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26th May, 2020

The Controller of Patents
Patent Office Mumbai
Boudhik Sampada Bhawan,
S. M. Road, Antop Hill,
Mumbai - 400 037

Re: Pre-grant Opposition against Indian Patent Application No. 2110/MUMNP/2013 dated on 13.04.2012 u/s 25(1) filed by Sankalp Rehabilitation Trust
Applicant: Janssen Pharmaceutica NV
Title: FREEZE DRIED DRUG NANOSUSPENSIONS
Opponent: Sankalp Rehabilitation Trust

Dear Sir,

We submit herewith a Representation under Section 25(1) of the Patents Act, 2005.

The Controller is requested to take the documents on record and proceed further in the matter and keep the Petitioner advised of each and every step taken in the matter.

Lastly, we request the Controller to grant us an opportunity of being heard before the above representation is finally decided.

Thanking you,

RAJESHWARI H. IN/PA-358
AGENT FOR THE OPPONENT
RAJESHWARI & ASSOCIATES

Encl:

1. Index
2. Form 7A
3. Pregrant opposition; and
4. Annexures

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, MUMBAI

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 Rule 55 of The Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

And

IN THE MATTER of Indian Patent Application No. 2110/MUMNP/2013 dated 13/04/2012 in the name of **Janssen Pharmaceutica NV**

REPRESENTATION BY:

Sankalp Rehabilitation Trust

.....**Opponent**

VS.

Janssen Pharmaceutica NV

.....**APPLICANT**

PRE-GRANT OPPOSITION BY Sankalp Rehabilitation Trust

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Dated this 26th day of May, 2020



RAJESHWARI H. - IN/PA-358
AGENT FOR THE OPPONENT
OF RAJESHWARI & ASSOCIATES

The Controller of Patents
The Patent Office, Mumbai

FORM 7A
THE PATENTS ACT,
1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[See Rule 55]

We, Sankalp Rehabilitation Trust, an Indian organization hereby give representation by way of opposition to the grant of patent in respect of application No: **2110/MUMNP/2013 dated 13th April, 2012 made by JANSSEN PHARMACEUTICA NV**

on the grounds:

- i. Section 25(1)(e): Lack of inventive step
- ii. Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
- iii. Section 25(1)(f): Invention is not patentable under section 3(e) and 3 (d)

(Detailed grounds are set out in the Opposition as attached)

My address for service in India is:

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Dated, this 26th day of May, 2020



RAJESHWARI H. - IN/PA-358
AGENT FOR THE OPPONENT
OF RAJESHWARI & ASSOCIATES

To
 The Controller of Patents,
 The Patent Office, Mumbai

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE,
MUMBAI

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 Rule 55 of The Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

And

IN THE MATTER of Indian Patent Application 2110/MUMNP/2013 dated 13/04/2012 in the name of **JANSSEN PHARMACEUTICA NV**

REPRESENTATION BY:

SANKALP REHABILITATION TRUST.....OPPONENT

VS.

JANSSEN PHARMACEUTICA NVAPPLICANT

REPRESENTATION BY WAY OF PRE-GRANT OPPOSITION UNDER
SECTION 25(1) OF THE PATENTS ACT, 1970

We, **SANKALP REHABILITATION TRUST**, an Indian organization, hereby submit our representation by way of opposition to the grant of patent in respect

of application no. 2110/MUMNP/2013 dated 13/04/2012 entitled“FREEZE DRIED DRUG NANOSUSPENSIONS” on the following grounds.

STATEMENT OF CASE OF OPPONENT

1. The Opponent has learnt that the Applicant has filed an Indian Patent Application No. 2110/MUMNP/2013 (hereinafter “the Impugned Application”) on 12/11/2013. The Impugned application was published in the Official Journal of the patent office on 10/10/2014, which is currently pending before the Patent Office. This Impugned application is the national phase entry of PCT (PCT/EP2012/056818), which was filed on 12/11/2013. The Impugned application takes the priority of US61/475811dated 15.04.2011.
2. The Impugned application is entitled““FREEZE DRIED DRUG NANOSUSPENSIONS”.
3. The impugned application 2110/MUMNP/2013has been examined by the Indian patent office.
4. The opponent by way of this present pre-grant opposition submits that the claims currently pending on record are not patentable under the provisions provided in this Act. Thepending claims as amended by the Applicant in the written submission filed on 18.04.2019 and

currently on record are annexed herewith as **Annexure-1** and reproduced herein below for ready reference:

