovery of any living thing or non-living substances occurring in nature ("product of nature") as not being patentable. An anti-PD-1 monoclonal antibody or an antigen-binding portion thereof in pending claim 1, or any of the claims dependent thereon is not a discovery or a product of nature:

a) **Not a discovery:** The claimed antibodies are novel as admitted by the Opponent because the claimed CDR sequences are not disclosed in any of the prior art documents, were not known before the priority date of the present invention, and are different from the human germline sequences. Therefore, the claimed antibody cannot be considered at the outset as merely a discovery of a natural or scientific phenomenon.

b) **Not occurring in nature/ not "product of nature"/ made by human intervention:** The antibodies recited in the pending claims are not occurring in nature and are not merely isolated from nature.

c) As stated in the **Biotech Guidelines (relevant page enclosed herewith as Annexure J)** issued in March 2013, for Section 3(c), "products such as microorganisms, nucleic acid sequences, proteins, enzymes, compounds, etc., which are **directly isolated** from nature, are not patentable subject-matter". However, the Opponents have failed to establish that the claimed antibody is
"**directly isolated**" from nature.

d) The Opponent failed to point out any naturally-occurring anti-PD-1 antibody containing the six CDR sequences recited in the pending claims. No references cited by the Opponent show an antibody or antigen-binding portion thereof that comprises the six CDRs recited in the pending claims. Even the experts of the Opponent fail to show or prove that the claimed antibodies are naturally occurring or isolated from nature.

e) Applicants also remind the Learned Controller that human PD-1 is a naturally-occurring protein in the human body. The claimed antibodies specifically bind human PD-1. A skilled artisan would have known that a human would not naturally produce an antibody against a self-antigen, PD-1. Said antibodies can only be created in an artificial system with human intervention.

f) Contrary to the assertions of the Opponent, **Figure 8** and **Figure 9, and Table 1** show that the CDRs of the 5C4 antibody recited in the pending claims are different from the CDRs of the germline sequence. Further, the 5C4 heavy chain CDR sequences are not even all derived from the same germline sequence. In particular, the VH sequence of the 5C4 antibody is derived from a combination of the VH 3-33 germline sequence and the VH JH4b germline sequence ***but is not the same as*** either sequence; therefore, the VH CDR1 and VH CDR2 sequences of the 5C4 antibody are derived from—but are not the same as—the VH 3-33 germline sequence, while the VH CDR3 sequence of the 5C4 antibody was derived from—but is not the same as—the VH JH4b germline sequence. *See* Figure 8. The Opponent failed to show that the particular combination of the two VH germline sequences (VH 3-33 and VL JH4b) is naturally-occurring, let alone showing

a naturally-occurring antibody or antigen-binding portion thereof that contains the VH CDR sequences recited in the pending claims with specific mutations. Therefore, an antibody or antigen-binding portion thereof which comprises the VH CDR1, VH CDR2, and/or VH CDR3 of the 5C4 antibody is not a naturally-occurring antibody or antigen-binding portion thereof.

g) In addition, **Figure 9** shows that the VL sequence of the 5C4 antibody is a combination of the VL L6 germline sequence and the VL JK4 germline sequence. The sequence alignment of the germline sequences and the VL sequence of the 5C4 antibody shows that the VL CDR1 and VL CDR2 are derived from—but not the same as—the VL L6 germline sequence. Similarly, the VL CDR3 is derived from a combination of the VL L6 germline sequence and the VL JK4 germline sequence—but is not the same as either the VL L6 sequence or the VL JK4 germline sequence. Again, the Opponent failed to show that the particular combination of the two VL germline sequences or the three VL CDRs recited in the pending claims (with specific mutation) are naturally-occurring. Therefore, an antibody or antigen-binding portion thereof which comprises the VL CDR1, VL CDR2, and/or VL CDR3 of the 5C4 antibody is not a naturally-occurring antibody or antigen-binding portion thereof.

h) In addition, the sequence alignment of the human germline sequences and the VH and VL sequences of the 5C4 antibody in Figures 8 and 9, respectively, clearly show that the six CDRs and the VH and VL sequences of the 5C4 antibody are not naturally-occurring. The 5C4 VH and VL sequences are clearly different from the germline

sequences. *See* Figures 8, Table 1 and Figure 9. Moreover, there has been no showing that even each of the CDR sequences or VH or VL sequences occurs naturally, let alone the combination of the CDRs or the VH and VL. Therefore, the combination of the six CDRs of the 5C4 antibody is not a product of nature.

i) **Recombinant technology using recombinant mouse strains**: Moreover, an antibody comprising the six CDRs of the 5C4 antibody is not naturally-occurring because the 5C4 antibody comprising the six CDRs was generated by several steps of recombinant techniques. The 5C4 antibody of the present application was prepared by immunizing recombinantly-prepared mouse strains. *See* Example 1. The recombinantly-prepared mouse strains are the HCo7 strain of HuMab transgenic mice and the KM strain of transgenic transchromosomic mice. Example 1 shows: In each of these mouse strains, the endogenous mouse kappa light chain gene has been homozygously disrupted as described in Chen et al. (1993) EMBO J. 12:811-820, and the endogenous mouse heavy chain gene has been homozygously disrupted as described in Example 1 of PCT Publication WO 01/09187. Each of these mouse strains carries a human kappa light chain transgene, KCo5, as described in Fishwild et al. (1996) Nature Biotechnology 14:845-851. The HCo7 strain carries the HCo7 human heavy chain transgene as described in U.S. Patent Nos. 5,545,806; 5,625,825; and 5,545,807. The KM strain contains the SC20 transchromosome as described in PCT Publication WO 02/43478. Therefore, the mouse strains used to generate the 5C4 antibody of the present application are not naturally-occurring, but were generated recombinantly.

j) Furthermore, to generate the 5C4 antibody, the recombinant mouse strains were immunized multiple times with human PD-1 antigen. As described in Example 1, 6-16 weeks old mice were first immunized with 5-50 µg of PD-1 fusion protein antigen and 5-10 x 10^6 cells were used to immunize the HuMab mice and KM mice™ intraperitoneally, subcutaneously (SC), or via footpad injection. Transgenic mice were then immunized twice with antigen in complete Freund's adjuvant or Ribi adjuvant IP, followed by 3-21 days IP (*up to a total of 11 immunizations*) with the antigen in incomplete Freund's or Ribi adjuvant. The immune response was monitored by retro orbital bleeds. The plasma was screened by ELISA, and mice with sufficient titres of anti-PD-1 human immunoglobulin were used for fusions. Mice were boosted intravenously with antigen 3 days before sacrifice and removal of the spleen. Therefore, the immunization steps described above, in addition to the recombinantly generated mouse strains, are not naturally-occurring steps.

k) Nonetheless, solely to expedite this opposition process, but not in acquiescence to the Opponent's argument or the Learned Controller's objection, Applicants are ready to amend the preamble of claim 1 to recite "a recombinant monoclonal antibody."

104. Applicants also request the Learned Controller to consider the fact that the antibodies disclosed

in this application, including the 5C4 antibody, and their uses have been patented in several countries as stated in the preceding paragraph.

105. Even following the strict United States recent case law and the USPTO Eligibility Guidelines for examination of nature-based products (issued after the strict interpretation of the US supreme Court in relation to "products of nature" in USA: Association for Molecular Pathology v. Myriad Genetics (2013) **relevant section enclosed herewith as Annexure K**), the antibodies comprising the six CDRs of the 5C4 antibody have been deemed patent eligible. The U.S. case law and the USPTO guidelines expressly require an evidence that such an antibody is naturally-occurring. In particular, example 8 of the USPTO Eligibility explicitly indicates:

Some murine antibodies to Protein S occur in nature, and it is possible that nature might randomly create a murine antibody having the CDR sequences of SEQ ID NOs: 7-12. ***But unless the examiner can show that this particular murine antibody exists in nature, this mere possibility does not bar the eligibility of this claim****. See, e.g., Myriad, 133 S. Ct. at 2119 n.8 ("The possibility that an unusual and rare phenomenon might randomly create a molecule similar to one created synthetically through human ingenuity does not render a composition of matter non-patentable" (emphasis in original)). Because the claimed antibodies have different CDRs than what exists in nature, they have different structural (e.g., different amino acid sequences and three- dimensional structures) and functional (e.g., bind to different antigens) characteristics. These differences rise to the level of a marked difference, and so the claimed antibodies are not "product of nature" exceptions. Thus, the claim is not directed to an exception (Step 2A: NO), and qualifies as eligible subject matter.*

106. Applicants, without prejudice to the above, submit that human monoclonal antibodies have been considered as being patentable by the Indian Patent Office, even under section 3(c**). A list of patents in which the granted claims are directed to monoclonal antibodies is enclosed herewith as Annexure-I. The antibodies disclosed in most of those patents were generated by the two most common methods of antibody generation: library-based methods and transgenic mouse-based methods.** These lists clearly show that the Indian Patent Office has taken the position that human monoclonal antibodies are patentable under section 3(c) of the Indian Patents act.

107. The Learned Controller (HEARING OFFICER: DR SHARAN GOUDA) himself has granted patents relating to monoclonal antibodies, and reliance in this regard is placed on the decision of the Ld. Controller in respect of patent application no. 263/CHENP/2009, wherein an objection was considered having been met as the antibodies were defines by sequences that could be called has "artificial" , : "*After having considered the submissions during hearing along with the amended claims 1 and 2 claiming for the defined antibody w ith a rtific ia l SEQ ID's… , the requirements of paragraph 1 of hearing notice is considered met*." The granted claim 1 of said patent is as follows :-

1. An isolated antibody, or an antigen-binding fragment thereof, wherein said isolated antibody and said fragment thereof specifically bind the extracellular domain of native human

FcγRIIB with greater affinity than said antibody or said fragment thereof binds native human FcγRIIA, wherein said antibody or said fragment thereof comprises the three complementarity determining regions from the light chain and the three complementarity determining regions from the heavy chain of the
8B5.3.4 antibody produced by hybridoma cell line having an ATCC accession number PTA-7610, said three complementarity determining regions from the light chain having the amino acid sequences of SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7, and said three complementarity determining regions from the heavy chain having the amino acid sequences of SEQ ID NO: 8, SEQ ID NO: 9 and SEQ ID NO: 10, wherein said antibody or said fragment thereof binds to the same epitope of FcγRIIB as that recognized by the 8B5.3.4 antibody produced by hybridoma cell line having ATCC accession number PTA- 7610, and wherein said antibody has a dissociation constant Kd (Koff/Kon) of less than 5 x 10-9 M as determined by surface plasmon resonance.

