

To
The Controller of Patents,
The Patent Office at Kolkata

Re. Opposition under Section 25(1) against

Patent Application no. **3939/KOLNP/2010** dated 21/10/2010

Applicant: ARIAD PHARMACEUTICALS, INC.

Opponent: Ms. Mita Sheikh

Dear Sir,

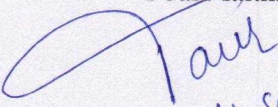
This letter is in reference to submission of 'Pre-Grant Opposition' under section 25(1) of Indian Patent Act of 1970 concerning the patentability of the invention on the issue of 'Inventive Step' of the claims among other grounds against Patent Application No. 3939/KOLNP/2010 dated October 21, 2010 titled: "PHOSPHOROUS DERIVATIVES AS KINASE INHIBITORS" of whose the Applicant is ARIAD PHARMACEUTICALS, INC.

In view of the above, Pre-Grant Opposition along with the relevant form and documents is being enclosed for your kind consideration.

Thanking you.

Dated: 11th September 2018

Yours faithfully,



11. Sept. 2018

Mr. Tarun Khurana
IN/PA/1325

Of Khurana and Khurana Advocates and IP Attorneys
(Agent of the Opponent)

Email: info@khuranaandkhurana.com, smitta@khuranaandkhurana.com

IN THE MATTER OF THE PATENTS ACT 1970

and

IN THE MATTER OF THE PATENT RULES 2003

(as amended by (Amendment) Rules 2006)

and

**IN THE MATTER OF INDIAN PATENT APPLICATION No. 3939/KOLNP/2010 DATED
21/10/2010 FILED BY ARIAD PHARMACEUTICALS, INC. OF 26 LANDSDOWNE
STREET, CAMBRIDGE, MA 02139, UNITED STATES OF AMERICA**

.....the Applicant

and

**IN THE MATTER OF REPRESENTATION BY WAY OF OPPOSITION UNDER SECTION
25(1) AND RULE 55 THERETO BY MS. MITA SHEIKH OF A001, NITESH CENTRAL
PARK, BAGALUR CROSS, YELAHANKA, BENGALURU-64, KARNATAKA, INDIA**

.....the Opponent

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**STATEMENT OF CASE FOR REPRESENTATION UNDER SECTION 25(1) OF THE
PATENTS ACT 1970**

A. BACK GROUND OF THE OPPONENT

1. I, Ms. Mita Sheikh, an Indian citizen, resident of A001, Nitesh Central Park, Bagalur Cross, Yelahanka, Bengaluru-64, Karnataka, India (hereinafter called “opponent”), make the following statement in support of the grounds of opposition submitted by me in opposing the grant of the patent application indicated in the cause title.

B. INDIAN PATENT APPLICATION NO. 3939/KOLNP/2010

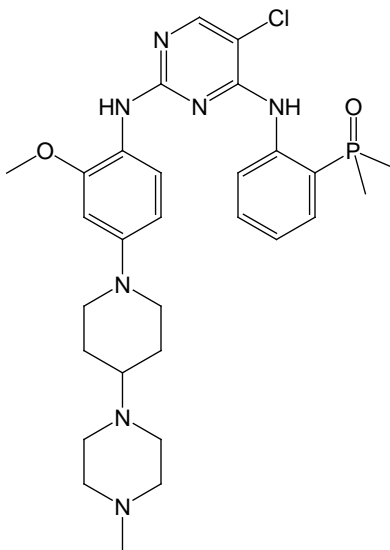
2. The patent application No. 3939/KOLNP/2010 (hereinafter referred to as “the ‘3939 application”), entitled “PHOSPHOROUS DERIVATIVES AS KINASE INHIBITORS” entered national phase in India on October 21, 2010 from the PCT International Application No. PCT/US2009/044918 dated May 21, 2009 which in turn claimed earliest priority of May 21, 2008. The ‘3939 application was published on December 24, 2010.
3. The ‘3939 application was filed in India with 22 claims broadly covering heterocyclic compounds having phosphorous containing substituent and their use in treating cancers and other diseases. The complete specification of the ‘3939 application and the set of as-filed 22 claims as obtained from the IPAIRS (Indian Patent Application Information Retrieval System) database made available by the Indian Patent Office on its official website are attached herein as **Annexure I and Annexure II** respectively.
4. The Indian patent office issued First examination report (F.E.R.) on February 15, 2016, attached herein as **Annexure III**, citing objections including, *inter alia*, inventive step, section 3(d), 3(e) and 3(i).
5. The Applicant submitted its response to the F.E.R. on August 22, 2016 along with an amended set of 72 claims annexed herewith as **Annexure IV**.
6. A hearing was fixed on June 28, 2017, and at the time of hearing the Applicant filed an amended set of 2 claims annexed herewith as **Annexure V**.