1. *A freeze-dried nanosuspension comprising E-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile base, a poloxamer which is a solid at room temperature, and polyvinyl pyrrolidone; wherein, in the nanosuspension to be freeze dried, the concentration of E-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile base ranges between 1 and 500 mg/ml; the concentration of the poloxamer ranges between 1 and 200 mg/ml; and the concentration of polyvinyl pyrrolidone ranges between 1 and 200 mg/ml.*
2. *A freeze-dried nanosuspension as claimed in claim 1 wherein the poloxamer is poloxamer 338.*
3. *A freeze-dried nanosuspension as claimed in any one of the preceding claims, wherein, in the nanosuspension to be freeze dried, the concentration of E-4-[[4-15 [[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]-amino]benzonitrile base ranges between 1 and 400 mg/ml or between 50 and 200 mg/ml or between 50 and 100 mg/ml or between 10 and 100 mg/ml or between 10 and 75 mg/ml or between 10 and 50 mg/ml or between 20 and 50 mg/ml or is about 200 mg/ml or is about 300 mg/ml.*
4. *A freeze-dried nanosuspension as claimed in claim 3 wherein, in the nanosuspension to be freeze dried, the concentration of E-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile base ranges between 50 and 200 mg/ml.*
5. *A freeze-dried nanosuspension as claimed in claim 3 wherein, in the nanosuspension to be freeze dried, the concentration of E-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile base is about 200 mg/ml or is about 300 mg/ml.*

6. *A freeze-dried nanosuspension as claimed in any one of the preceding claims, wherein, in the nanosuspension to be freeze dried, the concentration of poloxamer ranges between 10 and 100 mg/ml or between 10 and 75 mg/ml or between 10 and 50 mg/ml or between 20 and 50 mg/ml or is about 33.3 mg/ml or about 50 mg/ml.*
7. *A freeze-dried nanosuspension as claimed in claim 6, wherein, in the nanosuspension to be freeze dried, the concentration of the poloxamer ranges between 20 and 50 mg/ml.*
8. *A freeze-dried nanosuspension as claimed in any one of the preceding claims, wherein, in the nanosuspension to be freeze dried, the concentration of polyvinyl pyrrolidone ranges between between 10 and 100 mg/ml or between 10 and 75 mg/ml or between 10 and 50 mg/ml or between 20 and 50 mg/ml or 10 is about 12.5 mg/ml or about 25mg/ml or about 50 mg/ml or about 75 mg/ml.*
9. *A freeze-dried nanosuspension as claimed in claim 8, wherein, in the nanosuspension to be freeze dried, the concentration of polyvinyl pyrrolidone ranges between 20 and 50 mg/ml.*

5. Impugned Patent Application: The present pre-grant opposition is against Indian Patent Application 2110/MUMNP/2013 is entitled ““FREEZE DRIED DRUG NANOSUSPENSIONS” and is drawn towards a freeze-dried nanosuspension comprising E-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile base, a poloxamer which is a solid at room temperature, and polyvinyl pyrrolidone; wherein, in the nanosuspension to be freeze dried, with the concentration of E-4-[[4-

[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile base is in between 1 and 500 mg/ml; the concentration of the poloxamer ranges between 1 and 200 mg/ml; and the concentration of polyvinyl pyrrolidone ranges between 1 and 200 mg/ml.

6. Disclosure in the impugned patent application:

The impugned patent application discloses a freeze-dried or lyophilized nanosuspension of E-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile base (TMC278), with surfactant poloxamer which is a solid at room temperature, and a cryoprotectant polyvinyl pyrrolidone.

Pending claims 2-9 disclose poloxamer to be poloxamer 338, concentration of E-4-[[4-15 [[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]-amino]benzonitrile base (Rilpivirine) to be between 1 and 400 mg/ml and its preferable concentration in nanosuspension, the concentration of poloxamer between 10 and 100 mg/ml, and of polyvinyl pyrrolidone ranges between 10 and 100 mg/ml. The Applicant further states that the freeze-drying or lyophilization can increase the shelf life of the nanosuspension of the drug rilpivirine.