108. Reliance in this regard is also placed on Example 6 of the patent specification OF 263/chenp/2009 which showed that Transgenic mice were immunized with FcγRIIB purified from supernatant of 293 cells , and hybridoma cell lines from spleen cells of these mice were produced and screened. Thus, immaterial of the method that has been used for production of antibodies, be it page display, or a recombinant, transgenic mice,

109. In fact, the Indian equivalents of various prior art documents cited by the Opponent or their expert, which also prepare antibodies based on similar techniques of preparing human monoclonal antibodies, have also been granted:-

Number	**Indian Patent**
WO 2004/056875	239794
WO 2002/12500	236195
WO 2002/ 12502	225434

110. In view of the above, there can be no reason for the present Applicants being deprived of the right to obtain a patent for human monoclonal antibodies, when others in the field have been granted patents for human monoclonal antibodies, even after meeting a higher standard of showing that the antibodies are not only prepared by recombinant means and human ingenuity, but in addition, and above this, also have mutations in the sequences vis-à-vis the human germline.

111. In summary:

a) The Mab 5C4 is not naturally occurring;

b) No evidence of an expert has been led by the Opponent to state that the Mab antibody is naturally occurring. To the contrary, the applicant has filed extensive expert evidence to demonstrate that Mab 5C4 is generated through recombinant technology and is not naturally occurring

c) The SEQ ID's have been referred to as "Artificial" in the patent specification;

d) Human's don't produce antibody against their own antigen and therefore the claimed antibody cannot be naturally occurring

e) 5C4 antibody heavy chain **(SEQ ID 4)** is a combination of the VH 3-33 germline sequence and the VH JH4b germline sequence—but is not the same.

f) VH CDR1 (**(SEQ ID 18)** and VH CDR2 **(SEQ ID 25)** sequences of the 5C4 antibody are derived

from—but are not the same as—the VH 3-33 germline sequence of "Homo sapiens",

g) VH CDR3 **(SEQ ID 32)** sequence of the 5C4 antibody was derived from—but is not the same as—the VH JH4b germline sequence of "Homo sapiens"

h) 5C4 antibody light chain (SEQ ID 11) is a combination of the VL L6 germline sequence and the VL JK4 germline sequence —but is not the same.

i) VL CDR3 (SEQ ID 53) is derived from a combination of the VL L6 germline sequence and the VL JK4 germline sequence—but is not the same as either the VL L6 sequence or the VL JK4 germline sequence of "Homo sapiens".

j) The alignment of the claimed antibodies' amino acid sequence is different both within the CDR's and in the complete heavy chain and light chain sequences. The claimed antibodies are not naturally occurring and have modifications/mutations. The same can therefore be correctly called "**Artificial.**" As the amino acid sequence is artificial, the nucleic acid encoding the same is also artificial.

3.1.5 My findings for patentability of claims 1 to 6 and 8 under section 3(c):

Upon perusal of the submissions made by all the opponents and applicant along with affidavits and controller's decisions, in my opinion the monoclonal antibody claimed in amended claims 1 to 6 and nucleic acid claimed in amended claim 8 cannot be said as not patentable under section 3(c) of the Patents Act, 1970. The monoclonal antibody claimed in amended claim 1 is characterized with the SIX CDRs having SEQ ID No. 18, 25, 32, 39, 46 and 53. The amended sequence listing of these CDR sequences are as following:

<210> 18

<211> 5

<212> PRT

<213> Artificial

<220>

<223> VH CDR1 of 5C4 Antibody

<400> 18

Asn Ser Gly Met His

1 5

<210> 25

<211> 17

<212> PRT

<213> Artificial

<220>

<223> VH CDR2 of 5C4 Antibody

<400> 25

Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 32

<211> 4

<212> PRT

<213> Artificial

<220>

<223> VH CDR3 of 5C4 Antibody

<400> 32

Asn Asp Asp Tyr
1

<210> 39

<211> 11

<212> PRT

<213> Artificial

<220>

<223> VL CDR1 of 5C4 Antibody

<400> 39

Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1 5 10

<210> 46
<211> 7
<212> PRT
<213> Artificial
<220>
<223> VL CDR2 of 5C4 Antibody
<400> 46
Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 53
<211> 9
<212> PRT
<213> Artificial
<220>
<223> VL CDR3 of 5C4 Antibody
<400> 53
Gln Gln Ser Ser Asn Trp Pro Arg Thr
1 5

The amended SEQ listing clearly shows that the CDR sequences of SEQ ID No. 18, 25, 32, 39, 46 and 53 which are characterizations for the claimed monoclonal antibody in amended claim 1 are all "Artificial" i.e. not from natural source [<213>]. Considering this the antibody claimed in amended claim 1 is said to be non-natural and not occurring naturally, thus it cannot be said as not patentable as per the provisions of section 3(c) of the Patents Act, 1970.

The arguments of the all the opponents based on the method of its production cannot be agreed as the claimed antibody is very clearly characterized with its artificialness in its

structure as SIX CDR Sequences and hence the opponents arguments that the antibody claimed in amended claim 1 is naturally occurring is not tenable. Opponent 4 submitted that "these modifications are a result of the naturally-occurring somatic mutations and thus lacks any human intervention, whatsoever". This argument of opponent fails to establish that the antibody claimed in amended claim 1 is occurring naturally and the opponent has not clearly provided evidence to suggest that the modifications are naturally-occurring somatic mutations and in the absence of that the arguments of the opponent cannot be agreed. All the arguments of the opponents based on the process of its production or generation fails to prove that the claimed antibody with its CDR sequences in amended claim 1 is naturally occurring as the applicant has clearly defined in the Sequence listing that the claimed antibody with its SIX CDR sequences are artificial (in SEQ ID) in nature. Thus, I am in agreement with the applicant that the antibody claimed in amended claim 1 i.e. 5C4 Antibody is not naturally occurring as per the sequence characterizations and it cannot be said as not patentable under section 3(c) of the Patents Act, 1970. The amended claims 2 to 6 are dependent claims on amended claim 1 and hence they are also not naturally occurring and cannot be said as not patentable under section 3(c) of the Patents Act, 1970.

The amended claim 8 is claiming for an isolated nucleic acid encoding the monoclonal antibody or antigen-binding portion thereof as claimed in any one claims 1- 7, wherein the nucleic acid sequence encoding the heavy chain comprises sequence is characterized with sequences defined in Figure 4A and that encoding the light chain comprises sequence defined in figure 4B. The isolated nucleic acid claimed in claim 8 is encoding the antibody 5C4 of claim 1 and hence the nucleic acid claimed in this claim also is not naturally

occurring and it cannot be said as not patentable under section 3(c) of the Patents Act, 1970. Therefore, the opponents clearly failed to prove the non-patentability of the instant claimed invention product in amended claims 1 to 6 and 8 under section 3 (c) of the Patents Act, 1970. Thus, the invention claimed in amended claims 1 to 6 and 8 is the invention within the meaning of the Patents Act, 1970 and is patentable invention under the Patents Act, 1970.

3.2. SECTION 3(e)

3.2.1 Opponent-1 submissions for non-patentability of composition claim under Section 3(e) of the Patents Act, 1970:

Section 3(e)

According to Section 3(e) of The Patents Act, 1970 as amended by The Patents (Amendment) Act, 2005, "*a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance*" is not patentable.

As far as non-patentability of the claimed subject matter u/s 3(e) is concerned, the opponents submit the following.

1. The Ld. Controller may please note that the applicants of the impugned application have not provided any working example for the preparation of the composition allegedly claimed in Claim 16, Claim 19 & Claim 21 of the impugned application.
2. In absence of any working example, it cannot be surely said that the composition as claimed in Claim 16, Claim 19 & Claim 21 have actually been made and also that their effect have been checked.
3. Therefore in absence of the clear proof to the contrary the submissions made in para 104 and 105 of the applicants' reply on page XXX cannot be considered and it can be concluded that the composition claimed in Claim 16, Claim 19 & Claim 21 does not have any special beneficial effect and is a

result of mere admixture of two or more substances.

4. Since the applicants of the application have not provided any effect of the claimed composition, even the aggregation of the properties of the components of the composition can also not be acknowledged.

Thus, the claimed composition of Claim 16, Claim 19 & Claim 21 of the impugned application is not patentable u/s 3(e) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005.

3.2.2 Applicants submissions for patentability of composition claim under Section 3(e) of the Patents Act, 1970:

d. Section 3(e)

82. The presently-claimed antibodies are novel and inventive antibodies comprising six CDR sequences that were not known or disclosed before the priority date of this application. Therefore, the question of known substance does not arise in the context of Section 3(e). Any combinations of the novel and inventive antibodies with another substance would also be novel and inventive and cannot be considered a mere admixture of the known components. Therefore, the presently-claimed invention is not "a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof - - - " as prescribed by Section 3(e) of the Act. Therefore, under Section 3(e) of the Act, the presently-claimed invention is patentable subject matter.

3.2.3 My findings for patentability of claim 7 under section 3(e):

Upon perusal of the submissions made by opponent-1 and applicant along with affidavits, I am of the opinion that the composition claimed in amended claim 7 is not a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof and hence, the claimed composition in amended claim 7 cannot be termed as mere admixture. Thus, the opponent failed to prove the non-patentability of the said amended claim 7 under section 3 (e) of the Patents Act, 1970. Therefore, the invention claimed in amended claim 7 is the invention within the meaning of the Patents Act, 1970 and is patentable invention under the Patents Act, 1970.

