

To  
The Controller of Patents,  
The Patent Office at Delhi

**Re. Opposition under Section 25(1) against**

**Patent Application No. 8222/DELNP/2015 dated 10/09/2015**

**Applicant:** PFIZER INC.

**Opponent:** Dr. Meera Sharma

Dear Sir,

This letter is in reference to submission of 'Pre-Grant Opposition' under section 25(1) of the Indian Patent Act 1970 concerning patentability of invention on the issue of 'Novelty' and 'Inventive Step' of the claims among other grounds against Patent Application No. 8222/DELNP/2015 dated 10/09/2015 titled: "TOFACITINIB ORAL SUSTAINED RELEASE DOSAGE FORMS" of whose the Applicant is PFIZER 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: 26<sup>th</sup> April 2021

Yours faithfully,



Mr. Tarun Khurana  
IN/PA/1325

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**BEFORE THE CONTROLLER OF PATENTS**

**DELHI**

**REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT UNDER  
SECTION 25(1) OF THE PATENTS ACT, 1970 AGAINST PATENT APPLICATION  
NO. 8222/DELNP/2015 DATED SEPTEMBER 10, 2015**

Dr. Meera Sharma of B 304, Green Hills Apartment, Near Swaminarayan Temple, Adajan,  
Surat, Gujarat-395009, India

.....Opponent

-VS-

PFIZER INC. of 235, East 42<sup>nd</sup> Street New York, New York 10017, United States of America

.....Applicant

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**BEFORE THE CONTROLLER OF PATENTS**

**DELHI**

In the matter of Section 25(1) of The Patents  
Act, 1970 as amended by The Patents  
(Amendment) Act 2005;

And

In the matter of The Patents (Second  
Amendment) Rules 2006

And

IN THE MATTER of Indian Patent  
Application No. 8222/DELNP/2015 dated  
10/09/2015 in the name of PFIZER INC. of  
235, East 42<sup>nd</sup> Street New York, New York  
10017, United States of America

.....Applicant

And

IN THE MATTER of representation by way  
of opposition to grant of patent thereto by DR.  
MEERA SHARMA of B 304, Green Hills  
Apartment, Near Swaminarayan Temple,  
Adajan, Surat, Gujarat-395009, India

.....Opponent

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

**I. THE OPPONENT**

1. The Opponent herein is Dr. Meera Sharma of B 304, Green Hills Apartment, Near Swaminarayan Temple, Adajan, Surat, Gujarat-395009, India. The Opponent is an individual with a Doctoral degree in immunopathology and a Master of Science degree in life sciences and has over 20 years of academic, research and industry experience in the field of life sciences and pharmaceuticals. The Opponent also has wide experience in drafting and prosecuting patent applications in the field of life sciences and pharmaceuticals.

**II. THE INDIAN PATENT APPLICATION NO. 8222/DELNP/2015**

2. The Patent Application No. 8222/DELNP/2015 (hereinafter referred to as “the impugned application”) entitled “TOFACITINIB ORAL SUSTAINED RELEASE DOSAGE FORMS” was filed in India on Sep. 10, 2015 from the PCT International Application No. PCT/IB2014/059689 dated Mar. 12, 2014 which in turn claimed priority of Mar. 16, 2013. The impugned application was published in the official journal of the Indian Patent Office on Aug. 31, 2016.
3. The impugned application was filed in India with 114 claims broadly covering oral sustained release formulations of tofacitinib or pharmaceutically acceptable salts thereof. The complete specification of the impugned application as obtained from the IPAIRS (Indian Patent Application Information Retrieval System) database made available by the Indian Patent Office on its official website is attached herein as **Annexure I**.
4. The Indian Patent Office issued First Examination Report (F.E.R.) on May 09, 2018 citing objections including, *inter alia*, lack of novelty, lack of inventive step and non-patentability under section 3(d), 3(e) and 3(i). The Applicant submitted its response to the

F.E.R. on Oct. 08, 2018 along with an amended set of 1 to 25 claims, annexed herewith as **Annexure II**. This set of amended claims 1-25 (latest/current) is being challenged by way of this pre-grant opposition.

5. According to the Patent Office website the impugned application is not yet granted. The current status of the impugned application is “Application in Amended Examination”.

## **II.1 CLAIMS OF THE IMPUGNED APPLICATION**

6. The claims below represent the amended set of claims filed by the Applicant on Oct. 08, 2018 in respect of the impugned application in response to the FER.