7. After hearing, the Applicant submitted its written submission on July 07, 2017 along with an amended claim which is restricted to a single compound, known as brigatinib. This amended claim is annexed herewith as **Annexure VI** and is being challenged by way of this pre-grant opposition.
8. A pre-grant opposition u/s-25(1) was filed by Cancer Patients Aid Association on July 10, 2017.

C. AMENDED CLAIM (LATEST/CURRENT) OF THE '3939 APPLICATION

9. The claim below represents the amended claim filed by the Applicant on July 07, 2017.

Claim 1: A compound of the formula:



D. GROUND OF OPPOSITION:

10. The opponent submits that the impugned '3939 application of the applicant is invalid and therefore the grant of the patent ought to be refused. The opponent relies upon the following grounds in the instant pre-grant opposition:
 - i. **Section 25(1)(e)**– that the invention claimed in '3939 application is obvious and clearly does not involve any inventive step.

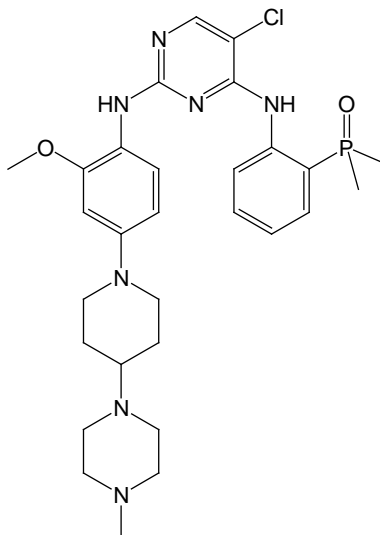
- ii. **Section 25(1)(f)** – that the subject of any claim of the complete specification, is not an invention within the meaning of this act or is not patentable under this act.
- iii. **Section 25(1)(g)** – that the complete specification of ‘3939 application does not sufficiently and clearly describe the invention or the method by which it is to be performed.

11. Prior Arts Referred to Herein:

Document	Patent No. / Article	Publication Date/Year
D1	WO 2004/080980 A1	23 September 2004
D2	Zhao et al. , “The synthesis of novel acetolactate synthase inhibitors, N-(asymmetrically disubstituted phosphoryl)-N’-(4,6-dimethoxypyrimidin-2-yl) urea”, Heteroatom Chemistry, Volume 10, Number 3, 1999, pages 237-241	1999
D3	Zhao et al. , “Bioisostere of Sulfonyl Moiety-The Synthesis of New ALS Inhibitors N-(Asymmetry Disubstituted Phosphoryl)-N’-(4,6-dimethoxypyrimidin-2-yl) Ureas”, Chinese Chemical Letters, 1998, Issue 5, Pages 455-458.	1998
D4	Zhao et al. , “Bioisosterism between sulfonyl group and phosphoryl group - The synthesis of new ALS inhibitors N’-(arylamino hydroxyl phosphoryl)-N’-(4,6-dimethoxypyrimidine-2-yl) ureas”, Chinese Chemical Letters, 1998, Issue 8, Pages 723-724+275	1998
D5	Schneider et al. , “Building blocks for oligonucleotide analogs with dimethylene-sulfide, -sulfoxide, and -sulfone groups replacing phosphodiester linkages”, Tetrahedron Letters, Volume 31, Issue 3, 1990, Pages 335-338.	1990

I. OBVIOUSNESS/LACK OF INVENTIVE STEP [Section 25(1) (e)]:

12. The Opponent respectfully submits that the compound as claimed in claim 1 of the impugned '3939 application lacks inventive merit and is obvious to a person skilled in the art in view of the prior art documents attached in the Annexures.
13. Claim 1 of the impugned '3939 application relates to a compound of the formula:



(also known as '**Brigatinib**')