3.3 SECTION 3(d)

3.3.1 Opponent-4's written submissions for NON-PATENTABLITY UNDER SECTION 3 (d):

The Applicant alleges that the opponent has failed to identify the "known substance" for non- patentability of claims on section 3(d). This is an odd allegation, since the representation has throughout evidenced that D1 discloses the known substance. Hence to reiterate:

a. Anti-human PD1 human antibodies were known, described and claimed in D1.In fact, the Applicants' own admittances are that D1 encompass nivolumab.
b. Thus the Applicants are trying to obtain a patent for the "same form of a known substance", which does not even meet the lowest threshold of what constitutes an invention under section 3(d) - the requirement of at least a "new form of a known substance".
c. Assuming arguendo that 5C4 has higher specificity and tighter binding, the alleged invention is at best a mere discovery of a new property of the antibody.

3.3.2 Applicant's written submissions

204. The other grounds relied upon by the opponent are section 3(d) and section 8. Applicants request that the reply statement be considered for said grounds, as no oral arguments were made in detail during the hearing as relating to these grounds.

3.3.3 My findings for patentability of claims 1 to 6 and 8 under section 3(d):

The opponent has not specifically argued for the non-patentability of the claimed antibody and nucleic acid claimed in amended claims 1 to 6 and 8 under section 3 (d) of the Patents Act, 1970. It is not clear how the antibody claimed in amended claim 1 (5C4 antibody) is the new form of a known substance i.e. disclosed antibody in cited document CD1? And in the absence of the specific disclosures in the cited document CD1, the antibody claimed in amended claim 1 cannot be said as the new form of an anti-PD1 antibody. Therefore, the opponent failed to prove the non-patentability of the said amended claims 1 to 6 and 8 under section 3 (d) of the Patents Act, 1970. Thus, the invention claimed in amended claims 1 to 6 and 8 is the invention within the meaning of the Patents Act, 1970 and is patentable invention under the Patents Act, 1970.

4 LACK OF SUFFICIENCY AND CLARITY [Section 25 (1) (g)] - PGO 1 and 3

4.1 Opponent-1 submissions for Lack of Sufficiency and Clarity in PGO-1:

LACK OF CLARITY AND SUFFICIENCY

For the purposes of this ground for opposition, the opponents humbly submit the following.

The specification of the impugned application does not disclose fully human monoclonal antibody-NIVOLUMAB

The opponents refer here definitions of "antibody", "isolated antibody" and "monoclonal antibody" as given in the specification of the impugned application.

The term "antibody" as referred to herein includes whole antibodies and any antigen-binding fragment (i.e., "antigen-binding portion") or single chains thereof. An "antibody" refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-*connected by disulfide bonds, or an antigen-binding portion thereof.* ***Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region.*** *The heavy chain constant region is comprised of three domains, CHI, CH2 and CH3.* ***Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region.*** *The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FRl, CDRl, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the*

immune system (e.g., effector cells) and the first component (CIq) of the classical complement system (Please see third paragraph, page no. 17 of the impugned application).

An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds PD-1 is substantially free of antibodies that specifically bind antigens other than PD-1). An isolated antibody that specifically binds PD-1 may, however, have cross-reactivity to other antigens, such as PD-1 molecules from other species. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals (Please see second paragraph, page no. 18 of the impugned application).

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope (Please see third paragraph, page no. 18 of the impugned application).

The definition of "antibody" as mentioned in the specification of the impugned application clearly shows that it can include whole antibody or antigen-binding portion. Here, claimed antibody of the present application is 'NIVOLUMAB' as per the applicants' submissions. NIVOLUMAB is a **fully human immunoglobulin (Ig) G4 monoclonal antibody** directed against the negative immunoregulatory human cell surface receptor programmed death-1 (PD-1, PCD-1,) with immune checkpoint inhibitory and antineoplastic activities (Please see Annexure-7). Further, structural formula of 'NIVOLUMAB' is disclosed in Annexure-8 (Please see pages 190-191 of Annexure-8). From the structure disclosed in Annexure-8, it is well understood that NIVOLUMAB has two heavy chain having 440 amino acid residues and two light chain having 214 amino acid residues. If the invention of the present application is NIVOLUMAB, the specification of the opposed application must have to disclose exact structure of NIVOLUMAB as disclosed in Annexure-8. It is the requirement under section 10(4) (a) of THE PATENT ACT, 1970 that *"Every complete specification shall— **fully and particularly describe the invention** and its operation*

or use and the method by which it is to be performed" The specification of the opposed application does not disclose 'NIVOLUMAB' product. If we agree with the applicants' submission that the present application first time discloses 'NIVOLUMAB', it is essential that the specification of the opposed application must have to provide exact structure of 'NIVOLUMAB'.

5C4 is not NIVOLUMAB

According to the applicants, antibody claimed in the present application is 'NIVOLUMAB'. If the opponents go with the assertion of the applicants then the K_D value (binding affinity) of NIVOLUMAB is **3.06 nM** for human PD-1 (Please see third paragraph, page 38 of the pharmacology review retrieved from drugs@FDA, Annexure-19), while the K_D value of the claimed antibody (5C4) given in the applicants' reply statement is **0.47 nM** (Please see para 77, pages 24-25 & Exhibit-35). Further, the K_D value of the claimed antibody (5C4) given in the impugned specification is **0.73 nM** (Please see Table 2 of the impugned specification). From above, it can be seen that there is a vast difference between the K_D value of NIVOLUMAB and the K_D value of 5C4. If we rely on the aforementioned document (i.e. Anneuxre-19, which is submitted by the applicants themselves during regulatory approval process) because it is the most authentic document for NIVOLUMAB, then NIVOLUMAB has K_D value 3.06 nM. In the present instance, the question is if the claimed antibody 5C4 is NIVOLUMAB then why it is showing completely different binding affinity characterization than 5C4? This is not clear. Here, the Ld. Controller would appreciate that the process for characterizing the binding affinity, i.e. Biacore analysis is also the same (Please see Example-3 of the impugned specification and process provided on page 38 of the pharmacology review retrieved from drugs@FDA). Thus the method for characterizing the binding affinity is also the same still the K_D value is different. Therefore one can reasonably say that 5C4 and NIVOLUMAB are not the same but different antibodies and also that 5C4 is not NIVOLUMAB.

CDR sequences of the claimed antibody (amended Claim 1)

Regarding CDR sequences of the alleged antibody claimed in Claim 1, the opponents submit the following.

1. The opponents have in above paragraphs substantially established that the claimed invention is a discovery of a non-living substance occurring in nature under the provisions of Section 3(c) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005.
2. The opponents have further argued that the applicants have done nothing in the modification of the claimed structure of the CDR sequences.
3. In light of the applicants' arguments that the claimed antibody is a result of substantial human intervention and therefore does not fall within the scope of Section 3(c), the opponents respectfully submit that Example-1 of the impugned application contradicts their arguments.
4. As discussed above, in entire Example-1 it is no where mentioned that the applicants' have done modifications in the claimed monoclonal antibody (in sequences) obtained from the transgenic mouse. The Ld. Controller may please note that Example-1 is the only working example in the entire complete specification that teaches generation of the antibody.
5. In absence of any clear proof to the contradictory, it is affirmed that the applicants' have not done any modification in the claimed antibody (in sequences) obtained from the transgenic mouse and the claimed antibody is indeed an antibody occurring in the nature.
6. Even if it is accepted for the sake of arguments that the claimed antibody is a result of the substantial human ingenuity and human intervention then the opponents would like to submit that the applicants' have not revealed the sequences of CDRs of the antibody initially isolated from the mouse.
7. If the claimed antibody is the result of the human ingenuity and substantial human intervention and it is structurally dissimilar as compared to the earlier isolated antibody from mouse, the applicants' have not taught how many modifications (amino acid mutations) they have carried out in the original CDR regions or variable regions of the structure of the earlier isolated

antibody and at what positions.

8. Thus if the applicant's claim that they have done modifications in the originally obtained antibody from mouse, the applicants have not (a) fully and particularly described the invention and its operation or use and the method by which it is to be performed, and (b) disclosed the best method of performing the invention which is known to the applicant and for which he is entitled to claim protection.

Deposition of Hybridoma producing allegedly claimed antibody

The Ld. Controller's kind attention is invited towards the fact that, the applicants of the opposed application have not provided any information as required u/s 10(4)(d)(ii) regarding deposition of the biological material used in the present invention (hybridomas producing antibodies of the present invention) which means the applicants have not deposited hybridomas producing claimed antibodies.

As far as requirement of deposition of the hybridoma is concerned, the opponents would like to submit that,

1. The Ld. Controller may please note that the applicants of the impugned application have not provided information regarding deposition of the biological materials, i.e. hybridomas of the present invention which is mandatory for the purposes of the requirements of Section 10(4)(d)(ii).
2. In absence of the above mentioned information, it is not clear whether the applicants have deposited hybridomas (biological material) which have been used in the present invention. Even till today's date the complete specification of the impugned application lacks such important information regarding deposition of the hybridoma producing the claimed antibody.
3. In the present instance the opponents would like to invite the kind attention of the Ld. Controller towards following observations of the Controller while examining the Indian Patent Application bearing number 2098/CHENP/2010 (Please see Annexure-16). While examining the said application the Ld. Controller raised an objection for not depositing biological material

(hybridoma producing antibody) used for the invention and stated that,

"***The hybridoma used for the production of the antibody(s) of the alleged invention forms an essential part to practice the invention. The name, address of the depository institution and the date and number of the same at the institution or IDA should be provided in the complete specification***".

In reply to the Controller's above objection the applicants did not submit anything why they did not deposit hybridomas used for their invention and therefore the Ld. Controller in his decision held that,

"***The arguments are not tenable as it will be undue experimentation (including preparation and selection from a large number of hybridoma lines) for a person seeking to further improve on the alleged invention to arrive at the hybridoma line producing antibody of the alleged invention***."

Thus, the Ld. Controller in the above mentioned case found it mandatory to deposit hybridomas producing antibodies claimed in the patent application.