7. **PRIOR ARTS:**

The opponent wishes to rely on the following prior art as evidence in support of the grounds of opposition.

- i. D1: Baert et al, entitled “Development of a long-acting injectable formulation with nanoparticles of rilpivirine (TMC278) for HIV treatment”. Publication date (6th March, 2009).
- ii. D2: WO 2009/007741 (Published on 15-01-2009).
- iii. D3: Abdelwahed, entitled: “Freeze-drying of nanoparticles: Formulation, process and storage considerations” Advanced Drug Delivery Reviews 58 (2006) 1688–1713.

Accordingly, the Opponent submits its opposition by way of representation under Section 25(1) in respect of the said Indian Patent Application 2110/MUMNP/2013 on the following grounds below, which are without prejudice and in the alternative to each other.

8. It is submitted that all claims of the impugned patent application are liable to be refused on following grounds as below:
 - i. Section 25(1)(e): Lack of inventive step
 - ii. Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

- iii. Section 25(1)(f): Invention is not patentable under section 3(e) and 3 (d)

GROUND 1: LACK OF INVENTIVE STEP

9. D1 discloses TMC278 (E-4-[[4-15 [[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]-amino]benzonitrile) or rilpivirine nanosuspensions prepared in an aqueous carrier and with average particle sizes in the 200–800 nm range. The D1 identifies the problem in the prior art of the drug rilpivirine being poorly soluble in water and oil. D1 thus provides a proof-of-concept of the long-acting release profile of the nanosuspension of the drug rilpivirine.
10. D1 also goes on to disclose preparation of nanosuspension of average particle size of 200-800nm using Elan's proprietary NanoCrystal technology. The nanosuspension of Rilpivirine was prepared in an aqueous carrier containing a hydrophilic surfactant.

The two non-ionic surfactants disclosed in D1 are poloxamer 338 and D-alpha-tocopheryl polyethylene glycol 1000 succinate (Page 503; Col 1: Para 2) as reproduced herein below:

The NNRTI rilpivirine (TMC278 (E)-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]-amino]-2-pyrimidinyl]-amino]-benzonitrile was

isolated as the free base or its corresponding HCl salt. Both are stable crystalline polymorphic forms and are largely insoluble in water and oil (less than 2×10^5 mg/mL): the physical status is crystalline and solubility in water or in phosphate buffer at pH 7 is <0.1 mg/mL (Tibotec, data on file). Unless specified as TMC278.HCl salt, TMC278 refers in the text to its form as base. Using Elan's proprietary NanoCrystal_ technology (Elan Corporation, Dublin, Ireland) [19], sterile nanosuspensions were prepared in an aqueous carrier containing a hydrophilic surfactant. Two non-ionic surfactants were tested: (1) poloxamer 338 (Pluronic F108, BASF) and (2) D-alpha-tocopheryl polyethylene glycol 1000 succinate (Vit-E TPGS, Eastman Chemical Company). The TMC278 crystals were nanosized by continuous wet milling on a US Stoneware roller mill, using zirconium beads with a diameter of 500 μ m (YTZ Balls, Nikkato Co., Japan) during all preparations. Grinding volume, grinding time and number of revolutions of the vial were adapted according to various experimental set-ups until the desired particle size was reached for concept testing of the nanosuspension as long-acting formulation: a typical milling duration was 3 days, while in-process control was performed by regular sampling of the milled suspension in order to obtain the targeted nanoparticle size. The suspensions were harvested from the roller mill with a syringe (initial small batches) or by pumping the

suspension through an appropriate stainless steel filter, retaining the beads. All formulations were produced under aseptic conditions; for this purpose, TMC278 starting material was subjected to gamma-radiation, which does not affect its stability (Tibotec, data on file).

11. D1 also disclose that the nanosuspension of the Rilpivirine thus produced as presented in the above para, were stable for over 6 months. D1 further discloses pharmacokinetic studies of the nanosuspension of Rilpivirine in beagle dogs and mice. The intramuscular and subcutaneous injection of 5 mg/kg of particle size (200 nm) in dogs, the subcutaneous route resulted in the most stable plasma levels (Abstract; Page 502, reproduced herein for ready reference).