1. A once daily pharmaceutical dosage form comprising a core comprising 11 mg of tofacitinib, or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof, and an osmagen, and a semi-permeable membrane coating surrounding the core wherein said coating comprises a water-insoluble polymer, wherein said dosage form is a sustained release dosage form, and when added to a test medium comprising 900 ml of 0.05M pH 6.8 potassium phosphate buffer at 37° C in a standard USP rotating paddle apparatus and the paddles are rotated at 50 rpm, dissolves not more than 30% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 1 hour, and not less than 35% and not more than 75% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 2.5 hours and not less than 75% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 5 hours and wherein said dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, to a subject primarily by osmotic pressure and wherein the water-insoluble polymer is a cellulose derivative that sustains release of the tofacitinib, or pharmaceutically acceptable salt thereof.

2. A once daily pharmaceutical dosage form comprising a core comprising 11 mg of tofacitinib, or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof, and an osmagen, and a semi-permeable membrane coating surrounding the core wherein said coating comprises a water-insoluble polymer, wherein the dosage form is a sustained release dosage form and when administered orally to a

subject provides an AUC in the range of 80% to 125% of the AUC of 5 mg of tofacitinib or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof administered as an immediate release formulation BID and provides a ratio of geometric mean plasma  $C_{max}$  to  $C_{min}$  from about 10 to about 100 and wherein the dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, to the subject primarily by osmotic pressure and wherein the water-insoluble polymer is a cellulose derivative that sustains release of the tofacitinib or pharmaceutically acceptable salt thereof.

3. The pharmaceutical dosage form of claim 2, wherein the AUC range is 90% to 110% and the geometric mean plasma concentration  $C_{max}$  to  $C_{min}$  from about 20 to about 40.

4. The pharmaceutical dosage form of claim 3, wherein the geometric mean plasma concentration  $C_{max}$  to  $C_{min}$  from about 20 to about 30.

5. The pharmaceutical dosage form of claim 2, wherein when the dosage form is administered orally to the subject provides a mean plasma  $C_{max}$  in the range of 70% to 125% of the mean plasma  $C_{max}$  of tofacitinib administered as the immediate release formulation BID at steady state.

6. The pharmaceutical dosage form of claim 2, wherein when the dosage form is administered orally to the subject provides a drug holiday in the range of 80% to 110% of the drug holiday of tofacitinib administered as the immediate release formulation BID over a 24 hour period.

7. The pharmaceutical dosage form of claim 2, having a drug holiday from about 15 to about 18 hours over the 24 hour period.

8. A once daily pharmaceutical dosage form comprising

a core comprising 11 mg of tofacitinib, or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof, and an osmagen,

and a semi-permeable membrane coating surrounding the core wherein said coating comprises a water-insoluble polymer,

wherein said dosage form is a sustained release dosage form, and when administered to a subject has a mean area under the plasma concentration versus time curve following administration from about 17 ng-hr/mL per mg of tofacitinib dosed to about 42 ng-hr/mL per mg of tofacitinib dosed and a ratio of geometric mean plasma C<sub>max</sub> to C<sub>min</sub> from about 10 to about 100 and wherein said dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, to the subject primarily by osmotic pressure and wherein the waterinsoluble polymer is a cellulose derivative that sustains release of the tofacitinib or pharmaceutically acceptable salt thereof.

9. The pharmaceutical dosage form of claim 8, wherein the ratio of geometric mean plasma C<sub>max</sub> to C<sub>min</sub> from about 20 to about 40.

10. The pharmaceutical dosage form of claim 9, wherein the ratio of geometric mean plasma C<sub>max</sub> to C<sub>min</sub> from about 20 to about 30.

11. The pharmaceutical dosage form of claim 8, wherein the subject has a single, continuous time above about 17 ng/ml from about 6 to about 15 hours and a single, continuous time below about 17 ng/ml from about 9 to about 18 hours over a dosing 24 hours interval.

12. The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time above about 17 ng/ml from about 6 to about 9 hours.

13. The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time below about 17 ng/ml from about 15 to about 18 hours.

14. The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time above about 17 ng/ml from about 11 to about 15 hours.

15. The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time below about 17 ng/ml from about 9 to about 13 hours.

16. The pharmaceutical dosage form of claim 8, wherein the subject has a mean maximum plasma concentration (C<sub>max</sub>) from about 3 ng/mL per mg to about 6 ng/mL per mg of tofacitinib dosed.