4. The complete specification of the impugned application therefore does not clearly and sufficiently disclose the present invention and is in clear contravention of requirements of Section 10(4)(d)(ii) of the Indian Patent Act 1970. In fact based on the provisions of Section 10(4)(d)(ii) , the impugned application is yet not complete without the submission of the biological materials (hybridomas).

<u>Why deposition of the hybridoma is mandatory?</u>

The opponents would like to emphasize why deposition of the hybridoma is mandatory in this case.

1. The Ld. Controller may please note that the complete specification of the impugned application illustrates only one example, i.e. Example-1 for the generation of the claimed antibody, 5C4. The process of obtaining the antibody is through the formation of hybridoma. It is also clear that there is no clarity or teaching which hybridoma will be produced by which mice and further which of the seven hybridomas will provide the 5C4 antibody. There is reference to a 5C4 hybridoma but it is merely a nomenclature without any

description. A skilled person will not be able to understand what this hybridoma is and what its constituents are. In absence of such information of the hybridomas, a skilled person will not be able to identify which of the hybridoma will result in 5C4. Further, a skilled person was not aware of nivolumab on the filing date of the opposed specification. In absence of details of hybridoma a skilled person will not be able to develop a full human antibody merely from the teachings of the impugned application.

2. The method claimed in Claims 24-26 of the opposed application may be considered as an alternative process for the preparation of the claimed antibody.
3. The Ld. Controller would also appreciate that Claims 24-26 of the opposed application were not part of the claims originally filed in 2007.
4. Also that the applicants have not provided any working example in support of their alleged method claims 24-26.
5. In absence of any specific example of host cell and the expression vector to be used in the method claims 24-26 and in the absence of any clear direction of the sufficient time for which the antibody or antigen-binding portion thereof is to be expressed in the host cell, claims 24-26 of the impugned application are not enabled.
6. Therefore the reader of the complete specification of the impugned application or the skilled person has to rely only on the Example-1 and follow the steps mentioned in Example-1 in order to reproduce the claimed invention.
7. It can be seen from Example-1 would appreciate that the transgenic mice gave seven (7) different hybridomas which means seven (7) different antibodies, *viz.* 17D8, 2D3, 4H1, 5C4, 4A11, 7D3 and 5F4 have been obtained.
8. Further, there is no guarantee that if a skilled person would reproduce the Example-1 of the present specification, he would definitely have hybridoma 5C4 from which claimed antibody is derived. This fact is well understood from the Example-1 of the specification. For the sake of explanation, we have elaborated each steps of the Example-1 of the specification (Please see supra pages 7-10). It clearly shows that generation of antibody according to the

example-1 (indeed, according to the present invention) cannot be controlled or monitored or directed at any step by human intervention till the antibody generating hybridoma is obtained by this method. Therefore, question arises that how a skilled person is enabled to generate only 5C4 hybridoma by following Example-1 of the specification. Even if it is possible to do by him, how would he confirm that the hybridoma generated is the same hybridoma which is disclosed in the opposed application because '5C4' is only notation given by the inventors, not a well-known nomenclature, which was known in the prior art.

9. Therefore if the skilled person wants to reproduce the invention or modify the invention as per the specification, undoubtedly he requires the hybridoma (5C4), obtained by the applicants in Example-1.
10. Therefore the applicants must deposit the hybridoma producing 5C4 so that everybody can have access to that hybridoma in order to repeat the invention in the opposed application.

Therefore it is opponents' humble submission that the impugned application must not be allowed since it is not complete because it lacks such important information which does not make the alleged invention reproducible and therefore enable a person skilled in the art to practice the alleged invention to its fullest. How can the Hon. Patent Office tolerate such a casual attitude of the applicants? The applicants are bound to fulfill all the requirements of each and every provision of the Patent Law at the time of filing of the Patent Application.

The deposition of the biological material is also mandatory within the prescribed time period in view of the direction of the Hon'ble Patent Office (Annexure-18)

The opponents humbly submit that the deposition of the hybridoma producing claimed antibody is mandatory also in view of the direction of the Hon. Patent Office. The Ld. Controller's attention is kindly invited towards the public notice dated 02.07.2014 issued by the Hon. Patent Office in the matter of deposition of the biological material. Relevant paragraphs of the said notice have been reproduced herein below for the Ld. Controller's ready reference.

"*It has been found that in a number of patent applications which require the deposition of biological material to an international depository authority under the Budapest Treaty as provided under Section 10(4)(d)(ii)(A) of the Patents Act, 1970, either the* ***date of deposition of biological material is later than the date of filing of the patent application or reference of deposition of such biological material is not mentioned at all, which contravenes the provisions of the Act***."

"*According to the provisions of the Act, the deposition of such material in an International Depository Authority (IDA) under the Budapest Treaty shall not be later than the date of filing of patent application in India. However, the reference of deposition of biological material in the patent application shall be made within three months from the date of filing of such application as per Rule 13(8) of the Patents Rules, 2003."*

"In view of the above, it is hereby informed that applicants should ensure that the deposition of the biological material to the IDA is made prior to the date of filing of patent application in India and the reference of such deposition in the specification is made within three months from the date of filing of such application, if the same is not already made."

"***In case of non-compliance of the above-mentioned provisions, the concerned applications are liable to be refused under the Act.***"

The opponents therefore humbly submit that the applicants of the opposed application have not complied with the abovementioned provisions of the Patents Act, 1970 and therefore should be straight away refused on this ground alone.

Claims 10 to 12 of the impugned application are not sufficiently disclosed

It is humbly submitted that amended Claims 10 to 12 are not fully supported by the specification of the opposed application. Example 21 shows 'Effect of human anti-PD-1 antibody on function of T regulatory cells' (Please see page no. 97 and 98 of the impugned application). We would like to draw the kind attention of the Ld. Controller towards the conclusion of the example 21. "*The addition of anti-PD-1 human*

monoclonal antibody ***5C4 partially released inhibition imposed by Treg cells on proliferation*** *and IFN-gamma secretion of CD4^{+}CD25^{-} T cells, indicating that anti-PD-1 antibodies have an effect on T regulatory* cells" (Please see lines 1-3, page no. 98 of the impugned application). It clearly shows that 5C4 is not able to inhibit completely the suppression of CD4^{+}CD25^{-}T cells by regulatory T cells. It is accepted by the Applicants also by their disclosure in the specification. Therefore, Claim 10 is not fully supported by the specification of the opposed application.

Examples 18 and 19 of the impugned application show 'Tumor Immunity in Mice Following anti-PD-1 Antibody Treatment and Re-Challenge with PD-Ll" Fibrosarcoma Cells' and for 'Tumor Immunity in Mice Following Single Antibody Therapy (anti-PD-1) or Combination Antibody Therapy (anti-CTLA-4 and anti-PD-1 Re-Challenged with PD-Ll" Colorectal Cancer Cells' , respectively (Please see pages 95-97 of the impugned application). Example 18 shows just an anti-cancer activity *in vivo* due to administration of rat anti-mPD-1 antibody 4H2.B3. But, it does not provide evidence that antibody claimed in Claim 11 (i.e. 5C4) can enhance antigen specific-memory response to a tumor or a pathogen. The skilled person can also not predict that the effect obtained by or related to the 4H2.B3 antibody will also be present in case of 5C4. The claim is for a human anti-PD1 antibody, while the data given is for rat anti-mPD-1 antibody. The applicants through many instances have differentiated the antibody of the impinged application as compared to prior art by stating that they are for the first time providing human anti-PD1 antibodies. From Example 18 it appears that the applicants are affirming that rat and human antibodies will act similarly otherwise they would not have relied upon data obtained using anti-mPD-1 antibody for showing effectiveness of the claimed anti-humanPD-1 antibody (5C4). If this is so, then the applicants' arguments in their reply statement that a person skilled in the art cannot reach to the alleged invention using teachings of the cited prior arts just because they disclose mouse or hamster anti-PD-1 antibodies is a mere attempt at misguiding the Ld. Controller.

Further, Example 19 provides effect of anti-PD-1 antibody 4H2 which is a rat anti-mPD-1 antibody. As mentioned above, the skilled person cannot predict the effect of

5C4 from the data obtained using 4H2. Moreover, it is also concluded in Example 19 that *"A group of 11 mice were tumor-free after the anti-PD1 antibody treatment (2 total) or the combination anti-PD-l/anti-CTLA-4 antibody treatment (9 total)* (Please see last two lines of first paragraph, Example 19 page no. 96 of the impugned application). It means that 4H2 antibody confers a persistent immunity to tumor relapse. Based on this example (i.e. Example 19) which is the only example in the specification for such type of a study, the applicants have predicted that 5C4 can also confer a persistent immunity to tumor relapse. If such effects can be anticipated for 5C4 upon looking at the effects shown by rat anti-mPD-1 antibody, i.e. 4H2 then why not for the fully human anti-PD-1 antibodies known in D8? It is also to be noted that the Applicants have failed to deposit the rat anti-mPD-1 antibody 4H2, as required under Section 10(4)(d)(ii) of the Indian Patent Act.

Claims 13 to 15 of the impugned application are not sufficiently disclosed

It is humbly submitted that amended Claims 13 to 15 are not supported by the specification. Since, the complete specification of the impugned application does not provide fully human antibody in terms of specific sequence of the claimed antibody (full length antibody), the subject-matter of Claims 13 to 15 is vague and unclear.

Compositions of the impugned invention (amended Claim 16, Claim 19 & Claim 21)

Regarding the composition allegedly claimed in Claim 16, Claim 19 and Claim 21 of the impugned application the opponents would like to submit that,

1. The applicants of the opposed application have not provided any working example illustrating the pharmaceutical compositions allegedly claimed in Claims 16, 19 & 21 of the impugned application.

2. The Ld. Controller may also note that the applicants have not specifically claimed pharmaceutically acceptable carrier in Claims 16, 19 & 21.

3. It should also be noted that the applicants have not specifically claimed ratio in which the antibody and pharmaceutically acceptable carrier (Claim 16); immunoconjugate and pharmaceutically acceptable carrier (Claim 19) & bispecific molecule and pharmaceutically acceptable carrier (Claim 21) to be

mixed.