“Long-acting parenteral formulations of antiretrovirals could facilitate maintenance and prophylactic treatment in HIV. Using the poorly water- and oil-soluble non-nucleoside reverse transcriptase inhibitor (NNRTI) TMC278 (rilpivirine) as base or hydrochloride (HCl), nanosuspensions were prepared by wet milling (Elan NanoCrystal_ technology) in an aqueous carrier. Laser diffraction showed that the average particles size were (1) close to the targeted size proportionality (200–400–800 nm), with increasing distributions the larger the average particle size, and (2) were stable over 6 months. Following single-dose administration, the plasma

concentration profiles showed sustained release of TMC278 over 3 months in dogs and 3 weeks in mice. On comparison of intramuscular and subcutaneous injection of 5 mg/kg 200 nm) in dogs, the subcutaneous route resulted in the most stable plasma levels (constant at 25 ng/mL for 20 days, after which levels declined slowly to 1–3 ng/mL at 3 months); 200 nm nanosuspensions achieved higher and less variable plasma concentration profiles than 400 and 800 nm nanosuspensions. In mice, the pharmacokinetic profiles after a single 20 mg/kg dose (200 nm) were similar with two different surfactants used (poloxamer 338, or D-alpha-tocopheryl polyethylene glycol 1000 succinate). In conclusion, this study provides proof-of-concept that 200-nm sized TMC278 nanosuspensions may act as long-acting injectable”

12. Thus, there is an explicit disclosure within D1 to make nanosuspension of rilpivirine with surfactant poloxamer 338 and to produce a particle size of the 200nm-800nm.
13. D2 (WO 2009/007441) published on 15-01-2009 discloses polymorph I of TMC278 and pharmaceutical formulations comprising this polymorph. D2 identifies the problem of pill burden i.e. number and/or volume of dosage forms that need to be administered of anti-HIV drugs. D2 goes to state that owing to the

pill burden in anti-HIV drugs, patient's compliance of the prescribed dosage regimen is a big challenge.

14. D2 further discloses a pharmaceutical composition of rilpivirine (TMC278). D2 teaches a nanoparticle pharmaceutical composition for administration by intramuscular or subcutaneous injection, comprising TMC278, in micro- or nanoparticle form, having a surface modifier adsorbed to the surface thereof, suspended in a pharmaceutically acceptable aqueous carrier (Page 4; Para4).
15. D2 discloses suitable surface modifiers can be selected from various excipients including polyvinylpyrrolidone (PVP), Pluronic F 108 (poloxamer 338). D2 also discloses that more than one surface modifiers can be combined in the pharmaceutical formulation (Page 14; Para 1-2). D2 also discloses a nanosuspension of Rilpivirine in Example 6 using Pluronic F 108 (poloxamer 338). D2 discloses TMC278 to the surface modifier in the range of 1:2 to about 20:1

Suitable surface modifiers can be selected from various excipients such as gelatin, casein, lecithin, salts of negatively charged phospholipids or the acid form thereof (such as phosphatidyl glycerol, phosphatidyl inositol, phosphatidyl serine, phosphatic acid, and their salts such as

alkali metal salts, e.g. their sodium salts, for example egg phosphatidyl glycerol sodium, such as the product available under the tradename Lipoid™ EPG), gum acacia, stearic acid, benzalkonium chloride, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives; polyoxyethylene stearates, colloidal silicon dioxide, sodium dodecylsulfate, carboxymethylcellulose sodium, bile salts such as sodium taurocholate, sodium desoxytaurocholate, sodium desoxycholate; methylcellulose, hydroxyethyl-cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, magnesium aluminate silicate, polyvinyl alcohol (PVA), poloxamers, such as Pluronic™ F68, F 108 and F 127 which are block copolymers of ethylene oxide and propylene oxide; tyloxapol; Vitamin E-TGPS (-tocopheryl polyethylene glycol succinate, in particular -tocopheryl polyethylene glycol 1000 succinate); poloxamines, such as Tetronic™ 908 (T908), which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine; dextran; lecithin; dioctyl ester of sodium sulfo succinic acid such as the products sold under the tradename Aerosol OT (AOT); sodium lauryl sulfate (Duponol P); alkyl aryl polyether sulfonate available under the tradename Triton™ X-200; polyoxyethylene sorbitan fatty acid esters

(Tweens™ 20, 40, 60 and 80); sorbitan esters of fatty acids (Span™ 20, 40, 60 and 80 or Arlacel™ 20, 40, 60 and 80); polyethylene glycols (such as those sold under the tradename Carbowax™ 3550 and 934); sucrose stearate and sucrose distearate mixtures such as the product available under the tradename Crodesta Fl 10 or Crodesta SL-40; hexyldecyl trimethyl ammonium chloride(CTAC); polyvinylpyrrolidone (PVP). If desired, two or more surface modifiers can be used in combination.

