Intellectual Property Appellate Board
Guna Complex Annexe-I, 2nd Floor, 443 Anna Salai, Teynampet, Chennai-600 018.
Tele: 24328902/03 Fax: 24328905 email id: ipab.tn@nic.in Website: http://www.ipab..gov.in

OA/26/2014/PT/MUM

MONDAY, THIS THE 9TH DAY OF NOVEMBER, 2020

HON'BLE SHRI JUSTICE MANMOHAN SINGH **CHAIRMAN**
HON'BLE DR. B.P. SINGH **TECHNICAL MEMBER (PATENTS)**

JINA PHARMACEUTICALS
A US COMPANY AT
28100 NORTH ASHLEY CIRCLE
SUITE 103, LIBERTYVILLE
ILLINOIS 60048
UNITED STATES OF AMERICA **…. APPELLANT**

(Represented by -Mr S Majumdar)

VERSUS

THE ASSISTANT CONTROLLER OF PATENTS & DESIGNS
THE PATENT OFFICE,
BAUDHIK SAMPADA BHAWAN
S M. ROAD, NEAR ANTOP HILLS POST OFFICE
ANTOP HILL
MUMBAI-400037 **… RESPONDENT**

(Represented by –None)

ORDER

Hon'ble Shri Justice Manmohan Singh, Chairman

Hon'ble Dr. B.P. Singh, Technical Member (Patents)

1. The present appeal is filed under Section 117A of the Indian Patents Act, 1970, against the order dated 03/08/2011, passed by the Respondent, being the Assistant Controller of Patents & Designs, under Section 15 of the Indian Patents Act, refusing to grant the Appellants' Indian patent application no. 2155/MUMNP/2007.

2. **The Invention of the Appellant:**

2.1 As submitted by the learned counsel of the appellant, the invention relates to the preparation of suspension, liposomes, lipid complex, or Micelles in an aqueous system. The said invention relates to new methods of preparation of compositions comprising active components / compounds e.g. pharmaceutical compounds and lipids including complexes emulsions, liposomes etc. **In all the embodiments of the said invention, the complex formation takes place in aqueous media.**

2.2 He further submits that **the lipid components of lipid-based formulations are normally insoluble in aqueous media and organic solvents must be used in order to solubilize lipids at some stage in lipid-based formulation preparation.** However, the organic solvents must be removed as much as possible from the final drug formulation because trace amounts of organic solvents can be toxic and can have adverse effects when administered to humans/animals and can also have deleterious effects on workers in manufacturing facilities.

2.3 The key features of the invention as submitted by learned counsel of the appellant are as under:

- No organic solvent is used at any stage of preparation in the present invention.
- Entire process is conducted in water leading to not only economic significance but also echo-system contribution.
- Use of high-pressure homogenizer to disperse active compound and lipid in water.
- Insoluble compounds such as hydrophobic active ingredient and lipids are dispersed in the water by adjusting the pH

between 1 and 8, thereby **completely avoiding the use of organic solvent** to make it miscible.

- Cholesterol derivatives specifically excluded (in prior art). Lipids are used in the invention.
- Specific particle size achieved by novel process.
- No restriction on phase transition temperature of the lipid.

2.4 He further submits that the crux of the invention as disclosed and claimed is *the process for preparing a lyophilized liposomal formulation.*

3. **Facts of the case:**

3.1 The learned counsel of the appellant has submitted that in the FER dated 06/07/2010, the Respondent cited two prior arts namely US' 20060110441 (referred to as D1) and US5616341 (referred to as D2.). However, only US'441 (D1) was actually effectively cited against the said application as evident from the Impugned order as well.

3.2 The Examination report issued on 15/03/2011 objected to the patentability of the Appellant's invention only on the face of the prior citation D1.

3.3 The Respondent erred in considering the process steps (especially step a) of the claim 1 of the present invention in complete isolation.

3.4 The Respondent erred while assuming that *"the organic solvent like ethanol in a small quantity 30 ml used in the prior art D1 is only to dissolve the lipid and hydrophobic drug and formed the solution."* A 30-ml ethanol cannot be construed as "small quantity" to dissolve 1.03 grams of the drug with 37.9 grams lipid. More so, when the present invention uses only water for dissolving the drug and lipids. Absolutely no organic solvent or ethanol is used in the invention.