4. Even the applicants have not mentioned how many pharmaceutically acceptable carriers are required to form composition as claimed in Claims 16, 19 & 21. What the applicants have provided is mere disclosure and general knowledge which is available to a skilled person. The disclosure of the impugned specification would have become relevant if the applicants would have provided specific excipients to be used, ration in which the excipients and the active ingredient (antibody or immunoconjugate or bispecific molecule) to be used and most important the effect of the claimed composition.

5. Further, in the absence of any example for making the claimed composition and in the absence of the clear proof to the contrary that the claimed composition shows any special beneficial effect, the skilled person, (a) cannot understand the exact scope of the claim for which protection is sought, (b) cannot practice the invention to its fullest and (c) cannot attribute any superior or surprising effect to the claimed composition.

6. In the present instance the opponents would like to invite the kind attention of the Ld. Controller towards the Controller's observations in the matter of Indian Patent Application bearing number 2098/CHENP/2010 (Please see Annexure-16). In the matter of the '2098 application the Controller objected the patentability of the composition claims and held that, "*the pharmaceutical composition claimed in claims 4 & 5 is not fully supported by the description with working examples to show the best mode of the claimed product. Hence are not allowable*."

7. In view of the Controller's above observation, it is amply clear that even the statute put stress on the applicants to provide working examples for the invention as claimed. And if the invention as claimed is not supported by working example it is liable to get rejected on that ground alone. The opponents therefore humbly submit that in absence of the working examples in the specification of the impugned application, Claim 16, Claim 19 & Claim 21 of the opposed application should also not be allowed.

Immunoconjugate of the impugned invention (amended Claim 17 & Claim 18)

Regarding the immunoconjugate allegedly claimed in Claim 17 and Claim 18 of the impugned application the opponents would like to submit that,

1. The applicants of the impugned application have not provided any working example for the preparation of the immunoconjugate allegedly claimed in Claim 17 and Claim 18 of the opposed application.
2. What the applicants of the opposed application have provided is general disclosure regarding immunoconjugate of the alleged invention. For the purposes of this disclosure the Ld. Controller may please refer to pages 48-50 of the specification of the impugned application.
3. From above disclosure it is apparent that the applicants have generally described examples of cytotoxins or cytotoxic agents. The applicants have very generally described what kind of linkers can be used. The applicants further described prior art references for further discussion of types of cytotoxins, linkers and methods for conjugating therapeutic agents to antibodies. The applicants further described that antibodies of the present invention also can be conjugated to a radioactive isotope to generate cytotoxic radiopharmaceuticals, also preferred to as radioimmunoconjugates. Methods for preparing radioimmunoconjugates are established in the art. Examples of radioimmunoconjugates are commercially available, including Zevalin™ and Bexxar™ and similar methods can be used to prepare radioimmunoconjugates using the antibodies of the invention.
4. The applicants further described that techniques for conjugating such therapeutic moiety to antibodies are well known. The applicants in further description describe prior arts which may be useful for preparing immunoconjugates of the present invention.
5. The Ld. Controller would very well appreciate that in the preparation of an immunoconjugate three components are important. (1) an antibody, (2) a linker and (3) a cytotoxin or therapeutic agent. By not specifically claiming linker and cytotoxin/cytotoxic agent/therapeutic agent, the applicants are trying to claim all the linkers and cytotoxins/cytotoxic agents/therapeutic agents which

means any linker with any cytotoxin/therapeutic agent will conjugated with the antibody of the invention will serve the purposes of the present invention.

6. Here, the Ld. Controller would also appreciate that the reactions for conjugation of antibody, linker and cytotoxins are critical and so specific which therefore cannot be generalized by just giving prior art describing similar subject matter.
7. In the absence of any proof to the contrary, the applicants cannot claim that the immunoconjugates of the present invention have any special beneficial effect. In the absence of any working examples of the immunocojugates and specific claims thereto, the claims and specification of the impugned application leaves the reader in doubt regarding claimed invention for which the protection is sought.

In view of above, the opponents humbly submit that the specification of the impugned application does not clearly and sufficiently disclose the invention as claimed in Claim 17 & Claim 18 of the opposed application.

Bispecific molecule of the impugned invention (amended Claim 20)

Regarding the bispecific molecule allegedly claimed in Claim 20 of the impugned application the opponents would like to submit that,

1. The applicants of the impugned application have not provided any working example for the preparation of the bispecific molecule allegedly claimed in Claim 20 of the opposed application.
2. What the applicants of the opposed application have provided is general disclosure regarding bispecific molecule of the alleged invention. For the purposes of this disclosure the Ld. Controller may please refer to pages 50-53 of the specification of the impugned application.
3. In the absence of any proof to the contrary, the applicants cannot claim that the bispecific molecule of the present invention has any special beneficial effect. In the absence of any working examples of the bispecific molecule and

specific claims thereto, the claims and specification of the impugned application leaves the reader in doubt regarding claimed invention for which the protection is sought.

In view of above, the opponents humbly submit that the specification of the impugned application does not clearly and sufficiently disclose the invention as claimed in Claim 20 of the opposed application.

Claimed Nucleic acid encoding the antibody (amended Claim 22)

Regarding the alleged nucleic acid encoding the antibody claimed in Claim 22, the opponents submit the following.

1. The opponents have in above paragraphs substantially established that the claimed invention is a discovery of a non-living substance occurring in nature under the provisions of Section 3(c) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005.
2. The opponents have further argued that the applicants have done nothing in the modification of the nucleic acid allegedly claimed in amended Claim 22.
3. In light of the applicants' arguments that the claimed antibody is a result of substantial human intervention and therefore does not fall within the scope of Section 3(c), the opponents respectfully submit that Example-1 of the impugned application contradicts their arguments.
4. As discussed above, in entire Example-1 it is no where mentioned that the applicants' have done modifications in either claimed monoclonal antibody (in sequences) or nucleic acid obtained from the transgenic mouse. The Ld. Controller may please note that Example-1 is the only working example in the entire complete specification that teaches generation of the antibody.
5. In absence of any clear proof to the contradictory, it is affirmed that the applicants' have not done any modification in the claimed nucleic acid (in sequences) obtained from the transgenic mouse and the claimed nucleic acid is indeed a nucleic acid occurring in the nature.
6. Even if it is accepted for the sake of arguments that the claimed nucleic acid is a result of the substantial human ingenuity and human intervention then the opponents would like to submit that the applicants' have not revealed the

sequences of the nucleic acid initially isolated from the mouse.

7. If the claimed nucleic acid is the result of the human ingenuity and substantial human intervention and it is structurally dissimilar as compared to the earlier isolated nucleic acid from mouse, the applicants' have not taught how many modifications (amino acid mutations) they have carried out in the structure of the earlier isolated nucleic acid and at what positions.

Thus the applicants do not (a) fully and particularly describe the invention and its operation or use and the method by which it is to be performed, and (b) disclose the best method of performing the invention which is known to the applicant and for which he is entitled to claim protection.

Expression vector of the impugned invention (amended Claim 23)

1. The opponents humbly submit that the applicants of the opposed application have not provided any working example illustrating method allegedly claimed in Claims 24-26 of the opposed application.
2. In absence of any working example, the applicants have not clearly taught which type of vectors can be used for the preparation of the alleged antibody of the present invention.
3. What the applicants have provided is very general description on page nos 45 & 46 of the impugned specification. From this general description, the person reading the specification cannot get idea which expression vector should be used in the alleged process of Claims 24-26.
4. Further, in absence of any specific example that which expression vector is useful for the purposes of the alleged invention (Claim 23 & Claims 24-26), Claim 23 and the complete specification of the impugned application leaves the reader in the doubt regarding exact scope of the invention for which protection is sought.
5. Further, the applicants of the opposed application have not provided very important information regarding deposition of the biological material used in the invention. From pages 45 & 46 of the impugned specification it is apparent that the applicants have not provided details regarding deposition of those

biological material (i.e. expression vector which have been generally described on pages 45 & 46) as required u/s 10(4)(d) as well as deposition details regarding expression vector (as required u/s 10(4)(d)) allegedly claimed in Claim 23 of the opposed application.

6. If the applicants of the opposed application have used the known vectors as described on pages 45 & 46 of the opposed application then the expression vector of the alleged Claim 23 is not novel in view of the applicants' own submissions. Further, if the applicants of the opposed application have used known vectors even though they could provide deposition number of those vectors too but the same is not found in the specification of the impugned application.
7. As mentioned above on page 36, line 14 to page 37, line 12 deposition of the biological material is mandatory in view of the direction from the Hon. Patent Office (Please see Annexure-18) whether it is known biological material or unknown biological material. The requirement is the applicants must have to include reference of the international depository as far as any biological material is used for the purposes of the invention claimed.
8. The Ld. Controller may please note that the Hon. Patent Office has very clearly instructed that in case of non-compliance of these provisions (Section 10(4)(d)) of the Act, such patent applications are liable to get rejected.

Method of producing a monoclonal antibody or antigen-binding portion thereof (amended Claims 24-26)

As discussed above (Please see *supra* pages 6-9) the subject matter allegedly claimed in amended Claims 24-26 have been newly added and was not originally claimed while filing the impugned application as a "national phase application" in India in 2007. Therefore the claimed subject matter is not allowable under the provisions of Section 59 of the Act.

Without prejudice to what has been submitted regarding why these claims should not be allowed, the opponents submit the following.

1. Regarding the method allegedly claimed in Claims 24-26, the opponents

would like to submit that the applicants have not provided any teaching in guise of working examples.