14. The Opponent submits that the pyrimidine derivatives as disclosed in D1 and the brigatinib compound as claimed in the impugned application have very close structural similarities and similar utilities. Thus, the prior art document D1 applies as the closest prior art. D1, annexed herewith as **Annexure VII**, discloses diphenylamino pyrimidine derivatives useful as pharmaceuticals. More particularly, D1 discloses pyrimidine derivatives of compounds of formula **27-9**, **28-5** (also known as TAE684) and **30-7**, which have very close structural similarities with the compound claimed in the impugned application, i.e., brigatinib. D1 also describes that the compounds **27-9**, **28-5** and **30-7** exhibit pharmacological inhibition of kinases such as anaplastic lymphoma kinase (ALK), focal adhesion kinase (FAK), etc. and that said compounds are useful in the manufacture of anti-cancer medicaments.
15. The structure of Compounds 27-9, 28-5 and 30-7 of D1 is compared with the structure of brigatinib in the following table.

<p align="center"><u>Prior art D1</u> (WO2004080980A1)</p>	<p align="center"><u>Impugned ‘3939 application</u> (Claim 1)</p>
<div data-bbox="154 252 544 714"> </div> <p>(Compound 27-9, Page 96)</p> <div data-bbox="600 252 990 714"> </div> <p>(Compound 28-5 (also known as TAE684), Page 98)</p> <div data-bbox="373 861 787 1344"> </div> <p>(Compound 30-7, page 106)</p>	<div data-bbox="1079 325 1429 798"> </div> <p>(Brigatinib)</p>

16. It is clear from the above comparative table that the only difference between the compounds of D1 and brigatinib is that the compounds of D1 contain a “sulfonyl” group on the phenyl ring linked to the 4-position of the pyrimidine core, while the claimed compound, brigatinib, contains a “dimethylphosphoryl group” at the corresponding position. The above comparison makes it clear that barring this modification, the pyrimidine derivative claimed in the impugned application, i.e. brigatinib is substantially same as that disclosed in D1.

17. The Opponent submits that substitution of sulfonyl groups with phosphoryl groups is obvious to a person skilled in the art as phosphoryl groups are known to be good bioisosteres of sulfonyl groups, as explained and shown in the prior art documents D2 to D5.

18. Looking at D2, annexed herewith as **Annexure VIII**, it can be seen that it was known at the priority date of the impugned '3939 application that phosphoryl groups are good bioisosteres of sulfonyl groups. Specifically, page 237, right column, paragraph 3 of D2 states:

“We have paid attention to the similarity between sulfonyl (-SO₂-) and phosphoryl groups [-P(O)R-, R=OR', NHR', etc.]. Their close homolgy in terms of size, bond angle, bond length, and configuration suggest that they have a good degree of isosterism. Recently, the literature [5,6] proved that the sulfonyl group was a bioisostere of the phosphoryl group and useful in bioisosteric replacement of the phosphoryl group.”

19. D3, annexed herewith as **Annexure IX**, also indicates that phosphoryl group is a good bioisostere of sulfonyl group:

“In view of the isosterism of the sulfonyl (-SO₂-) and phosphoryl groups [-P(O)(OR-), R=H, CH₃, C₂H₅, etc], two new types of ureas, N-(N-aryl-O-alkyl phosphoryl)-N'-(4, 6-dimethoxy pyrimidin-2-yl) ureas 2 and N-(N-aryl-N-alkyl phosphoryl)-N'-(4, 6-dimethoxy pyrimidin-2-yl) ureas 3, were synthesized by treating N-(arylaminochlorophosphoryl)-N'-(4,6-dimethoxy pyrimidinyl-2-) ureas 4 with alcohols or amines. Compounds 4 were obtained by reacting dichlorophosphoryl isocyanate with 4,6-dimethoxy-2-aminopyrimidine, and then with aromatic amines. The enzyme tests (in vitro) indicated that compounds 2 and 3 were two novel classes of acetolactate synthase (ALS) inhibitors, which showed that the phosphoryl group, [-P(O)(OR)-], or [-P(O)(NHR)-], was a good bioisostere of the sulfonyl group (-SO₂-) in sulfonylurea.”