3.5 The Respondent ignored that D1 uses organic solvents to dissolve the unsaturated lipid and hydrophobic drug. This is the primary important step in the method of preparation of liposome and cannot be dispensed with.

3.6 Instead of the interpreting the process as a whole the Respondent dissected the steps of the process claim and incorrectly compared it with D1.

3.7 The Respondent further went on to compare the process steps with 'other routine step for preparation of liposome" without the slightest thought that organic solvent is essential and indispensable component for dissolution of lipid and drug in the prior art.

3.8 The Respondent compared the process of prior art and impugned invention and ignored the key step of using organic solvent and 'not using organic solvent' respectively.

3.9 The Respondent further went on to compare the product characteristics of the present invention and the prior art ignoring that the processes per se are different contrary to its own statement *"During hearing, the applicant argued countering the objections already on record. The applicant's agent at the outset admitted to delete all the product claims and restricts only to the process claims. Such an amendment by the applicant was allowed. Hence, I state that any discussions on any product aspect of the invention while passing an order will not be debated."*

3.10 Though, the Respondent did acknowledge that *"major difference between the process aspect of the impugned invention over the prior art what the applicant argues and as per my assessment is that the impugned invention uses a suspension of lipid and active drug in water whereas the prior art US2006/0110441 uses suspension of lipid and active drug*

in hydration medium by adding solution of lipid and active drug in small quantity of ethanol." but eventually concluded that the effort does not make a surprising/substantial contribution to the overall process aspect of the invention for which a patent can be granted.

3.11 The Respondent failed to note that lipid components of lipid based formulations normally are insoluble in aqueous media and require organic solvent to solubilize lipids. The Respondent also failed to appreciate that the Appellant was claiming a process and the inventive step of the process ought to be evaluated by the differences highlighted over the process disclosed in D1 and ought not to have made any comparison between the products obtained by the process of the Appellant and the process of D1.

3.12 The learned counsel of the appellant submitted that Dr. Eric J Mayhew who is an authority in lipid based drug delivery systems has opined that *"lipid particle particularly liposome preparation necessarily requires the use of organic solvents at some point in the formulation process, therefore the method described in the patent application is not obvious."*

3.13 The Respondent failed to appreciate the benefits of using aqueous medium over the disadvantages associated with the use of organic solvent.

3.14 While adjudicating the matter the respondent relies on 'presumption' without attempting to appreciate the key difference of elimination of an essential component of the prior art. The Respondent erroneously rejected all these distinctive features to qualify as inventive and rejected that Application for want of 'surprising effect'. The Respondent did not appreciate the distinguishing features at all and held that

the invention as contained herein is obvious and does not involve an inventive step.

4. The appellants have submitted distinguishing features of their invention vis-a vis the cited prior art D1 as follows:

Present invention 2155/MUMNP/2007	D1: US20060110441(Wong et al)	Distinguishing features (Advantages of the Appellant's invention)
Our invention (para (00133) teaches very simple and economic method of preparation of lipid drug complex in aqueous system without using any organic solvent. In the pending patent: there is no use of any organic solvent in the entire preparation process. The entire process in our invention is carried out in water by applying high pressure homogenizer (internal page no 7, first para of impugned Order ---------- No organic solvent: Instead water is used. The entire process of the invention is carried out in water by applying high pressure homogenizer (page 5 of reply to hearing- July 6, 2011) ---------- It is submitted that use of organic solvent free process in the Appellant's invention	Wong (Dl) para [0082]- Example 1) teaches first dissolving lipid and drug in organic solvent by incubation with stirring at 50°C until all of the lipid and drug were completely dissolved followed by extrusion to achieve desired particle size and finally the organic solvent is removed by diafiltration by exchanging with sucrose solution of pH 6.0. At the end, the formulation is concentrated to maximize the drug concentration (internal page 6, last para of impugned Order ---------- The abstract, specification, examples and claims of the prior art patent application no. US200610110441 highlights the following restricting characteristics of the process. i. Use of organic	No organic solvent is used in the present invention. Entire process is conducted in water leading to not only economic significance but also echo-system contribution. -Use of high pressure homogenizer to disperse active and lipid in water. - Insoluble compounds such as hydrophobic active ingredient and lipids are dispersed in the water by adjusting the pH between 1 and 8, thereby completely avoiding the use of organic solvent to make the miscible. -Cholesterol derivatives and others specifically excluded (in prior art). Lipids are used in the invention. -the distinctive element of transition temperature as