17. The pharmaceutical dosage form of claim 8, wherein said dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, by a system selected from the group consisting of an extrudable core system, a swellable core system, and an asymmetric membrane technology.
18. The pharmaceutical dosage form of claim 8 wherein, said cellulose derivative is cellulose acetate.
19. The pharmaceutical dosage form of claim 8, wherein said coating further comprising a water soluble polymer having an average molecular weight between 2000 and 100,000 daltons.
20. The pharmaceutical dosage form of claim 19, wherein said water soluble polymer is selected from the group consisting of water soluble cellulose derivatives, acacia, dextrin, guar gum, maltodextrin, sodium alginate, starch, polyacrylates, and polyvinyl alcohols.
21. The pharmaceutical dosage form of claim 20, wherein said water soluble cellulose derivatives comprises hydroxypropylcellulose, hydroxypropylmethylcellulose or hydroxyethylcellulose.
22. The pharmaceutical dosage forms of claim 8, wherein the osmagen is a sugar.
23. The pharmaceutical dosage form of claim 22, wherein the sugar is sorbitol.
24. The once daily pharmaceutical dosage form of claim 8 wherein the subject has a mean steady-state minimum plasma concentration (C<sub>min</sub>) less than about 0.3 ng/mL per mg of tofacitinib dosed.
25. The once daily pharmaceutical dosage form of claim 8, wherein when administered orally to the subject has a mean fed/fasted ratio of the area under the plasma concentration versus time curve from about 0.7 to about 1.4 and a mean fed/fasted ratio of the maximum plasma concentration (C<sub>max</sub>) from about 0.7 to about 1.4.

### **III. GROUNDS OF OPPOSITION**

7. The Opponent submits that the impugned application of the applicant is invalid and therefore grant of patent ought to be refused. The opponent relies upon the following grounds in the instant pre-grant opposition:

- i. **Section 25(1)(b)(ii)**– that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim in India or elsewhere, in any other document.
- ii. **Section 25(1)(e)**– that the invention claimed in the impugned application is obvious and clearly does not involve any inventive step.
- iii. **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.
- iv. **Section 25(1)(g)**– that the complete specification of the impugned application does not sufficiently and clearly describe the invention or the method by which it is to be performed.

### **IV. PRIOR ART RELIED UPON**

<b>Document</b>	<b>Patent No. / Article</b>	<b>Publication Date/Year</b>
D1	WO 2012/100949 A1. Annexed herein as <b>Annexure III</b>	Aug. 02, 2012
D2	US 2007/0031496 A1. Annexed herein as <b>Annexure IV</b>	Feb. 08, 2007

## **V. THE PERSON SKILLED IN THE ART**

8. A person skilled in the art at the time of earliest filing date of the impugned application would have had at least a Bachelor's degree in pharmaceutical sciences with several years' experience in pharmaceutical formulations and dosage form design and development, or alternatively, an advanced degree (Masters or Ph.D.) in pharmaceutical sciences or pharmacy with emphasis in these same areas.

## **VI. LACK OF NOVELTY / ANTICIPATION [Section 25(1)(b)]**

### **9. The subject-matter of Claim 1 lacks Novelty in view of D1**

10. D1, annexed herewith as **Annexure III**, discloses an oral dosage form for modified release of tasocitinib (synonym of "tofacitinib", see, page 1, lines 1-7 and lines 18-19) which may be in the form of a tablet (page 3, lines 12-13) for administration once daily (page 31, lines 20-21). In particular, D1 discloses (see, page 27, line 34 to page 28, line 4) an osmotic controlled release device, in form of a tablet, comprising:
  - (A) a core comprising tofacitinib and an osmotic agent, and
  - (B) a water-permeable coating comprising a non-erodible polymer.
11. D1 discloses that the osmotic agent contained in the core may be an osmogen, such as xylitol or sorbitol (see, D1, page 28, lines 16-17, and page 29, lines 4-7). D1 further discloses that the water-permeable coating, which comprises a non-erodible polymer, surrounds the core and controls release of the drug (see, D1, page 28, lines 10-14). D1 mentions that the non-erodible polymer may be a cellulose derivative (see, page 8, lines 13-16), such as cellulose acetate (see, Example 10 including the table on page 39, lines 19-24). It is clear from the above that the "water-permeable coating" and the "non-erodible polymer" of the osmotic controlled release tablet according to D1 correspond, respectively, to the "semi-permeable membrane coating" and to the "water-insoluble polymer" of the instantly claimed dosage form. This coating is therefore not a distinguishing feature over the disclosure of D1.

12. As regards the claimed amount of 11 mg of tofacitinib, D1 discloses that its oral dosage form comprises 1-100 mg of tofacitinib, which encompasses the amount recited by instant claim 1 (see, D1, page 6, lines 1-5). D1 further states that its oral dosage form may be a sustained release dosage form, as recited by claim 1 of the impugned application (see, D1, page 3, lines 22-28, and page 4, lines 5-8).
13. Furthermore, Example 10 of D1 discloses an osmotic controlled release tablet comprising all the structural features of instant claim 1 in the combination recited in the claim.