2. What the applicants have provided is a general information and disclosure regarding method of producing a monoclonal antibody or antigen-binding portion thereof on pages 45-47 of the impugned application.
3. The applicants have very generally mentioned the preferred mammalian host cells for expressing the antibodies of the invention which include Chinese Hamster Ovary (CHO) cells, NSO myeloma cells, COS cells and SP2 cells.
4. The applicants have not provided specific examples of the suitable vector for expressing the antibody of the present invention.
5. Further, the applicants mentioned that when recombinant expression vectors encoding antibody genes are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the antibody into the culture medium in which the host cells are grown. (Please see page 46; first paragraph of the international application)
6. The applicants further mentioned that antibodies can be recovered from the culture medium using standard protein purification methods. (Please see page 46; first paragraph, last lines of the international application)
7. In absence of any particular method having particular culture medium, specified time period for the expression of the antibody, particular purification method by following which antibody of the present invention can be produced and purified, it can be concluded that the method claimed in Claims 24-26 is well within the facets of the skilled person working in the relevant art.
8. Further, the general disclosure of the applicants regarding the method claimed in Claims 24-26 itself suggests that for producing antibody of the present invention the skilled person does not require any specific teachings in terms of working example and definite process (working example) and any process known to a skilled person will do.

When the disclosure of the method producing antibody provided on pages 44-46 of the international application is read by the eyes of the skilled person, it is apparent he will not require further assistance/guidance regarding which host cell to choose, which expression vector to use, for how much time to culture a host cell to allow it for expression of the monoclonal antibody and lastly which protein purification process to use to purify antibody produced. He can easily pick up any of the host cells based on his knowledge and experience, any of the expression vectors based on his knowledge and experience and can culture a host cell for the time he knows sufficient to express an antibody based on his knowledge and experience.

9. This means no special skills are required and there will be no difficulty encountered if a person skilled in the art follows any of the processes known to him. This fact itself renders the method claimed in Claims 24-26 so obvious and within the skills of the skilled artisan and therefore does not involve an inventive merit.
10. In absence of any proof to the contrary, if the opponents accept for the sake of arguments that the method allegedly claimed in Claims 24-26 is inventive and required inventive ingenuity, then the same is not sufficiently and clearly disclosed and taught by the applicants.
11. If the method of producing antibody claimed in Claims 24-26 is so specific and the antibody cannot be produced using methods generally available to the skilled person, the applicants have not clearly disclosed those special features of the process which can enable a person ordinary skilled in the art to reproduce the method of Claims 24-26 and work the claimed invention to its fullest.

<u>K_D value as described in the specification is not clear and definite parameter to assess the inventiveness of the invention of the impugned application</u>

According to the applicants, antibody claimed in the present application is 'NIVOLUMAB'. If the opponents go with the assertion of the applicants then the K_D value (binding affinity) of NIVOLUMAB is **3.06 nM** for human PD-1 (Please see third paragraph, page 38 of Annexure-19), while the K_D value of the claimed antibody

(5C4) given in the applicants' reply statement is **0.47 nM** (Please see para 77, pages 24-25 & Exhibit-35). Further, the K_D value of the claimed antibody (5C4) given in the impugned specification is **0.73 nM** (Please see Table 2 of the impugned specification). From above, it can be seen that there is a vast difference between the K_D value of NIVOLUMAB and the K_D value of 5C4. If we rely on the aforementioned document (i.e. the pharmacology review retrieved from drugs@FDA which is submitted by the applicants themselves) because it is the most authentic document for NIVOLUMAB then NIVOLUMAB has K_D value equivalent to the K_D value of the reference antibodies of D8. In the present instance, the question is if the claimed antibody 5C4 is NIVOLUMAB then why it is showing completely different binding affinity than 5C4 is not clear. Here, the Ld. Controller would appreciate that the process for characterizing the binding affinity is also the same (Please see Example-3 of the impugned specification and process provided on page 38 of the pharmacology review retrieved from drugs@FDA). Thus the method for characterizing the binding affinity is also the same still the K_D value is different. Therefore one can reasonably believe that 5C4 and NIVOLUMAB is not the same but different antibodies.

The specification of the opposed application does not clearly mention the inventiveness of the present application

It is an essential requirement under the law that every specification, whether provisional or complete, *shall describe the invention* and shall begin with a title sufficiently indicating the subject-matter to which the invention relates. Also, as mentioned above, it is a requirement under section 10(4) (a) ***that fully and particularly describe the invention*** and its operation or use and the method by which it is to be performed. According to the definition of "invention" under section 2 (j), "invention" means a new product or process involving an inventive step and capable of industrial application. It means that invention should have two essential parameters novelty and inventive step. Therefore, the specification should disclose the invention claimed in such a manner that it can show clearly that the subject-matter of the present invention is new and involves an inventive step. It has to clearly show that K_D value of the claimed antibody (5C4 as per the specification) is superior, unexpected

and higher in view of the antibodies disclosed in the cited documents therein. The applicants have compared K_D value of 5C4 with the antibodies disclosed in the cited prior art document and data has been submitted in their reply statement (Please see Table at the top of page xxiv of the applicants' reply). Here, we would like to bring the attention of the Ld. Controller towards the K_D values mentioned for the reference antibodies of the cited prior art documents. K_D values of the reference antibodies are already covered under the definition of the "high affinity". The definition of "high affinity" for IgG antibody as per the specification of the instant application covers antibody with K_D of 10^{-8} M or less (Please see 1st paragraph, page 20 of the impugned application). Few of the embodiments of the specification of the instant application

disclose KD value 1×10-7 M or less. Preferred KD values according to few embodiments are 5×10^{-8} M or less (Please see 2nd paragraph, page 3; 3rd paragraph, page 5; 7th paragraph, page 19; 4th paragraph, page 21; 4th paragraph, page 28; last paragraph, page 38 of the impugned application). Moreover, Applicants have initially covered human PD-1 antibody with a K_D of 1×10^{-7} M or less (claim 1 of the PCT application of the impugned application). If we go with the disclosure of the specification, it appears that the invention of the instant application covers those antibodies which have K_D value 1×10^{-8} M or less. It also covers the reference antibodies of the cited document D8. It means that the inventiveness of the invention addressed by the applicants in reply statement is the 'later found' property of the invention. The specification does not support the inventiveness of the claimed invention and therefore, does not clearly disclose the invention.

There is no evidence in the specification of the opposed application that the claimed invention provides surprising effect which is not provided by the prior art antibodies.

4.2 Opponent-3 submissions for Lack of Sufficiency and Clarity in PGO-3:

LACK OF CLARITY AND SUFFICIENCY

Section 25(1)(g)- The Opposed Specification is insufficient and does not clearly describe the alleged invention i.e. Nivolumab

5.1 Without prejudice, it is respectfully submitted that the present invention does not sufficiently and clearly disclose Nivolumab.

5.2 The full-length amino acid sequence of claimed antibodies is not provided in the opposed Indian Patent Application No. 5057/CHENP/2007.

5.3 It is the Applicants' case that Nivolumab, which is an IgG4 isotype antibody, is covered by the prior art document D3.

5.4 The data provided in the specification is of 5C4 antibody. It is not clear whether it is IgG1 or IgG4. For the sake of argument, the Opponents assumed that the specification teaches the IgG4 subtype of the claimed monoclonal antibody and aligned the sequence of Nivolumab with the IgG4 subtype of claimed monoclonal antibody. It was revealed that the amino acid sequence of the claimed antibody was different from that of Nivolumab with there being a single mutation at the Hinge Region of Nivolumab. Reliance is placed on pages 30-31 of the Opponent's evidence and pages 130-31 of the Opposition.

5.5 Applicant has submitted during hearing that the single amino acid difference as highlighted by the Opponent is a routine mutation which is known to the skilled person for the development of therapeutic IgG4 antibody. In response, it is respectfully submitted that it is not necessary that the skilled person would carry out this single mutation whenever he would make therapeutic antibody. There are numerous therapeutic IgG4 antibodies where this mutation is not present in the Hinge region. Some examples of such antibodies are Natalizumab and Ibalizumab. Thus, the highlighted single amino acid difference is neither essential nor an obvious mutation for the person skilled in the art. Therefore, if such mutation is done in the antibody, it has to be disclosed or taught in the specification to make it enabled for the person skilled in the art. The highlighted mutation is not disclosed in the opposed specification so as to enable the skilled person to arrive at Nivolumab.

5.6 The K_D value of the claimed $5C_4$ antibody is 0.47 nm, as disclosed in paragraph 149 of the Applicants' Reply Statement, while the K_D value of Nivolumab is 3.06 nm as disclosed in document D33, page 1319 of the Opponent's documents. D33 is USFDA pharmacology review of Opdivo (nivolumab).

Thus, the claims of the opposed specification do not sufficiently and clearly describe the claimed invention and the specification is thus liable to be refused on this ground alone.

4.3 APPLICANT'S SUBMISSIONS FOR SUFFICIENCY AND CLARITY

4.3.1 Applicant's submissions for Sufficiency and Clarity in PGO-1:

c. The Present Application Sufficicutly Discloses The Claimed Invention

69. The Opponent argued during the hearing that the application docs not meet the requirement ol' section l 0(4)(c) as the recombinant mouse used ror prcparing the antibodies has not been deposited under the Budapest treaty. Applicants disagree. as the rcquiren1cnts of section 10(4)(c) do not apply to the present application.

70. Section 1 0(4) requires that Applicants deposit claimed subject matter, such as a living bacterial culture, if it is not possible to describe the subject matter completely and sufficiently in words for a POSA to reproduce the invention.

71. The present invention claims an antibody. An antibody is a protein, which can be easily, clearly, and completely understood by a POSA by its sequence. The specification clearly and completely provides the sequences of the CDRs and the complete VH and VL sequences of the 5C4 antibody that is embodied in the specification.