has various benefits. Firstly, reduces the cost of organic solvent. Secondly, it reduces the steps i.e. time period of the process wherein the first step of dissolution of lipid and hydrophobic drug in organic solvent as well as the later step of removal of organic solvent are not required. Thirdly, there is no danger that the final drug formulation may contain trace amount of organic solvents. Fourthly, working with organic solvent is hazardous for the worker in the manufacturing facility.	(ethanolic) solvent. ii. Use of buffer for pH regulation. iii. Mention of only the pH of the buffer and not of the solution. iv. Use restricted to only unsaturated lipids. v. Particle size description, prior and later. vi. Cholesterol derivatives specifically excluded from the scope of the invention (internal page no 5, last para of impugned Order ---------- Organic solvents: D1 uses organic solvents to dissolve the unsaturated lipid and hydrophobic drug. This is the primary important step in the method of preparation of liposome as disclosed inD1. This is evident from the claims, examples and detailed description of D1	highlighted in earlier reply (*i.e., page 2 of reply to hearing dated May 2, 2011*) -Specific particle size achieved by novel process. -No restriction on phase transition temperature of the lipid. [internal pg 6,second para of impugned Order -In addition, vesicle-forming lipid derivatized with "hydrophilic polymer" is not used in formulation process - There is no teaching in Dl which even remotely suggests that the invention in Dl can be performed without the use of organic solvent. -the biggest advantage of this preparation is that the drug-lipid complex is free from any toxic organic solvent

5. **Case laws**

The learned counsel relies on the following case laws:

5.1 **Thomas Brandt vs Controller of Patents & Designs – AIR 1989 DEL 249.**

"2. Page 7 of the Impugned order shows that the Attorney for the appellant had cancelled earlier statements of claims and

as such the learned counsel for the appellant has limited his appeal to the rejection of the patent claim in respect of the above reproduced statement of claims only.

3. "…." "Reading of S.2(i)(j) confirms that even 'any new' and useful art process, method or manner of manufacture qualifies as an invention for the purposes of grant of patent. Such a 'process of manufacture' is independent of the substance produced by the manufacture. 'Process of manufacture' has a distinct identity of its own. Thus, a patent can be claimed in respect only of a new process of manufacture." "….." "Whether a particular process of manufacture involves novelty and an inventive step so as to qualify as an invention would thus be a mixed question of law and fact and would depend mainly upon the circumstances of each case."

6. "…" "The Controller has further gone wrong in assuming that it was only an 'invention' of a process of manufacture which results in production of a machine, apparatus or other articles, substance or goods which can be patented. He has observed that a process of manufacture unconnected with the product of manufacture cannot be patented. All this shows that the Controller has misconstrued the provisions of the Act. Learned Counsel for the respondent has not been able to bring out anything from the impugned order which goes to suggest that the Controller has considered that provisions of S.5 of the Act while rejecting the application of the appellant which shows that a process may be patented while product may not be."

7. "…" "All these facts go to show that the Controller has failed to apply his mind to the entire case of the appellant and

as such the impugned order cannot be sustained and is liable to be set aside."

It is humbly submitted that the facts and circumstances of the Appellant's case here is very similar to the aforesaid case law. Here the Respondent has compared the product of the Appellant's with that of D1 and arrived at the conclusion "Had it been different, the claimed invention would be having a product distinguishable over the prior art in terms of the superiority in properties." These statements of the Respondent clearly go to show that the process does not have any independent existence despite the process been novel and inventive.

5.2 **Raj Parkash vs Mangat Ram Chowdhry & Ors – ILR 1977 (2) DEL 412-435**

It was held in this case that *"The invention for which patent is claimed may be a product or an article or a process. In the case of an article, the patent is in the end product or the article; in the case of a process, the patent does not lie in the end product, but only in the process by which it is arrived at."*

In the Appellant's invention, the inventive step lies in the process and it was total non-application of mind on the part of the Respondent to conclude that the process is not inventive by comparing the product of the Appellant's invention and that of D1.

5.3 **Delhi High Court Cipla Ltd. vs F.Hoffmann-La Roche Ltd. & Anr, delivered on November 27, 2015.**

Reliance is placed on para 139 on page 42 continued to page 43. It is stated therein that

"The teaching of the prior art should be as a whole and various steps cannot be surgically put together."