<b>D1- Example 10</b>		
	<b>Component</b>	<b>Weight</b>
Active-containing layer of Core	<b>Tasocitinib citrate</b> (= Tofacitinib citrate)	10 mg (based on the free base)
	PolyOx® WSR-N80	193 mg
	<b>Xylitol</b>	93 mg
	Magnesium stearate	4 mg
Second layer of Core	PEO WSR	129 mg
	Avicel® PH 200 (FMC)	51.6 mg
	Sodium chloride	17.2 mg
	FD&C #2 Blue Lake	0.6 mg
	Magnesium stearate	1 mg
Coating on bilayer Core	Polyethylene glycol (PEG 3350)	8.0 mg
	Water	40 mg
	Acetone	920 mg
	<b>Cellulose acetate</b>	32 mg

14. As can be seen in the table above, the osmotic controlled release tablet of Example 10 of D1 comprises an active core and a coating surrounding the core. The core comprises tofacitinib as active ingredient and xylitol as osmogen. The coating comprises cellulose

acetate which is a water-insoluble cellulose derivative. Hence, all the structural features mentioned in claim 1 of the impugned application are disclosed by D1.

15. Claim 1 of the impugned application additionally encompasses the phrase “*when added to a test medium comprising 900 ml of 0.05M pH 6.8 potassium phosphate buffer at 37° C in a standard USP rotating paddle apparatus and the paddles are rotated at 50 rpm, [the dosage form] dissolves not more than 30% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 1 hour, and not less than 35% and not more than 75% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 2.5 hours and not less than 75% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 5 hours*”.
16. As should be acknowledged, the above-cited phrase does not actually introduce any structural limitation whatsoever to the dosage form of present claim 1. It merely recites functional characteristics (dissolution properties) that cannot distinguish the claimed dosage form structurally from the dosage form of D1. The above-mentioned phrase therefore has to be disregarded when assessing the presence of novelty.
17. The Opponent therefore states that the subject-matter of claim 1 of the impugned application is not novel in view of D1.
18. **The subject-matter of Claim 2 lacks Novelty in view of D1**
19. As noted above, D1 discloses a tofacitinib oral dosage form comprising all the structural features required by the claimed dosage form. The pharmacokinetic characteristics recited in claim 2, i.e., “*when administered orally to a subject provides an AUC in the range of 80% to 125% of the AUC of 5 mg of tofacitinib or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof administered as an immediate release formulation BID and provides a ratio of geometric mean plasma C<sub>max</sub> to C<sub>min</sub> from about 10 to about 100*” do not necessarily distinguish the claimed dosage form structurally from the dosage form of D1. The pharmacokinetic characteristics recited in claim 2 therefore have to be disregarded when assessing the presence of novelty.

20. Claim 2 is therefore not novel for the reasons set forth above with respect to claim 1 in view of D1.

21. **The subject-matter of Claims 3 to 7 lacks Novelty in view of D1**

22. Claims 3 to 7, depending on claim 2, merely indicate pharmacokinetic characteristics of the claimed dosage form, but do not provide any technical teaching (such as for example, the addition of particular excipients or specific production conditions) permitting to obtain a dosage form having such desired properties. The pharmacokinetic characteristics recited in claims 3 to 7 therefore have to be disregarded when assessing the presence of novelty.

23. In consequence, claims 3 to 7 do not encompass any additional characterizing features, and are therefore not novel for the reasons set forth above with respect to claim 1 in view of D1.

24. **The subject-matter of Claim 8 lacks Novelty in view of D1**

25. As discussed above, D1 discloses a tofacitinib oral dosage form comprising all the structural features required by the claimed dosage form. The pharmacokinetic characteristics recited in claim 8, i.e., “*when administered to a subject has a mean area under the plasma concentration versus time curve following administration from about 17 ng-hr/mL per mg of tofacitinib dosed to about 42 ng-hr/mL per mg of tofacitinib dosed and a ratio of geometric mean plasma C<sub>max</sub> to C<sub>min</sub> from about 10 to about 100*” do not necessarily distinguish the claimed dosage form structurally from the dosage form of D1. The pharmacokinetic characteristics recited in claim 8 therefore have to be disregarded when assessing the presence of novelty.

26. Claim 8 is therefore not novel for the reasons set forth above with respect to claim 1 in view of D1.

27. **The subject-matter of Claims 9-16, 24 and 25 lacks Novelty in view of D1**

28. Claims 9-16, 24 and 25, depending on claim 8, merely indicate pharmacokinetic characteristics of the claimed dosage form, but do not provide any technical teaching (such as for example, the addition of particular excipients or specific production conditions) permitting to obtain a dosage form having such desired properties. The pharmacokinetic characteristics recited in claims 9-16, 24 and 25 therefore have to be disregarded when assessing the presence of novelty.