(D3, Abstract)

20. D4, annexed herewith as **Annexure X**, states:

“In view of the isosterism of sulfonyl group (-SO₂-) and phosphoryl group [-P(O)(OR)-, R=H, CH₃, C₂H₅, etc], a new type of ureas, that is, N-

phosphoryl-N'-(4,6-dimethoxypyrimidin-2-yl) ureas 2 were synthesized and shown to be a new class of acetolactate synthase (ALS) inhibitors.”

(D4, Abstract)

21. D5, annexed herewith as **Annexure XI**, describes that sulfonyl groups are isosteric analogs of phosphoryl groups, and are stable to chemical and biochemical degradation, making them ideal analogs for phosphoryl groups on other grounds as well. See, D5, page 335.
22. It is evident from the teachings of the prior art documents D2 to D5 that sulfonyl and phosphoryl groups can be used in the alternative since they are bioisosteric and thus replacing one with the other would necessarily result in the same biological activity. Starting at D1 and combining the teachings of any of documents D2 to D5, a person skilled in the art can easily replace the sulfonyl group of D1 with dimethylphosphoryl group when trying to form an alternative kinase inhibitor compound with reasonable expectation of success. This is only trial and error and a person skilled in the art, looking for an alternate kinase inhibitor compound, is left to verify the result with dimethylphosphoryl when compounds with same structure except with sulfonyl group are known from D1. It is therefore respectfully submitted that the brigatinib compound as claimed is obvious to try with reasonable expectation of success and cannot be regarded as inventive given the teachings of D1 to D5.
23. Further, as pointed out above, Compounds 27-9, 28-5 and 30-7 of D1 are known as inhibitors of kinases such as ALK, FAK, etc. It would therefore have been clearly obvious to a person skilled in the art that similar compounds wherein the sulfonyl group on the phenyl ring linked to the 4-position of the pyrimidine core is replaced with a dimethylphosphoryl group would also expectedly possess similar activity. Therefore all the applicant has done in this case is replaced the sulfonyl group of D1 by dimethylphosphoryl group to form the structure of compound of the impugned application in line with the impetus provided by the teachings of D1 to D5 and verified the results. Such verification of results cannot be considered as inventive. The Opponent further submits that obviousness cannot be avoided simply by showing of some degree of unpredictability in the art as long as there was a reasonable probability of success.
24. Thus, the brigatinib compound as claimed in claim 1 of the impugned application is obvious with respect to the disclosure and teachings of D1 combined with any of documents D2-D5.

II. LACK OF INVENTIVE STEP [Section 25(1) (e)]:

25. The Applicant in its '3939 application has mentioned that the problem solved by his invention is to provide compounds that are useful as protein kinase inhibitors and therefore useful in the treatment of protein tyrosine-kinase related diseases. However, it has not been shown that the claimed compound, brigatinib, possesses the type and level of therapeutic activity required to achieve the technical effect essential for the resolution of the problem. Thus, a skilled person would have reasonable doubt that the claimed compound, brigatinib, is a solution to the problem of providing further compound as inhibitors of protein kinases.
26. Inventive step thus should not be acknowledged for the compound as claimed in the impugned application.
27. The specification of the impugned application states that the compounds disclosed therein inhibit proliferation of Ba/F3 NMP-ALK, Ba/F3 EML4-ALK, Karpas 299 and/or SU-DHL-I cells with a potency at least as great as the potency of known ALK inhibitors such as NVP-TAE684 and PF2341066 among others, preferably with a potency at least twice that of known ALK inhibitors, and more preferably with a potency at least 10 times that of known ALK inhibitors as determined by comparative studies. Therefore, the technical advance as canvassed by the Applicant in its complete specification is the provision of ALK inhibitors with potency as great as or twice or at least 10 times that of known ALK inhibitors. However, there is no data/disclosure in the specification of the impugned application to substantiate the ALK-inhibiting activity of the claimed compound, neither is there any comparative data to show improved inhibition of ALK by the claimed compound.
28. Thus, the claimed compound cannot be considered to involve an inventive step.
29. The Applicant, in its written submission to the hearing letter, submitted an affidavit of Dr. William C. Shakespeare to show that the claimed brigatinib compound exhibits a weaker InsR IC50 binding activity compared to TAE684, and thereby lowers potential risk of side effects when dosed in patients. It is a known jurisprudence that an alleged advantage or effect, if any, to support an inventive step must be made plausible by the complete specification. However, the complete specification of the impugned application is completely silent on this alleged advantage or effect of weaker InsR inhibitory activity.
30. Therefore, data to show an alleged weaker or less potent InsR inhibition exhibited by the claimed compound cannot be introduced as an argument or evidence and, even if introduced, is not

relevant to the determination of the inventive step of the compound as claimed in the impugned application.