It is our humble submission that in the given case the Respondent has overlooked the use of organic solvent in the prior art D1 and separated out the other steps in D1 and a made selective comparison with the Appellant's invention and observed that the product of the present invention will be the same as the product of the prior art and concluded that a similarity of the product can be achieved only by a similarity of the processes.

5.4 **The United States Court of Appeals of the Federal Court in Plas-Pak Industries, Inc. v. Sulzer Mixpac AG decided on January 27, 2015** held that

"[O]bviousness is a question of law based on several underlying factual findings," In re Baxter, 678 F.3d at 1361, including what a reference teaches, Rapoport v. Dement, 254 F.3d 1053, 1060–61 (Fed. Cir. 2001), and whether proposed modifications would change a reference's "principle of operation," see In re Mouttet, 686 F.3d 1322, 1332 (Fed. Cir. 2012) (finding "the Board's determination that eliminating the optical components of Falk would not destroy its principle of operation to be supported by substantial evidence"). Where *"a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield predictable results."* KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 416 (2007). However, combinations that change the *"basic principles under which the [prior art] was designed to operate,"* In re Ratti, 270 F.2d 810, 813 (CCPA 1959), or that render the prior art "inoperable for its intended purpose," In re Gordon, 733 F.2d 900, 902 (Fed. Cir. 1984), may fail to support a conclusion of obviousness. …. (emphasis added)

In the Appellant's invention the proposed modification (i.e. invention without organic solvent/ethanol) alters the reference's principal of operation (D1-Wong essentially with ethanol) D1, therefore fails to support the conclusion of obviousness. It is our humble submission in obviousness analysis that one cannot modify prior art in a way that disrupts the reference's contribution to the art (D1 in the present case). Such a change in a reference's 'principle of operation' is unlikely to motivate a person of ordinary skill to pursue a combination with that reference.

5.5 **OSI PHARMACEUTICALS, LLC, Appellant v. APOTEX INC, USC, Federal Circuit, 2018-1925**

On appeal, the Federal Circuit reversed the Board's obviousness determination, holding that the Board misinterpreted the prior art to "teach more than substantial evidence supports." The Court reasoned that the references offer "no more than hope," and that no information about erlotinib's success in treating NSCLC was disclosed. The Court made clear a reasonable fact finder could not find a reasonable expectation of success in this case.

The Board observed: "Obviousness is a question of law based on underlying findings of fact." In re Kubin, 561 F.3d 1351, 1355 (Fed. Cir. 2009). "An obviousness determination requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so." Regents of Univ. of Cal. v. Broad Inst., Inc., 903 F.3d 1286, 1291 (Fed. Cir. 2018).

5.6 In the present case, the prior art citation D1 does not teach beyond the use of ethanol for solubilizing the active ingredient and the lipid. Accordingly, starting from D1, there is not even

a reasonable expectation of success in eliminating the use of ethanol as the solvent leave alone the suggestion or motivation to employ water as a suitable substitute for ethanol.

6. It appears relevant to have a look on the brief history of the case, as under:

6.1 Initially the instant patent application was filed with 38 claims, wherein claims 1-20 were oriented towards "A method of treating a disease …", claims 21-34 were relating to "A process of preparation of lipid formulation of an active compound …." And claims 35-38 were relating to "A method of treating a cell…".

6.2 The First Examination Report (Report) was issued on 06/07/2010 wherein claims 21-35 were objected for lacking in 'novelty' on the basis of D1 i.e. US 2006/0110441. Claims 1-20 were objected to being 'obvious' based on the same document. Further, claims 1-20 and 36-38 were objected to being 'obvious' based on document D2 i.e. US 5616341. Claims 1-20 & 35-38 were held as not patentable as per provision of Section 3 (i) of the Patents Act, 1970.

6.3 The applicants/appellant amended the claims on 03/08/2010 to 34 in number, wherein claims 1-20 were oriented towards "A composition for treating… " and claims 21-34 were oriented towards "A process for preparation of lipid formulation….".

6.4 A hearing notice was issued on 17/12/2010 wherein the objections of FER were retained.

6.5 The claims were further amended by the applicants/appellant on 02/05/2011 to 28 in numbers wherein claim 1-9 were relating to "A process for preparation of lyophilized

formulation…..” and claims 10-28 were oriented towards “ A lyophilized composition….”