29. In consequence, claims 9-16, 24 and 25 do not encompass any additional characterizing features, and are therefore not novel for the reasons set forth above with respect to claim 1 in view of D1.

30. **The subject-matter of Claim 17 lacks Novelty in view of D1**

31. Example 10 of D1 discloses an osmotic controlled release tablet which comprises tofacitinib tablet core coated with cellulose acetate membrane. The cellulose acetate membrane coating includes a delivery port in communication with the tofacitinib-containing tablet core for allowing release of the drug (see, Example 10, particularly page 39, lines 19-34). Thus, the osmotic controlled release tablet of Example 10 of D1 uses extrudable core system for delivering tofacitinib.

32. Thus, also the subject-matter of claim 17 lacks novelty over the disclosure of D1.

33. **The subject-matter of Claim 18 lacks Novelty in view of D1**

34. As discussed in detail supra, Example 10 of D1 (see, Example 10 including the table on page 39, lines 19-24) discloses an osmotic controlled release tablet, comprising a core which contains tofacitinib as active ingredient and xylitol as osmogen, and a coating around the core, wherein the coating comprises cellulose acetate.

35. Thus, also the subject-matter of claim 18 lacks novelty over the disclosure of D1.

36. **The subject-matter of Claim 19 lacks Novelty in view of D1**

37. As discussed in detail supra, Example 10 of D1 (see, Example 10 including the table on page 39, lines 19-24) discloses an osmotic controlled release tablet, comprising a core containing tofacitinib as active ingredient and xylitol as osmogen, and a coating surrounding the core. The coating comprises, in addition to cellulose acetate (a water-insoluble cellulose derivative), polyethylene glycol which is a water-soluble polymer. Thus, D1 also meets the limitation of instant claim 19.
38. Thus, also the subject-matter of claim 19 lacks novelty over the disclosure of D1.
39. **The subject-matter of Claims 22 and 23 lacks Novelty in view of D1**
40. D1 discloses that the osmotic agent contained in the core may be an osmogen, such as sorbitol or xylitol (see, D1, page 28, lines 16-17, and page 29, lines 4-7).
41. Thus, also the subject-matter of claims 22 and 23 lacks novelty over the disclosure of D1.
42. In summary, all essential features of claims 1-19 and 22-25 of the impugned application are derivable directly and unambiguously from D1. Thus, the subject-matter of claims 1-19 and 22-25 lacks novelty in view of D1 and as such is not patentable under section 25(1)(b)(ii) read with section 2(1)(j) of the Patents Act.

## **VII. OBVIOUSNESS / LACK OF INVENTIVE STEP [Section 25(1)(e)]**

43. Without prejudice and in the alternative to the above, the Opponent states that the subject-matter of all the claims 1-25 of the impugned application lacks inventive merit and is obvious to a person skilled in the art in view of the prior art documents annexed in the instant pre-grant opposition.
44. **Claims 1-19 and 22-25 lack an inventive step over the disclosure of D1 alone**
45. As shown above under the discussions of novelty ground, the subject-matter of claims 1-19 and 22-25 of the impugned application is anticipated by the disclosure of document

D1, thereby lacking novelty within the meaning of section 2(1)(j) of the Patents Act. Consequently, claims 1-19 and 22-25 also lack inventive step.

46. **Claim 1 lacks an inventive step over D2 in combination with D1**

47. D2, annexed herewith as **Annexure IV**, discloses (see, abstract and claim 1) an osmotic dosage form comprising:

an osmotic core;

a semi-permeable membrane that surrounds the osmotic core and comprises a blend of a cellulose acetate polymer (a cellulose derivative) and an acrylate copolymer; and

an exit formed through the semi-permeable membrane.

48. The osmotic core of D2 comprises at least one osmotically active substance (i.e., “osmagent”) and at least one drug (see, para [0027] and [0039]). D2 mentions that the semi-permeable membrane, which comprises cellulose acetate polymer and an acrylate copolymer, provides sustained drug release over an extended time period (see, paragraphs [0040] and [0041]).

49. The claim 1 of the impugned application thus differs from the disclosure of D2 in that:

(i) the latter does not disclose the active ingredient of claim 1, i.e., tofacitinib or a pharmaceutically acceptable salt thereof, and the amount of the active as instantly claimed (but does refer to therapeutic drugs in general), and

(ii) the latter does not disclose the dissolution properties of the dosage form recited in claim 1.