Particular surface modifiers are selected from poloxamers, - tocopheryl polyethylene glycol succinates, polyoxyethylene sorbitan fatty acid esters, and salts of negatively charged phospholipids or the acid form thereof. More in particular the surface modifiers are selected from Pluronic™ F 108, Vitamin E TGPS, Tween™ 80, and Lipoid EPG.

One or more of these surface modifiers may be used. Pluronic F 108 corresponds to poloxamer 338 and is the polyoxyethylene / polyoxypropylene block copolymer that conforms generally to the formula $HO-[CH_2CH_2O]_x-[CH(CH_3)CH_2O]_5-[CH_2CH_2O]_z-H$ in which the average values of x, y and z are respectively 128, 54 and 128.

Other commercial names of poloxamer 338 are Hodag Nonionic™ 1108-F and Synperonic™ PE/F108. In one embodiment, the surface modifier comprises a - - combination of a polyoxy ethylene sorbitan fatty acid ester and a phosphatidyl glycerol salt (in particular egg

phosphatidyl glycerol sodium).The relative amount (w/w) of polymorph I of TMC278 to the surface modifier may vary but can be in the range of 1 :2 to about 20: 1 , in particular in the range of 1 : 1 to about 10:1, e.g. about 4:1.

Table given in Example 6

Ingredient	Formula 1	Formula 2	Formula 3	Formula 4
Polymorph I of TMC278	5 g	300 mg	300 mg	300 mg
Pluronic TM F108	1.25 g	-	-	-
Tween TM 80	-	75 mg	75 mg	75 mg
Lipoid TM EPG	-	9.375 mg	9.375 mg	9.375 mg
Glucose	-	50 mg	50 mg	50 mg
NaH ₂ PO ₄ 1aq	-	-	2 mg	2 mg
citric acid. 1aq	-	-	-	1 mg
NaOH 1 N	-	at pH 6.72	at pH 6.98	at pH 6.99

16. In conclusion,D2 discloses nanosuspension of Rilpivirine with combination of two surfactant poloxamer 338, polyvinylpyrrolidone and Rilpivirine: surfactant ratio of 1:2 to 20:1. Therefore much before the priority date of the impugned application the nanosuspension of the drug rilpivirine with poloxamer 338, and polyvinylpyrrolidone was known. The ratio of rilpivirine with surfactants/surface modifiers

disclosed in D2 alsoencompasses the ratio of Rilpivirine: surfactant as disclosed in the impugned application.

17. D3 identifies the problem that aggregation or particle fusion and hydrolysis of the polymer material forming the nanoparticles. D3 states that drug leakage and chemical reactivity of medicine during storage can be the major challenges in long term storage of nanoparticles (Page 1690; Col1: Para 3) reproduced herein below for ready reference. The article teaches use of the freeze-drying or lyophilisation to improve the long term stability of the colloidal nanoparticles (abstract).

Nevertheless, the major obstacle that limits the use of these nanoparticles is due to the physical instability (aggregation/particle fusion) and/or to the chemical instability (hydrolysis of polymer materials forming the nanoparticles, drug leakage of nanoparticles and chemical reactivity of medicine during the storage) which are frequently noticed when these nanoparticle aqueous suspensions are stored for an extended periods

18. D3further discloses stabilizers can improve the stability of the nanoparticles and prevent their aggregation. D3 also discloses poloxamer 338 as a stabilizer. Table 3 on page 1696 clearly teaches the use of poloxamer as stabilizing agent. D3 also disclose that the

use of poloxamer in the nanoparticle without the use of a cryoprotectant may impair the maintenance of nanoparticles.