6.6 A further examination report was issued on 15/03/2011 wherein the applicants were asked to delete claims 10-28 and in respect of claim 1-9 it was held that *“The process claims (1-9) are considered because of the fact that water is used as a solvent instead of alcohol in the prior art. The process aspect are different from the prior art and not the product.”*

6.7 A further hearing notice was issued on 15/06/2011 containing the following objections:

> *“The above said pending patent application is evaluated on the basis whether a patent can be granted or not considering carefully your reply dated 02/05/2011 to First Examination Report. However, there are objections still outstanding which are as follows to be met.*
>
> *1. Reference is made to following documents while evaluating the patentability aspect of the invention claimed in any of the claims. Document of particular relevance is (i) D1: US2006/0110441(cited in first examination report) as well as the International preliminary report on patentability of International Bureau.*
>
> *Amended claim 1 dated 2 May 20011 is not satisfying requirement of section 2(1)(j) of Patents Act. being not novel. Document D1 teaches a process for preparing a lipid formulation of defined particle size (abstract) wherein said process comprises*
>
> *(a) preparing suspension comprising said at least one active compound and said at least one lipid in a first aqueous medium (para 0080) at pH between about 4.0-pH 8.0 (para 0082);*

(b) treating said suspension to form a lipid compound suspension of defined particle size (para 0080);

(c) Lyophilizing the lipid-compound suspension of defined particle size to form lyophilized material (para 0080) such as the lyophilized cake

(d) Reconstituting (para 0065) said lyophilized material with a second aqueous medium to obtain a suspension of lipid formulation of defined particle size (para 0068) said defined size having a mean particle size of less than 5 microns (para 68).

Regarding claim 2. D1 teaches that treating such suspension comprising extruding said suspension through a selected size aperture; (para 71)

Regarding claim 3; D1 teaches treating suspension comprises high pressure split homogenization (para 71) such that the reference teaches homogenization and since it the complex is extruded through a pore it must be under high pressure.

Regarding claim 4, D1 teaches said lyophilizing is in the presence of a cryoprotectant (para 0022) since it is frozen).

Regarding claim 5, D1 teaches wherein said active compound comprises an active compound selected from the group consisting polyene antibiotic, a macrolide, an anticancer drug and immunosuppressant (para 0052)

Regarding claim 6, D1 teaches said active compound comprises a compound selected from the group consisting of docetaxel, paclitaxel, doxorubicin, epirubicin, tamoxifen. endoxifen, endoxifen, etoposide: anthacylines. Amphotericin B? tacrolimus and sacrolimus.(para 0020)

Regarding claim 7, D l teaches wherein said one lipid is egg phosphotadylcholine (EPC) for example (para 0011); Reading claim 8, D1 teaches the compound and cholesterols sulfate and (para 0040) but does not specifically recite ratio. which is obvious modification to person skilled in an. in absence of technical advancement.

Regarding claim 9, D1 teaches the composition mean particle size upon reconstitution is about 10-5000 nm (para 0068).

2. Claims 10-28 which seek protection for the product are characterized in terms of process steps which should be characterized by the product constituent. therefore, claim 10-28 is not definitive in terms of the product features. You have failed to demonstrate the distinguishing features of the product over the product of the prior art.

3. Subject matter claimed in claim 10-28 which is incorporated as the amended claims, is not allowable according to section 59 of Patents Act, as these claims are not part of the original claims published by International Bureau of WIPO. Seeking protection for product claims which was not claimed during filing generally expands the scope of protection and not within the scope of the claims before amendment.

4. The said application is entered as a national phase application without having priority (refer to the form I filed on 18/12/2007) and no extra feed for the additional priority is filed. However, the PCT pamphlet states that the said application seeks priority of two US applications. Under such circumstances, I find the said

application is not filed in prescribed manner with incomplete fees. Refer to Section 142 of Patents Act: 2005, and make it convincing that the application can't be treated as an application for the reason that incomplete fees paid is unintentional.

5. The applicant is advised to furnish the information relating to the objections, if any, in respect of the novelty and patentability of the invention including the claims of the application allowed of the corresponding application prosecuted before European Patent Office and USPTO within prescribed period under Rule 12(3) of Patents Rule 2003, as amended.