50. The Opponent states that the first distinguishing feature (i) of claim 1 would lack an inventive step, as it is known from the prior art D1 that tofacitinib is a therapeutic drug and that it can be formulated as an osmotic controlled release tablet for oral administration (see, D1, page 1, lines 9-19, and Example 10). The person skilled in the art would also know from D1 that tofacitinib can present in oral dosage forms in a dose of 1 to 100 mg, preferably 4 to 12 mg, based on the free base weight of tofacitinib (see, D1, page 6, lines

1-5). In light of D1's disclosure that tofacitinib is a therapeutic drug that is known to be used in osmotic oral dosage forms, it would have been obvious to a person skilled in the art to combine the teachings of D2 with the teachings of D1, and try using D1's tofacitinib (in amounts disclosed by D1) as the drug in the osmotic dosage form of D2, as a person skilled in the art has good reason to pursue known options within his or her technical grasp. The first distinguishing feature (i) of present claim 1 is therefore obviously derivable from the combination of documents D2 and D1.

51. The second distinguishing feature (ii) concerns the dissolution properties of the claimed oral dosage form. Claim 1 specifies *"when added to a test medium comprising 900 ml of 0.05M pH 6.8 potassium phosphate buffer at 37° C in a standard USP rotating paddle apparatus and the paddles are rotated at 50 rpm, [the dosage form] dissolves not more than 30% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 1 hour, and not less than 35% and not more than 75% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 2.5 hours and not less than 75% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 5 hours"*.
52. As should be acknowledged, the above-cited term does not actually introduce any structural limitation whatsoever to the dosage form of claim 1. It merely recites functional characteristics (dissolution properties) that cannot distinguish the claimed dosage form structurally from the dosage form of D2. When assessing the presence of an inventive step, the drug dissolution properties recited in claim 1 will therefore have to be disregarded.
53. In any event, tablets having the above-cited drug dissolution properties may be easily found on the basis of routine trial and error experiments.
54. In summary, it is therefore respectfully submitted that the subject-matter of claim 1 is rendered obvious by D2 in combination with D1.

55. **Claim 2 lacks an inventive step over D2 in combination with D1**

56. As discussed in detail supra, the combination of D2 with D1 renders obvious all the structural features of the claimed dosage form. The pharmacokinetic characteristics recited

in claim 2, i.e., “*when administered orally to a subject provides an AUC in the range of 80% to 125% of the AUC of 5 mg of tofacitinib or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof administered as an immediate release formulation BID and provides a ratio of geometric mean plasma C<sub>max</sub> to C<sub>min</sub> from about 10 to about 100*” do not necessarily distinguish the claimed dosage form structurally from the dosage form of D2. When assessing the presence of an inventive step, the pharmacokinetic characteristics recited in claim 2 will therefore have to be disregarded.

57. In any event, tablets having the above-cited properties may be easily found on the basis of routine trial and error experiments.

58. Thus, also the subject-matter of claim 2 is rendered obvious by D2 in combination with D1.

59. **Claims 3 to 7 lack an inventive step over D2 in combination with D1**

60. Claims 3 to 7, depending on claim 2, merely indicate pharmacokinetic characteristics of the claimed dosage form, but do not provide any technical teaching (such as for example, the addition of particular excipients or specific production conditions) permitting to obtain a dosage form having such desired properties. The pharmacokinetic characteristics recited in claims 3 to 7 therefore have to be disregarded when assessing the presence of an inventive step.

61. Thus, also the subject-matter of claims 3 to 7 is rendered obvious by D2 in combination with D1.

62. **Claim 8 lacks an inventive step over D2 in combination with D1**

63. As discussed above, the combination of D2 with D1 renders obvious all the structural features of the claimed dosage form. The phrase “*when administered to a subject has a mean area under the plasma concentration versus time curve following administration*

*from about 17 ng-hr/mL per mg of tofacitinib dosed to about 42 ng-hr/mL per mg of tofacitinib dosed and a ratio of geometric mean plasma C<sub>max</sub> to C<sub>min</sub> from about 10 to about 100*” cannot distinguish the dosage form defined in claim 8 from the dosage form of D2 as it does not actually introduce any structural limitation whatsoever to the dosage form of claim 8. It merely recites a functional property (pharmacokinetic characteristics) that cannot distinguish the claimed dosage form structurally from the dosage form of D2. When assessing the presence of an inventive step, the pharmacokinetic characteristics recited in claim 8 will therefore have to be disregarded.

64. In any event, tablets having the above-cited properties may be easily found on the basis of routine trial and error experiments.