Another studies have reported that poloxamer used as stabilizer of nanoparticles crystallize upon freezing impairing the maintenance of nanoparticles properties in the absence of cryoprotectives. On the contrary, their presence dehydrates the surfactant in the bulk

Table 3
Examples of successful freeze-drying nanoparticles

Method of preparation	Polymer	Stabilizer	Cryo or lyoprotectant	S_f/S_i	References
Nanoprecipitation	PCL	Poloxamer	Glucose, sucrose, (10%)	1.2	[65]
Nanoprecipitation	PCL, PLGA	Poloxamer	Glucose, sucrose (20%)	1.5	[37]
Salting out	PLA, PLA-PEO	PVA	Trehalose	1	[38]
			Ratio tr/np 1/1 or 2.5/1		
Double emulsion	MPEO-PLA	PVA	Sucrose 0.5–8% w/w	1	[59]
Microemulsion method	Emulsifying wax	Hexadecyltrimethyl ammonium	Lactose, sucrose (1–5% w/v)	1	[74]
Emulsion–evaporation	PCL-dextran	Na cholate (0.1%)	Glucose 5%	1	[57]
		Poloxamer 1%			
		PVA 1%			
Polymerization	Poly(methylidene malonate 2.1.2)	Dextran 1%	Dextran 1%	1.07	[90]
Melt homogenization method	Tricaprin	Tween 80	Sucrose 5%	1.45	[62]
		Egg Phosphatidylcholine			

S_f/S_i : ratio of nanoparticles size after and before freeze-drying.

19. D3 disclose the use of cryoprotectants for stabilization of the nanoparticles during the process of lyophilization or freeze drying. D3 teaches that the process of lyophilization induces stress to the nanoparticles that is related to freezing and drying. Further in the process of lyophilization there is a phase separation of ice and cryo-concentrated solution. This phase separation can lead to aggregation or fusion of nanoparticles. Therefore the addition cryoprotectants

such as sugar, trehalose, and poly vinyl pyrrolidone is taught by D3 (Table 2; Page 1694).

Table 2
Some of cryoprotectants used in literature for the freeze-drying of nanoparticles

Cryoprotectant	References
Glucose	[15,18–20,37,65,69,80,82]
Sucrose	[18–20,37,59,62,65,69,74]
Trehalose	[15,16,18,41,63,71,76,86]
Lactose	[16,74,82]
Mannitol	[15,41,82]
Sorbitol	[6,7,37]
Aerosil (colloidal silicon dioxide)	[10]
Maltose	[16]
Poly(vinyl pyrrolidone)	[19,20]
Fructose	[76]
Dextran	[15,90]
Glycerol	[41]
Poly(vinyl alcohol)	[18,20,52]
Glycine	[63]
Hydroxypropyl- β -cyclodextrin	[19,20]
Gelatine	[63]

20. In conclusion, D3 clearly teaches that freeze drying can increase the stability and shelf –life on nanoparticle suspension and use of stabilizer poloxamer and cryoprotectant polyvinyl pyrrolidone.
21. The Opponent states that starting from D1 that discloses nanosuspension of rilpivirine with surfactant poloxamer 338 to produce a particle size of the 200nm-800nm and combining the teaching of D2 that discloses nanosuspension of Rilpivirine with

combination of two surfactant poloxamer 338, polyvinylpyrrolidone in the ratio of 1:2 to 20:1 and D3 that discloses freeze drying technique increases the stability and shelf –life of nanoparticle suspension and the use of stabilizer poloxamer and cryoprotectant polyvinyl pyrrolidone, the disclosures of the impugned application are obvious.

It is clear from the above that nanosuspension of the drug rilpivirine was well known in the prior art to circumvent the problem of sparingly solubility of rilpivirine in water and oil. The nanosuspension of rilpivirine was also made to make the long acting formulations of the drug and to reduce the pill burden. Thus the nanosuspension of the drug rilpivirine along with poloxamer and polyvinyl pyrrolidone were well known in the prior art much before the priority date of the impugned application. Similarly the lyophilization of the nanosuspension with use of stabilizer poloxamer and cryoprotectant polyvinyl pyrrolidone was also known in the prior art to increase the stability of the nanoparticles.