7. Let's look at the operating portion of the order of the respondent:

7.1 At the outset the respondent mentions in his order that the he has allowed the amendment of claims made by the applicant. He further mentions in the para shown below that the applicants restricts the claims to only process claims deleting the product claims as objected by the respondent. He also states that while passing the order, no discussion on the product aspect of the invention claims will be debated.

Hearing fixed as per the above schedule was attended by the applicant's agent, Ms. Ketana L. Babaria. The basic issue of the hearing were exclusively related to the objections raised vide office letter dated 14th March, 2011. During hearing, the applicant argued countering the objections already on record. The applicant's agent at the outset admitted to delete all the product claims and restricts only to the process claims. Such an amendment by the applicant was allowed. Hence, I state that any discussions on any product aspect of the invention while passing an order will not be debated. After a detailed discussion on the patentability aspect of the process claims, the applicant's agent argument was not convincing and therefore was advised to file a written submission in support of her argument. Written submission of the argument along with confirmed copy of the amended claims was filed by the applicant on 06th July, 2011 vide their Ref. No. Aq-110704 dated 04th July, 2011 which is as follows:

7.2 The respondent in his order holds that the basic issue of the hearing were exclusively related to the objections raised vide letter dated 14th March 2011, though his hearing letter was dated 15/06/2011(Diarized on 14/06/2011). We have reviewed the letters issued by IPO; and found that there is no such letter on record. It is either of 15/03/2011 or of 15/06/2011 (Diarized on 14/06/2011). If we consider the former, the respondent held that *"The process claims (1-9) are considered because of the fact that water is used as a solvent*

instead of alcohol in the prior art. ***The process aspect are different from the prior art and not the product."*** And the latter is the hearing notice itself. The Controller stand appears contradicting with each other. [Emphasis added]

7.3 Further, he considers amended claims 1-6 on record and annotates the crux of inventions quoted herein below:

> After hearing the case and in view of the applicant's written submission and the amended process claims (1-6) available on record, I draw the following conclusion on the patentability issue of the instant application and infer whether a patent can be granted or refused under the provisions of the Act.
>
> The crux of the applicant's invention as disclosed and claimed is a process for preparing a lyophilized liposomal formulation following the steps of preparing a suspension of a hydrophobic active compound and a lipid selected from both saturated and unsaturated fatty acids in water; maintaining the pH of the medium between 4.0 and 8.0;
>
> homogenizing/sonicating the said suspension using high Pressure split homogenization to form a lipid-compound suspension; extruding said suspension through a selected size aperture to obtain particle size having a mean particle size of less than 5 microns and lyophilizing the lipid-compound suspension in presence of a cryoprotectant to form lyophilized material by reconstitution prior to administration.

7.4 He analyses the prior art D1 and comments that "*it is important to note that organic solvent like ethanol in small quantity (30 ml in example 1) in the prior art is used only to dissolve the lipid….*". He further hold that "*Had it been different, the claimed invention would be having a product distinguishable over the prior art in terms of the superiority in properties. When the product of the prior art and the impugned invention are analyzed they are having the same characteristics like the particle size, association of a cryoprotectant, reconstitution by addition of water before administration etc. I also find the following similarity between the process of the prior art and the impugned invention: (i) input of the process like lipid and hydrophobic drug are same; (ii) in both the cases the system is suspended in a hydration medium at a selected pH; (iii) extrudation of the particles in*

selected sizes; (iv) separation of liposomes; and (v) addition of cryoprotectants.

From the above teaching of the prior art, I find that its process aims at making a lipid and drug suspension by addition of solution of the drug and lipid to a hydration buffer having pH 6.1, wherein ethanol is used as a solvent for drug and lipid. After a uniform suspension is formed it is then subjected to extrusion to produce multilamellar vesicles (LUVs) and finally obtaining liposomes containing desired drug. Further, the liposomes are lyophilized using water and a cryoprotectant. It is important to note that organic solvent like ethanol in a small quantity (30 ml in example 1) in the prior art is used only to dissolve the lipid and hydrophobic drug and the formed solution is added to large excess of hydration buffer (270 ml as in example 1) for