65. Thus, also the subject-matter of claim 8 is rendered obvious by D2 in combination with D1.

66. **Claims 9-16, 24 and 25 lack an inventive step over D2 in combination with D1**

67. Claims 9-16, 24 and 25, depending on claim 8, merely indicate pharmacokinetic characteristics of the claimed dosage form, but do not provide any technical teaching (such as for example, the addition of particular excipients or specific production conditions) permitting to obtain a dosage form having such desired properties. The pharmacokinetic characteristics recited in claims 9-16, 24 and 25 therefore have to be disregarded when assessing the presence of an inventive step.

68. Thus, also the subject-matter of claims 9-16, 24 and 25 is rendered obvious by D2 in combination with D1.

69. **Claim 17 lacks an inventive step over D2 in combination with D1**

70. D2 discloses (see, abstract and claim 1) an osmotic dosage form comprising: an osmotic core which comprises at least one osmotically active substance (i.e., “osmagent”) and at least one drug (see, para [0027] and [0039]); a semi-permeable membrane that surrounds

the osmotic core and comprises a blend of a cellulose acetate polymer and an acrylate copolymer; and an exit port which is formed through the semi-permeable membrane, and through which the drug is delivered upon osmotic operation of the osmotic oral dosage form (see, paragraphs [0039] to [0041]). Thus, the osmotic dosage form of D2 uses an extrudable core system for drug delivery.

71. Thus, also the subject-matter of claim 17 is rendered obvious by D2 in combination with D1.

72. **Claims 18 to 21 lack an inventive step over D2 in combination with D1**

73. D2 discloses an osmotic dosage form, which is composed of a core coated with cellulose acetate polymer and acrylate polymer coating membrane (see, abstract and claim 1 of D2).

74. Thus, also the subject-matter of claims 18 to 21 is rendered obvious by D2 in combination with D1.

75. **Claims 22 and 23 lack an inventive step over D2 in combination with D1**

76. The core of the osmotic dosage form of D2 comprises at least one osmotically active substance (i.e. “osmagent”) and at least one drug (see, claim 1, para [0027]), wherein the osmotically active substance includes sugars such as sorbitol (see, para [0062]).

77. Thus, also the subject-matter of claims 22 and 23 is rendered obvious by D2 in combination with D1.

78. In summary, it is therefore respectfully submitted that the subject-matter of claims 1 to 25 of the impugned application is obvious and does not involve an inventive step when starting from D2, and combining this with the teachings from document D1.

79. For the reasons set forth above, it is therefore respectfully submitted that the subject-matter of all the claims 1 to 25 of the impugned application is obvious and does not meet the

requirements with regard to inventive step, and as such is not patentable under the provisions of Section 25(1)(e) read with Section 2(1)(ja) of the Patents Act.

#### **VIII. NOT AN INVENTION/ NOT PATENTABLE [Section 25(1)(f)]**

80. Section 25(1)(f) of the Patents Act, 1970 governs the case where 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.

#### **Not an Invention / Not Patentable u/s 3(e)**

81. The subject-matter of claims 1 to 25 of the impugned application is squarely covered by Section 3(e) in light of the submissions below.

Section 3(e) of the Indian Patent Act bars patentability of a subject-matter wherein the subject-matter is "*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*".

82. As substantiated earlier, the once daily pharmaceutical dosage form comprising a core comprising 11 mg of tofacitinib as claimed in the impugned application is not novel and not based on an inventive step. The Opponent further states that the claimed once daily dosage form is not patentable within the meaning of Section 3(e) of the Patents Act as the dosage form composition does not exhibit any unexpected or surprising effect. For claims covering a composition to be patentable, it is required to be shown that the composition comprising the components provides not only the aggregation of properties expected from the components, but an unexpected property resulting from the combination. As discussed in more detail supra, the prior art document D1 discloses an osmotic controlled release dosage form comprising all the structural features of the independent claims 1, 2 and 8 in the combination recited in the claims (see, e.g. Example 10 and page 6, lines 1-5). Hence, the once daily dosage form comprising a core comprising 11 mg of tofacitinib as claimed in the impugned application is nothing but a combination of known components exhibiting

a mere aggregation of known, expected properties and no unexpected effect is evident. Furthermore, the as-filed specification of the impugned application does not contain any data comparing the claimed once daily dosage form with the closest prior art D1 (WO2012100949A1). This is a clear case of ever greening the monopoly without any inventive ingenuity.

83. It is therefore asserted that the once daily pharmaceutical dosage form as claimed in the impugned application is clearly hit by Section 3(e) of the Patents Act, 1970 and does not form a patentable invention under the Act.
84. The Opponent therefore humbly implores that the impugned application be rejected under this ground alone.