72. Accordingly, no deposition under the Budapest treaty 1s required for the present application.

73. Further, the present application discloses extensive data for the disclosed antibodies with the help of 54 Figures and 25 Examples. Certain examples and figures from the present application are listed below:

a. Example l describes the production of human monoclonal antibodies against PO-l using transgenic mice and hybridoma.

b. Example 2 characterizes the anti-PD-l antibodies obtained from Example I, one of which is the 5C4 antibody. The VH and VL sequences of the anti-PO-l

antibodies are shown in Figures 1*A*, lB, 2A, 28, 3A, 38, 4A, 48, *SA*, 58, 6A, 68, 7A, and 78, indicating the CDR sequences therein. Figures 8 and II show an alignment of the selected anti-PO-l VH sequences, and Figures 9, 10, and 12 show an alignment of the selected anti-PO-l VL sequences. **(Claim 2)**

c. Example 3 discloses binding affinity and specificity for the selected anti-PO-l antibodies, including the 5C4 antibody. Binding affinity and kinetics were determined by Biacore analysis. Binding specificity was analyzed using flow cytometry. ELISA was used to investigate binding specificity with respect to the other CD28 family members - !COS. CTLA-4 and C028. The binding affinity and the on and off rates for the antibody 5C4 are found in Table 2. Figure 13A discloses the specificity of 5C4 for human PO-l. **(claim** 6, 7 **and** 8) Figure 14 discloses that the antibody 5C4 does not show cross-reactivity to !COS, CTLA-4 or CD28. **(Claim 5)**

d. Example 4 discloses the binding of the 5C4 antibody to **PD-1** expressing cells. See also Figures l*SA*, l58, and l*SC*. **(Claim 9)**

e. Example 5 examines the effect of the 5C4 antibody on cell proliferation and cytokine production. Figures 16A, 168, and 16C show that the 5C4 antibody promotes T cell proliferation, IFN-y secretion, and IL2 secretion in the mixed lymphocyte reaction in a concentration-specific manner.

f. Example 6 describes the ability of the 5C4 antibody to block ligand binding to human PD-1 expressed on the surface of CHO cells. The results shown in Figure 17 demonstrate that the 5C4 antibody can block the binding of the ligand to PD-1 in a dose-dependent manner.

g. Examples 7 and 9 demonstrate the effect of the 5C4 antibody on the release of cytokines and cytokine secretion. Example 7 shows that the 5C4 antibody does not stimulate human blood cells to release the cytokines IFN-y, TNF-a., IL-2, IL-4, IL-6, IL-l 0 and IL-12. Example 9 indicates that the 5C4 antibody 1ncreases lFN-y secretion in a concentration-dependent manner.

h. Example 8 shows that the 5C4 antibody does not have an effect on T-cell apoptosis.

1. Example 21 describes the effect of the 5C4 antibody on the function of T regulatory cells. Figures 51A and 5I8 show that the 5C4 antibody partially releases inhibition imposed by the Treg cells on proliferation and the IFN-y secretion of CD4+/CD25- T cells, which demonstrates that the 5C4 antibody has an effect on T regulatory cells. **(Claim 10)**

J· Example 22 reports the etTect of the 5C4 antibody on T cell activation. Figures 52A and 5213 shovv that PD-1 blockade by the 5C4 antibody results in enhanced T cell proliferation and IFN-y secretion.

k. Examples 23 and 24 assessed the ADCC activity and complement-dependent cytotoxicity of the 5C4 antibody. Figure 53 demonstrates that the ADCC activity of the 5C4 antibody is related to the Fe region. Figure 54 demonstrates that the 5C4 antibody is not involved in complement-dependent cytotoxicity. **(Claim 14)**

74. In summary, the present application includes extensive data, including methods of producing the claimed antibodies, the sequences of the antibodies, the binding affinity and specificity of the antibody, the ability of the antibodies to induce an immune response, and the ability of the antibodies to treat tumor. In light of the extensive disclosure of the specification as filed, Applicants submit that the specification is not deficient and indeed teaches the exact invention in the way it is to be performed.

75. The ground of insufficiency as several other grounds has to be seen through the eyes of a person skilled in the art and the person skilled in the art is a hypothetical construct that has certain attributes of having a qualification in the area of technology to which the invention relates, having read all the prior art documents and also having common general knowledge. Further, for the purpose of insufficiency routine experimentation is permissible. In this regard we refer to Narayanan, Fourth edition, page 456:

"The .specification of a patent is not addressed to the general public but

addressed to persons who knmv something about it .....1vhether or not the specification is SL!f!lciently described must bejudgedji-om the standard of' a "person possessing average skill in. and average knowledge of,' the art to which the invention relates."

76. It is for this reason that as a patent specification need not contain every detailing of the technology in question as the patent specification is neither a technical knowhow document nor a product specification. Therefore. it is not essential to include in the specification examples for each and every embodiment. for instance the compositions and the bispecific molecules etc. as the same can be worked by a person skilled in the art on reading the claims in light ofthe specification. The person skilled in the art if provided with complete specification would be able to generate the bispecific antibody containing the claimed sequence or a composition containing the claimed antibody, inparticular on reading the specification for instance on Page 49-59 work the bispecific molecules, composition etc.

77. The patent specification is not a production document and is addressed to a person who has skill in the particular field - the so called skilled men in the art. The complete specification of the instant invention has been fully elaborated so that the notional skilled man would be able to practice the invention. With regard to the assessment as to the knowledge of the person skilled in the art for determination of insufficiency, we wish to rely on para 14, page 265 of in F.H. and B. Corporation v. Unichem Laboratories, [AIR 1969, Bom 255]:

"14. Dealing first with the ground rf inst!fficiency of description it is stated in Halsburry ...that the claim need only be as clear as the subject admits, and that a patentee need not so simpl[jj; h;s clah11 as to make h easy for infhngers to evade it..... The . pecification and claims are addressed to those with a high degree of'know!edge ofthejield ofsdence to which they relate. particularly when they relate to chemistry and allied subjects. It is not necessmy to describe processes on the Claims to a specification when they are part ol the common knovvledge available to those skilled in the science who con, afier reading them, refer to the

technical literolure on 1he subject .fcJr the pw]Jose of' carrying them into effect. "An embodiment" o/1he invention is, Ihere/ore, in my opinion, sufficiently described in the plointiff.\ potent and that description is not zmnecessaril1· difficult tofollow. if being sufficient to enable the invention to he carried info effect "1t'ithmtlmakingfitr!her inventions"

78. Also, the Opponent has taken the ground of obviousness and insuf'ficiency 111 the same breadth. It is submitted that if <111 invention is ohvious. it cannot be insufficient md the reason for the same is that the person skilled in the art having regard to the prior art documents and his common general knowledge considers. the invention as being obvious it cannot then be considered as being insufficient. In this regard, we wish to rely on Terrell on the Law of Patents as reproduced below:

"It is not common for the grounds of obviousness and insz4ficiency to be argued in the alternative, the contention in an appropriate case being that either the difference between the cited prior art and the claims is such that the invention would have been obvious to the skilled addressee given the state ol his/her common general knowledge, or if not (because some necessary aspect was not part of the common general knowledge) then the pec[fication insz!fficiently discloses the hovv the invention is to be performed. "

79. It is further submitted that Section 10(4) of the Indian Patents Act does not require the examples in the specification. Having said this, it is submitted that it is not necessary that the specification is cluttered with examples. Even otherwise, the applicant has provided sufficient examples **in** the patent specification so as to allow the person ski lied in the art to carry out the invention without undue experimentation. In this regard, we refer to **In** re Gay, 135 USPQ, the Court of Customs and Patent Appeals held that

11. One final point remains to be discussed- the Patent Office requirement based on Rule 71 (b) that a ":;pec[fic embodiment" ol appellant's invention be described in the specification. No direct statut01y

basis exists for this requirement other than portion [A] of section 112. which it appears to implement.

13. The 11·ord ··. pecific" is a somewhat indefinite term in that it involves a mutter of degree- the question. ..... Not eve1y last detail is to he describhed. else patent specifications would turn mto production . pecificutions. 11·hich they were never intended to be..... "

80. In this regard. we also refer to Application of Rainer, [3!J7 F.2d 57!J]. the United States Court of Customs and Patent Appeals on page 3 held that

> ".....There is no need for Appellants to have burdened the specification with 53 specific working examples in order to claim each of the 53 specific materials Appellants have set forth as being operative. To hold with the Board of Appeals would mean that specifications instead of being concise and terse, would amount to tomes of many hundreds of pages which would result in making it more difficult for those skilled in the art to ascertain the invention."

81. Therefore, specification need not contain a working example at all or for all embodiments, if one skilled in the art is able to perform the invention/ that embodiment based on the textual description without undue experimentation.

4.3.2 Applicant's submissions for Sufficiency and Clarity in PGO-3:

SUFFICIENCY OF DISCLOSURE

84. The Opponent during the hearing briefly argued this ground, on limited point that Nivolumab is not described by the present invention. The Applicant in the present submissions would reply to the same limited point and for other assertions the pleadings may be considered by the Learned Controller.

85. The Opponent incorrectly asserts that, the present invention is for nivolumab, and that the specification does not fully describe the same. The claims of the present invention

are not directed to nivolumab alone. Nivolumab is the commercial product covered by the invention and comprises the CDR‘s as provided in the claims.

86. Opponent has not been able to show that nivolumab does not comprise the CDR‘s of claim 1. Further, the 5C4 antibody disclosed in the specification is nivolumab, which has been explicitly described in the specification and examples. Applicants note that the VH and VL sequences of the 5C4 antibody (SEQ ID NOs: 4 and 11) and the VH and VL sequences of nivolumab are identical. See also **Annexure F.**

87. The sequence identity has been also been confirmed at least by one third party. In particular, IUPHAR/BPS Guide to Pharmacology at http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=7335 which confirms that "[s]equence analysis of the light and heavy chain variable region peptides of nivolumab shows exact matches with claimed peptide sequences of monoclonal 5C4 contained in patent WO2006121168." It is also accepted by the industry and by the FDA that the 5C4 antibody is nivolumab. Undoubtedly Nivolumab is covered by the claims of the present invention. Further, 5C4 (i.e., nivolumab) is clearly and completely disclosed, described and exemplified in the specification.

88. As far as the sufficiency requirement of the present application is concerned, the present invention claims antibodies with the CDR sequences of the 5C4 antibody which are described in the specification. The six CDR sequences listed in claim 1 define the claimed antibodies' sequence and specificity. Dependent claims also provide and require specific full VH and VL sequences.

89. The specification discloses that constant regions were "known in the art." See, e.g., PCT Specification, p. 40. In describing the known constant regions, the specification states that "[t]he heavy chain constant region can be an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region, but most preferably is an IgG1 or IgG4 constant region." Id.