suspension of the drug and lipid at a pH of 6.1. So what the impugned application achieves like preparation of a suspension of a hydrophobic active compound and a lipid in water; maintaining the pH of the medium between 4.0 and 8.0, has already been disclosed in the prior art. The other routine steps for preparation of a liposome and further lyophilization like extrudation, obtaining specific particle size and addition of cryoprotectants, reconstitution etc. are not distinguishable from prior art. Had it been different, the claimed invention would be having a product distinguishable over the prior art in terms of the superiority in properties. When the product of the prior art and the impugned invention are analyzed they are having the same characteristics like the particle size, association of a cryoprotectant, reconstitution by addition of water before administration etc. I also find the following similarity between the process of the prior art and the impugned invention: (i) input of the process like lipid and hydrophobic drug are same; (ii) in both the cases the system is suspended in a hydration medium at a selected pH; (iii) extrudation of the particles in selected sizes; (iv) separation of liposomes; and (v) addition of cryoprotectants.

7.5 Here, it is noted that the Respondent again contradicts his statement. At first, he holds that the product aspect of invention will not be debated in the order and now he considers the products of the instant invention (the claims which were altogether deleted by the appellant earlier) and compares with that of prior art. The issue here is whether the process claimed in the instant invention is anticipated by the cited prior art document D1? To this, he again contradicts when he hold that prior art requires *small amount of organic solvent to dissolve the lipid* and tries to show the similarity in both the processes in four steps in the above quoted paragraph. Not only that, in the paragraph quoted below he annotates the major difference in the process aspect of the *impugned invention* over the prior art and accepts that the

impugned invention uses a suspension of lipid and active drug in water directly whereas the prior art (US 2006/0110441) uses a suspension of lipid and active drug in small quantity of ethanol. Now whether the use of ethanol used in prior art is small or not can be well seen in example 1. A 30-ml ethanol cannot be construed as "small quantity" to dissolve 1.03 grams of the drug with 37.9 grams lipid.

> The major difference between the process aspect of the impugned invention over the prior art what the applicant argues and as per my assessment is that, the impugned invention uses a suspension of lipid and active drug in water directly whereas the prior art US2006/0110441 uses a suspension of lipid and active drug in hydration medium by adding a solution of the lipid and active drug in small quantity of ethanol. However, such an effort does not make a surprising/substantial contribution to the overall process aspect of the invention for which a patent can be granted. Again such an idea is simply derivable from the prior art teachings which discloses that lipid and active drug are suspended in a hydration medium at a pH of 6.1 when a solution of lipid and drug in ethanol is added to it.

7.6 He, further, holds in the parahraph quoted below that such an effort by the present inventor is very much obvious to a person skilled in the art. This statement is totally void of any assessment of the "inventive step". The respondent holds that the use of organic solvent in prior art in place of water in the instant invention is "not appreciated". The present invention uses only water for dissolving the drug and lipids. There is no organic solvent or ethanol used in the invention. D1 uses organic solvents to dissolve the unsaturated lipid and hydrophobic drug. It is an important step in the method of preparation of liposome and cannot be dispensed with as held by the respondent.

> Such an effort by the present inventor is very much obvious to a person skilled in the art. Merely stating that the present invention is applicable for both saturated and unsaturated lipids whereas the prior art is only for unsaturated lipids, the present invention does not use organic solvent, also does not uses a buffer but uses sodium hydroxide as pH regulator, etc. without a surprising effect does not amount to be involving an inventive step. The applicant's contention of the limitations of the prior art like use of organic solvent, use of buffer for pH regulation, mention of only the pH of the buffer and not of the solution, restricted to only unsaturated

lipids, particle size description, prior and later, exclusion of cholesterol derivatives from the scope of the invention, selection of a cryoprotectant wherein the phase transition temperature of the lipid is greater than a freezing point of the cryoprotectant solution etc. are not appreciated.

After having considered the submissions submitted by the applicant in the hearing, the written submission and amended claims filed, in view of the above discussions and findings by me, it is hereby ordered that the invention disclosed and claimed in the instant application i.e., "AQUEOUS SYSTEMS FOR THE PREPARATION OF LIPID-BASED PHARMACEUTICAL COMPOUNDS; COMPOSITIONS, METHODS, AND USES THEREOF" is obvious and does not involve an inventive step as discussed above and I therefore, hereby refuse this Application No. 2155/MUMNP/2007 to proceed further.