#### **IX. LACK OF SUFFICIENCY OF DESCRIPTION [Section 25(1)(g)]**

85. According to the claims, all that the claimed dosage form requires in terms of physical components is a core containing the active (tofacitinib or a pharmaceutically acceptable salt thereof) and an osmogen, and a semi-permeable membrane coating comprising a water-insoluble polymer which is a cellulose derivative. The claims also recite that the dosage form must be able to deliver the active by osmotic pressure and must exhibit a particular in vitro dissolution profile/ pharmacokinetic (PK) property for the active.
86. The Ld. Controller has argued in the FER that the claims of the impugned application lack novelty over WO2012100949A1 (D1). In response to this objection, the applicant provided test data which the applicant alleges shows that the dosage form of Example 10 of D1 possess dissolution profile and PK parameters that fall outside of the claimed ranges. However, it cannot be seen why the osmotic dosage form of Example 10 of D1 does not possess the claimed dissolution profile/PK parameters.
87. Example 10 of D1 discloses an osmotic controlled release tablet which is composed of a core coated with cellulose acetate membrane. The core comprises tofacitinib citrate as active ingredient and xylitol as osmogen. The core is coated with a composition comprising cellulose acetate (a water-insoluble polymer) that forms a semi-permeable

membrane around the core. The Opponent therefore states that Example 10 of D1 is a disclosure comprising all the structural features of the independent claims 1, 2 and 8 in the combination recited in the claims. Furthermore, as shown in the table below, the bilayer osmotic tablet described in Example 6 of the impugned application has substantially the same composition as the bilayer osmotic tablet of Example 10 of D1.

D1- Example 10			Impugned application – Example 6		
	Component	Weight		Component	Weight
Active-containing layer of Core	Tasocitinib citrate (= Tofacitinib citrate)	10 mg (based on the free base)	Active-containing layer of Core	Tofacitinib citrate	17.76 mg
	PolyOx® WSR-N80 (=Polyethylene oxide WSR N80)	193 mg		Polyethylene oxide WSR N80	101.04 mg
	Xylitol	93 mg			
	Magnesium stearate	4 mg		Magnesium stearate	1.20 mg
Second layer of Core	Polyethylene oxide (PEO WSR)	129 mg	Second layer of Core	Polyethylene oxide	32.52 mg
	Avicel® PH 200 (=Microcrystalline cellulose)	51.6 mg		Microcrystalline cellulose	12.00 mg
	Sodium chloride	17.2 mg		Sodium chloride	15.00 mg
	FD&C #2 Blue Lake	0.6 mg		FD&C Blue No2 Lake	0.18 mg
	Magnesium stearate	1 mg		Magnesium stearate	0.30 mg
Coating on bilayer Core	Polyethylene glycol (PEG 3350)	8.0 mg	Coating on bilayer Core	Polyethylene glycol (PEG 3350)	6.32 mg
	Water	40 mg		Water	23.4 mg
	Acetone	920 mg		Acetone	343.2 mg
	Cellulose acetate	32 mg		Cellulose acetate	17.08 mg

88. Since, D1's Example 10 is fairly suggestive of the dosage form claimed and described in the impugned application, a person skilled in the art would expect that the osmotic tablet of Example 10 of D1 would also exhibit a dissolution profile and PK property similar to the claimed one. Thus, it cannot be said that the dosage form of Example 10 of D1 would

exhibit a significantly different dissolution profile/PK parameters. In order to work out why the dosage form of Example 10 of D1 does not possess the claimed dissolution profile/PK parameters would have required the skilled person to look beyond the content of the impugned application and carry out extensive experimentation to work out how to reformulate the dosage form of Example 10 of D1 so that it can exhibit the claimed dissolution profile/PK parameters.

89. It is not possible, on the basis of the teaching in the impugned application, to see why the dosage form of Example 6 of the impugned application possesses the claimed dissolution profile/PK parameters but the dosage form of Example 10 of D1 does not. A reading of the independent claims and the specification of the impugned application would have led the skilled person to expect that the dosage form of Example 10 of D1 would have had the claimed dissolution profile/PK parameters. However, if the claimed dosage form has a significantly different PK and dissolution profile than the dosage form of Example 10 of D1, then there is not enough information in the impugned application to allow the skilled person, without undue effort, to produce a dosage form which possesses the claimed dissolution profile/PK parameters.
90. It is respectfully submitted that upon detailed and careful analysis of the impugned application, several lacunae, infirmities, defects, insufficiencies and ambiguities are borne out. It is for this reason that the opponent has established various grounds of opposition under section 25(1) and the impugned application is therefore ought not to be granted.

## **X. RELIEF SOUGHT**

91. 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 8222/DELNP/2015 application *in toto*

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

92. 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 26<sup>th</sup> day of April 2021



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To

The Controller of Patents,

Patent Office,

Delhi