90. The specification further states that "[t]he light chain constant region can be a kappa or lambda constant region, but most preferably is a kappa constant region." Id. As such, a person of skill would have been aware of the sequence of the constant regions and would have been able to use them in concert with the claimed CDR sequences. See, e.g., Id., pp. 8, 40, 81-84, and 98-99.

91. Thus the specification provides the sequence of the claimed antibodies and the Opponent's allegation is unfounded.

92. It is of no import whether a sequence fabricated by the Opponent aligns with nivolumab. The specification does not refer to P01861 sequence that the opponent arbitrarily combined with SEQ ID NO: 4; rather, the specification generally discloses using an IgG4 constant region (amongst others), but not necessarily that disclosed by the opponent. There are different alleles of IgG4 and more than one sequence would have been recognized by those of skill in the art as being "IgG4." Accordingly, it is irrelevant that the Opponent has found a constant region sequence with a different constant region sequence than nivolumab (e.g., the UNIPROT P01861 entry states that "There are several different alleles"). See Dr. Fife‘s third evidence filed in December 2017 and its Annexure.

93. The opponent actually proves that nivolumab is disclosed by the instant specification – the opponent showed that the entire heavy chain variable region (i.e. SEQ ID NO:4) aligns perfectly with nivolumab – the single difference noted in the alignment is in the constant region arbitrarily selected by the opponent.

94. The present application further discloses extensive data for the disclosed antibodies: 54 Figures and 25 Examples. Certain examples and figures from the present application are listed below:

a. Example 1 describes the production of human monoclonal antibodies against PD-1 using transgenic mice and hybridomas, including the 5C4 antibody.

b. Example 2 characterizes the anti-PD-1 antibodies obtained from Example 1, one of which is the 5C4 antibody. The VH and VL sequences of the anti-PD-1 antibodies are shown in Figures 1A, 1B, 2A, 2B, 3A, 3B, 4A, 4B, 5A,
5B, 6A, 6B, 7A, and 7B, indicating the CDR sequences therein. Figures 8 and 11 show an alignment of the selected anti-PD-1 VH sequences, and Figures 9, 10, and 12 show an alignment of the selected anti-PD-1 VL sequences.

c. Example 3 discloses binding affinity and specificity for the selected

anti- PD-1 antibodies, including the 5C4 antibody. Binding affinity and kinetics were determined by Biacore analysis. Binding specificity was analyzed using flow cytometry. ELISA was used to investigate binding specificity with respect to the other CD28 family members: ICOS, CTLA-4 and CD28. The binding affinity and the on and off rates for the antibody 5C4 are found in Table 2. Figure 13A discloses the specificity of 5C4 for human PD-1. Figure 14 discloses that the antibody 5C4 does not show cross-reactivity to ICOS, CTLA-4 or CD28.

d. Example 4 discloses the binding of the 5C4 antibody to PD-1 expressing cells. See also Figures 15A, 15B, and 15C.

e. Example 5 examines the effect of the 5C4 antibody on cell proliferation and cytokine production. Figures 16A, 16B, and 16C show that the 5C4 antibody promotes T cell proliferation, IFN-γ secretion, and IL2 secretion in the mixed lymphocyte reaction in a concentration-specific manner.

f. Example 6 describes the ability of the 5C4 antibody to block ligand binding to human PD-1 expressed on the surface of CHO cells. The results shown in Figure 17 demonstrate that the 5C4 antibody can block the binding of the ligand to PD-1 in a dose-dependent manner.

g. Examples 7 and 9 demonstrate the effect of the 5C4 antibody on the release of cytokines and cytokine secretion. Example 7 shows that the 5C4 antibody does not stimulate human blood cells to release the cytokines IFN-γ, TNF-α, IL-2, IL-4, IL-6, IL-10 and IL-12. Example 9 indicates that the 5C4 antibody increases IFN-γ secretion in a concentration-dependent manner.

h. Example 8 shows that the 5C4 antibody does not have an effect on T-cell apoptosis.

i. Example 21 describes the effect of the 5C4 antibody on the function of T regulatory cells. Figures 51A and 51B show that the 5C4 antibody partially releases inhibition imposed by the Treg cells on proliferation and the IFN-γ secretion of CD4+/CD25- T cells, which demonstrates that the 5C4 antibody has an effect on T regulatory cells.

j. Example 22 reports the effect of the 5C4 antibody on T cell activation. Figures 52A and 52B show that PD-1 blockade by the 5C4 antibody results in enhanced T cell proliferation and IFN-γ secretion.

k. Examples 23 and 24 assessed the ADCC activity and complement-dependent cytotoxicity of the 5C4 antibody. Figure 53 demonstrates that the

ADCC activity of the 5C4 antibody is related to the Fc region. Figure 54 demonstrates that the 5C4 antibody is not involved in complement-dependent cytotoxicity.

95. In summary, the present application includes extensive data, including methods of producing the claimed antibodies, the sequences of the antibodies, the binding affinity and specificity of the antibody, the ability of the antibodies to induce an immune response, and the ability of the antibodies to treat tumor. In light of the extensive disclosure of the specification as filed, Applicants submit that the specification is not deficient and indeed teaches the exact invention in the way it is to be performed.

96. The claims therefore clearly and completely define the invention claimed.

4.4 My findings w.r.t Sufficiency and Clarity:

The Opponents 1 and 3 allegation is that the complete specification is not sufficiently and clearly disclose the monoclonal antibody or or antigen-binding portion thereof, claimed in amended claims 1 to 6 and also the composition claimed in amended claim 7 along with the nucleic acid claimed in amended claim 8.

The amended claim 1 is claiming for the antibody which is characterized with six CDR sequences and these sequences are defined and described in the SEQ listing. This description of the antibody in the complete specification gives clarity of the product (antibody) claimed in amended claim 1. I am in agreement with the statement of the applicant that "The present

invention claims an antibody. An antibody is a protein, which can be easily, clearly, and completely understood by a POSA by its sequence. The specification clearly and completely provides the sequences of the CDRs and the complete VH and VL sequences of the 5C4 antibody that is embodied in the specification". Therefore, in my opinion the amended claims 1 to 6 are clearly defined with their product technical features to meet the requirements of section 10(4) (c) of the Patents Act, 1970. The amended claim 7 is also clear as it claims for the composition with the monoclonal antibody or antigen-binding portion thereof as claimed in any one claims 1-6 and a pharmaceutically acceptable carrier. The amended claim 8 is claiming the isolated nucleic acid encoding the monoclonal antibody or antigen-binding portion thereof as claimed in any one claims 1- 7 with a characterization that the nucleic acid sequence encoding the heavy chain comprises sequence defined in Figure 4A and that encoding the light chain comprises sequence defined in figure 4B. Therefore, in my opinion the amended claims 7 and 8 are also clearly defined with their product technical features to meet the requirements of section 10(4) (c) of the Patents Act, 1970.

The example 1 in the complete specification describes the production of human monoclonal antibodies against PD-l using transgenic mice and hybridoma. Thus, it can be said that the complete specification is describing the invention to meet the requirements of the provisions of Sec 10(4) (a) and (b) of the Patents Act, 1970. The requirement of the developed hybridoma deposition as argued by the opponent is not tenable as the invention is for the monoclonal antibody, its encoding nucleic acid and its composition. Thus, the complete specification is sufficiently describing the process for production of the claimed products and defined with their product characteristics.

Therefore, in my opinion the complete specification is sufficiently describing the invention to understand by the person skilled in the art and that supports fully the products claimed in amended claims 1 to 8 to meet the requirements of the section 10 of the Patents Act, 1970. Therefore, the opponents failed to establish this ground of opposition u/s 25 (1) (g) of the Patents Act, 1970.

5. FAILED TO DISCLOSE INFORMATION UNDER SECTION 8 [Section 25 (1) (h)]-PGO 4

5.1 Opponent-4's submissions for failure of applicant to disclose information under section 8 in PGO-4:

II. Section 25(1)(h): BREACH OF SECTION 8

The Opponent submits that as shown under the ground of anticipation, D1 relates to the same invention as the impugned patent application and thus ought to have been acknowledged in the impugned application as well as disclosed under Section 8(1). The Applicant failed to do so in Form-3 repeatedly and thus the impugned application ought to be rejected since the same was done by the Applicant deliberately to materially suppress information.

5.2 Applicant's submissions for Section 8 in PGO-4:

In Hearing written submissions

204. The other grounds relied upon by the opponent are section 3(d) and section 8. Applicants request that the reply statement be considered for said grounds, as no oral arguments were made in detail during the hearing as relating to these grounds.

In reply statement:

178. The Applicant has therefore complied with the requirements of section 8 and D1 is not the ―same or substantially the same invention‖ as the present invention as required by section 8 of the Act.

5.3 My findings w.r.t Information under Section 8:

Opponent-4 did not specifically argue on this ground of the opposition under section 25(1) of the Patents Act, 1970 during the hearing and in the written submissions mainly stated that the CD1 (D1) relates to the same invention as the impugned patent application and thus ought to have been acknowledged in the impugned application as well as disclosed under Section 8(1). In reply, the applicant already stated that CD1 (D1) is not the ―same or substantially the same invention as the present invention as required by section 8 of the Act. Considering the applicant's declaration that CD1 (D1) is not the same or substantially the same invention as the present invention and hence it cannot be said that applicant has not complied with the provisions of section 8 of the Patents Act, 1970. Therefore, the opponent-4 failed to establish this ground of opposition u/s 25 (1) (h) of the Patents Act, 1970.

In view of my findings as above, the amended claims 1 to 8 of the instant patent application do meet the requirements of the Patents Act, 1970 and hence I herewith order for grant of a patent for patent application no. 5057/CHENP/2007 by rejecting all the pregrant representations filed u/s 25(1) of the Patents Act, 1970.

Dated this 30th day of June 2020 **Dr. SHARANA GOUDA**
ASSISTANT CONTROLLER OF PATENTS & DESIGNS