7.7 The appellant has also drawn our attention to the opinion of Dr. Eric J Mayhew- an authority in lipid based drug delivery systems which states that *"lipid particle particularly liposome preparation necessarily requires the use of organic solvents at some point in the formulation process, therefore the method described in the patent application is not obvious."*

7.8 The appellant has submitted a table (para 4 ante) showing the distinguishing features of the instant invention with the closest prior art. We are convinced that there is marked difference of the use of organic solvent in prior art as against use of water in the instant invention.

7.9 We have noted that D1 does not teach or suggest that the invention in D1 can be performed without the use of organic solvent. This is admitted by the respondent also when he holds the use of organic solvent in small quantity in prior art.

7.10 We also note that the biggest advantage of the preparation with water as solvent is that the drug-lipid complex is free from any toxic organic solvent.

7.11 Keeping in view the above facts the objection on "novelty" is not sustainable. The respondent has also held the invention to be lacking "inventive step' as well. So in the following paragraphs we will confine our discussion to 'inventive step' requirements.

7.12 We have noted that the invention is trying to find a solution of problem as mentioned in para 011 of the complete specification mentioned herein below:

"Several formulations have been made to solublize the taxanes and to circumvent the toxicities associated with it. All of these formulations, including lipid-based formulations (for example, liposomes), have required use of organic solvents to solubilize the active compound during the formulation process (Straubinger, et.al. US5,415,868, 1995; Bisery, et al US6,146,663, 2000). As noted above, the use of organic solvents results in a cumbersome process and hence an organic solvent-free formulation is needed to overcome the problems associated with the existing formulations." Further para 0043 mentions that "The inventive method is simple, rapid and less expensive method to produce organic solvent-free aqueous liposome system…"

8. It is the contention of the respondent that the effort of using an "organic- free solvent" i.e. water is 'obvious' to person skilled in the art. But such a statement is void of any reasoning and objective assessment of inventive step. Hon'ble Supreme Court of India[1] has laid down the test of 'inventive step'

"25. The expression "does not involve any inventive step" used in Section 26(1) (a) of the Act and its equivalent word "obvious", have acquired special significance in the terminology of Patent Law. The 'obviousness' has to be strictly and objectively judged. For this determination several forms of the question have been suggested. The one suggested by Salmond L. J. in Rado v. John Tye & Son Ltd. is apposite. It is: "Whether the alleged discovery lies so much out of the Track of what was known before as not naturally to suggest itself to a

[1] Biswanath Prasad Radhey Shyam vs Hindustan Metal Industries Ltd (AIR 1982 SC 1444)

person thinking on the subject, it must not be the obvious or natural suggestion of what was previously known." (Emphasis Supplied)

26. Another test of whether a document is a publication which would negative existence of novelty or an "inventive step" is suggested, as under:

"Had the document been placed in the hands of a competent craftsman (or engineer as distinguished from a mere artisan), endowed with the common general knowledge at the 'priority date', who was faced with the problem solved by the patentee but without knowledge of the patented invention, would he have said, "this gives me what I want?" (Encyclopaedia Britannica; ibid). To put it in another form: "Was it for practical purposes obvious to a skilled worker, in the field concerned, in the state of knowledge existing at the date of the patent to be found in the literature then available to him, that he would or should make the invention the subject of the claim concerned ?" Halsbury, 3rd Edn, Vol. 29, p. 42 referred to by Vimadalal J. of Bombay High Court in Farbwrke Hoechst & B. Corporation v. Unichem Laboratories.‖ (Emphasis Supplied).

9. We have also considered the case laws submitted by the learned counsel of the appellant and quoted above (para 5 ante) and find that the respondent has not followed any of the well- settled principles of the assessment of 'inventive step' and therefore his order is not sustainable.

10. We have reviewed the claims and found that though the use of water is apparently mentioned therein; the fact that the process is using an "organic- free solvent", is not clearly mentioned in the claims.

11. We, therefore, direct the learned counsel of the appellant to file amended set of claim, bringing out this fact of "organic- free

solvent" clearly in the principal claim, to the respondent within 2 weeks from the issuance of this order.

12. The respondent is directed to grant the patent on claims 1-6 strictly within two weeks from the date of filing of the amended set of claims by the appellant.

13. Appeal is allowed with above conditions. No cost.

-Sd/-

(Dr. B.P. Singh)
Technical Member (Patents)

-Sd/-

(Justice Manmohan Singh)
Chairman