31. It seems that the Applicant is misusing the patent office's discretion by attempting to show an alleged advantage by providing comparative data for InsR activity, an off-target activity, rather than ALK inhibitory activity.
32. Inventive step thus should not be acknowledged for the claimed brigatinib compound.

III. NOT AN INVENTION / NOT PATENTABLE WITHIN THE MEANING OF THE ACT **[Section 25(1) (f)]**

Section 2(1)(j)/Section 2(1)(ja):

33. The opponent states that the claimed invention falls under the mischief of section 2(1)(ja) by virtue of failing the requirements of an 'invention' and also being devoid of inventive step. Section 2(1)(ja) of the Act defines "inventive step" to mean "a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art". Thus, to possess inventive step, an invention must have a feature that (i) involves technical advance as compared to the existing knowledge and (ii) is not obvious to a person skilled in the art. It is an established position of law that both these requirements set out in the definition of 'Inventive Step' have to be satisfied.
34. As described above, there is structural and functional similarity between D1 and claim 1 of the impugned application. Further, the Applicant has not mentioned any problems faced in the prior art. Starting with D1 as a reference compound, the Applicant has only replaced sulfonyl group with dimethylphosphoryl group and verified the results. It is stated that such verification of results is obvious to try with respect to the teachings of D1 read with any of documents D2-D5 as there is no unexpected result to support inventive merit.
35. It is stated that the Applicant has failed to demonstrate superior and unexpected activity of the claimed brigatinib compound over known compounds, especially those of D1. There is no data in the specification of the impugned application to substantiate unexpected result, neither is there any comparative data to show improved effect. In fact, the Applicant has admitted certain known ALK inhibitors in the specification like TAE684 and PF2341066 but even failed to provide any data comparing the impugned structure of the compound of claim 1 over the same. It is stated that the data furnished in the affidavit of Dr. William C. Shakespeare is inconclusive regarding the

presence of an inventive step. Thus, the brigatinib compound claimed in the impugned application is nothing but alternate compound having properties of inhibiting tyrosine kinase activity of ALK, FAK, etc. as expected from its structure as already described in D1.

36. Based on the above, the Opponent submits that the Applicant is merely formulating an alternative compound for the inhibition of protein kinase activity with no demonstration of technical advance/enhanced efficacy and therefore is not entitled to a patent and ought to be rejected in toto.

IV. NOT AN INVENTION / NOT PATENTABLE U/S 3(d):

37. Section 3(d) of the Patents Act, specifies that mere discovery of new form of a known substance is not patentable under the Act, unless it results in the enhancement of the known efficacy of that substance. Explanation to Section 3(d) further clarifies that salts, esters, ethers..... and **derivatives of known substance** shall be considered as same substance unless they differ significantly with regard to efficacy.
38. As shown above in the comparative table, the only difference between the impugned structure of claim 1 and the compounds of D1 is the presence of a sulfonyl group in D1 instead of a dimethylphosphoryl group as in the impugned structure of claim 1. Further, the compounds of D1 are used in the treatment of protein tyrosine-kinase related diseases which is also the function of compound of claim 1 of the impugned application. Considering the very close structural similarities and similar utilities, it will only be fair to mention that the impugned application claims a new form (derivative) of the known substance.
39. Thus, the claimed compound, brigatinib, can be considered as patentable u/s 3(d) only if an enhancement of known efficacy is demonstrated by the Applicant.
40. The Applicant in its '3939 application has mentioned that the problem solved by his invention is to provide compounds that are useful as protein kinase inhibitors and therefore useful in the treatment of protein tyrosine-kinase related diseases. However, the specification of '3939 application lacks any data/information demonstrating that the brigatinib compound results in enhanced therapeutic efficacy over the previously known kinase inhibitors, especially Compounds 27-9, 28-5 and 30-7 of D1.
41. While replying to the hearing letter, the Applicant has submitted an affidavit of Dr. William C. Shakespeare, one of the co-inventors, to show that the brigatinib compound exhibits a weaker InsR IC50 binding activity compared to TAE684 and therefore provides better patient tolerance

and lowers the risk of potential side effects. However, the affidavit of Dr. William C. Shakespeare as well as the specification of the impugned application neither indicate any enhanced effect of brigatinib nor demonstrate any significance of such properties with regard to ‘therapeutic efficacy’ in view of the known substance. To this end, one may take into consideration the law settled by Hon’ble Supreme Court in the case-*Novartis vs. Union of India and Ors.*; *Natco Pharma Ltd. v. UoI & Ors.*; *M/S Cancer Patients Aid Association v. UoI & Ors.* decided on April 1, 2013. Refer excerpts:

*“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 to “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**.”*

42. When the applicant was aware that it is providing additional compounds over known ones it was incumbent upon the applicant to provide data to show enhanced therapeutic efficacy if any. In absence of any enhanced therapeutic efficacy over the known compounds which are structurally so close as mentioned above, the brigatinib compound as claimed in the impugned application attracts the provision of Section 3(d) of the Patents Act, 1970. Thus the impugned application is liable to be rejected on this ground alone.
43. Further, the Applicant has submitted the affidavit of Dr. William C. Shakespeare on June 28, 2017 along with its written submission to the hearing letter. It is important to take notice of the fact that a Patentee or an Applicant is required to show the technical effect of an invention at the time of filing of the complete specification. Having failed to provide such information raises serious doubts on whether or not the Applicant actually possessed the invention at the time of filing. In the instant fact situation, the aforementioned technical affidavit containing InsR inhibitory data was submitted much after the filing of the ‘3939 application without having any reference to the date on which the experiments were carried out, thereby challenging the veracity of the Application itself.
44. In view of the above submissions, it is submitted that the impugned invention is not patentable under section 3(d) of the Act.

V. INSUFFICIENCY OF DISCLOSURE IN SPECIFICATION:

45. The alleged invention falls **woefully short of the requisite standards of disclosure under** the law. The '3939 application suffers from insufficiency of disclosure as the description of the '3939 application does not enable a skilled artisan to work the invention. It does not even demonstrate that the inventor was in possession of the alleged invention at the time of filing the application. These issues have been elaborated further in the paragraphs *infra*.
46. The specification of the impugned application states that the compounds disclosed therein inhibit proliferation of Ba/F3 NMP-ALK, Ba/F3 EML4-ALK, Karpas 299 and/or SU-DHL-I cells with a potency at least as great as the potency of known ALK inhibitors such as NVP-TAE684 and PF2341066 among others, preferably with a potency at least twice that of known ALK inhibitors, and more preferably with a potency at least 10 times that of known ALK inhibitors as determined by comparative studies. However, the specification lacks any experimental data to support this alleged advantage or effect. This surely amounts to insufficiency of disclosure.
47. Further, the Applicant admits in his disclosure that the impugned compound is useful as protein kinase inhibitor and therefore useful in the treatment of protein tyrosine-kinase related diseases. However, the applicant has failed to demonstrate the working of the impugned compound in treatment of any of the said diseases. Having failed to provide such information raises serious doubts on whether or not the Applicant actually possessed the invention at the time of filing.
48. Furthermore, there is no comparative experimental data provided demonstrating improved efficacy or any unexpected advantage of the claimed brigatinib compound over the prior art.
49. The claimed invention thus lacks support and sufficiency (enablement) of disclosure and ought to be rejected on this ground alone.

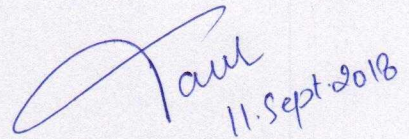
E. RELIEF SOUGHT:

50. The Opponent states that it has established and made out a case on each of the aforesaid grounds of opposition and pray to the Learned Controller for the following relief(s):
 - (a) Take on records the present representation
 - (b) Leave to file further evidence
 - (c) Opportunity to be heard
 - (d) Refusal of the '3939 application in *toto*

(e) Such other relief(s) as the Learned Controller may deem appropriate.

51. The opponent requests for a Personal Hearing before the Controller of Patents, before a decision adverse to the Opponent is taken in this matter.

Dated this 11th day of September 2018



Mr. Tarun Khurana

IN/PA/1325

(Agent of the Opponent)

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Of Khurana and Khurana Advocates and IP Attorneys

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To
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