Therefore a person skilled in the art can easily combine the disclosures of D1 with D2, and D3 to arrive at the disclosures of the impugned application. The Opponent therefore submits that the impugned application has no inventive merit in the view of the

combined disclosures of D1-D3 and therefore should be refused *in toto* on this ground only.

GROUND 2: INSUFFICIENCY OF DISCLOSURE

22. The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed. The impugned patent application does not provide sufficient support in the specification. The claim 1 is drawn towards a freeze-dried nanosuspension comprising E-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile base, a poloxamer which is a solid at room temperature, and polyvinyl pyrrolidone; wherein, in the nanosuspension to be freeze dried, with the concentration of E-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile base is in between 1 and 500 mg/ml; the concentration of the poloxamer ranges between 1 and 200 mg/ml; and the concentration of polyvinyl pyrrolidone ranges between 1 and 200 mg/ml.

The specification does not support the broad ranges of the claim 1 by any example wherein the concentration of the rilpivirine is at more than 300mg/ml. The concentration of both poloxamer and

polyvinylpyrrolidone is in the range of 1-200 mg/ml is way too broad and is not supported by any of the given examples.

23. The property of poloxamer “*which is a solid at room temperature*” is inherent property of the poloxamer and hence is not patentable as claimed in claim 1.

Hence, in view of aforementioned details claims of the impugned application are broad and vague. The invention claimed by the impugned patent application is not sufficiently disclosed and does not provide enough motivation to a person skilled in the art to understand the invention and reproduce it.

GROUND 3: Claims not patentable under Section 25(1)(f)

24. The Opponent states that the claimed invention clearly falls under the section 3 (d) which clearly states that the mere discovery of a new form of a known substance which does not result in the enhancement of known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process results in a new product or employs at least one new reactant is not patentable under this Act.

25. The Opponent states that the freeze dried nanosuspension of rilpivirine as claimed in impugned application is the new form of the known rilpivirine nanosuspensions disclosed in D1 which does not result in the enhancement of known efficacy and thus not patentable under section 3 (d). Complete specification of the impugned application does not provide any comparative data to demonstrate enhancement in the therapeutic efficacy with respect to the known efficacy of rilpivirine nanosuspensions disclosed in D1. The Opponent states that the applicant miserably failed to provide data demonstrating enhanced 'therapeutic' efficacy as there is no comparative data disclosed in the impugned application showing improved efficacy of freeze dried nanosuspension of rilpivirine of impugned application over rilpivirine nanosuspensions disclosed in D1.
26. The Opponent thus states that alleged invention claimed in the impugned application is a mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of 'rilpivirine nanosuspensions' disclosed in D1. The Applicant fails to provide any pharmacokinetic studies as presented in D1 to establish the plasma levels *in vivo* to demonstrate the therapeutic efficacy of the freeze dried nanosuspension of the

rilpivirine as disclosed in the impugned application. The impugned application thus falls under section 3 (d) and ought to be rejected *in toto* under this ground alone.

27. Bare perusal of the contents of Claim 1 to claim 9 makes it explicably clear that subject matter as claimed therein is nothing but a mere admixture resulting only in the aggregation of the properties of the components thereof. The claims disclose the claimed compounds and pharmaceutical acceptable excipients. It is explicably clear that the claimed composition is nothing but a mere admixture resulting only in the aggregation of the properties of the components thereof. There is no data given in the specification to prove the synergistic effect between the combinations or with pharmaceutical acceptable carriers. Hence, claim 1 to 9 falls within the ambit of Section 3(e) that creates a statutory bar for grant of patent.

28. **CONCLUSION**


In view of the above, the claims are not inventive, not patentable and insufficient. The pre-grant opposition as filed may be allowed and the subject patent application may be refused.

29. In the fact and circumstances of the case, the Opponent prays as follows:

- i. that the Controller take the present Opposition on record;
- ii. that the Indian application 2110/MUMNP/2013, be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;
- iii. that the Opponent may be allowed to file further documents as evidence if necessary to support their averments;
- iv. that the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;
- v. that the Opponent may be allowed to make further submissions in case the Patentee makes any amendments in the claims;
- vi. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this the 26th day of May, 2020

The Controller of Patents,
Patent Office, Mumbai.


Rajeshwari H.
Agent for the Opponent,
Rajeshwari and Associate