The Patents (Amendment) Act, 2005
And
The Patent (Amendment) Rules, 2006

In the matter of application no. 2899/DELNP/2005
National phase entry on 29/06/2005
In the matter of representation u/s 25(1)
In the matter of hearing held u/s 14

M/s Abraxis BioScience LLC, USA …….The Applicant

M/s Natco Pharma Ltd., Hyderabad (India) ……The Opponent

Hearing u/s 14 and u/r 55 held on 01/04/2014, 02/04/2014 and 17/04/2014

Present –

Ms Archana Shankar, Ms Arpita Kulshrestha and Mr Devinder Singh Rawat
Of M/s Anand and Anand, New Delhi…….. ……Agent of the applicant

Mr S Majumdar, Ms Amrita Majumdar, Ms Surana Pandey
Of M/s S Majumdar & Co., Kolkata ……..Agent of the opponent

Mr M Adinarayana …….. Representative of opponent

Decision u/s 15

1.An application for grant of patent titled as 'Sterile pharmaceutical composition' entered national phase on 29/06/2005. International filing date of the instant application is 09/12/2003 (PCT/US2003/038941). The application claimed priority of four US applications having application no. 60/432,317 dated 09/12/2002; 60/526,544 dated 03/12/2003; 60/526, 773 dated 04/12/2003 and 60/ 527,177 dated 05/12/2003.

2.The application was examined u/s 12 and 13 of the Patents Act, 1970 and the first examination report (FER) was issued on 07/01/2008. The applicant submitted reply to FER on 06/01/2009 with amended claims 1 to 18 as under -

Claim 1 –

A sterile pharmaceutical composition comprising a water insoluble pharmaceutical agent of the kind such as herein described and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises albumin, wherein the ratio (w/w) of albumin to pharmaceutical agent in the pharmaceutical composition is 1:1 to 9:1, wherein the pharmaceutical composition comprises nanoparticles comprising the water insoluble pharmaceutical agent and albumin, and wherein the nanoparticles have a particle size of less than 200 nm.

Claims 2 to 18 are dependent on claim 1.

On 08/04/2009, the applicant submitted another amended set of claims 1 to 12 as under –

Claim 1 –

A sterile pharmaceutical composition comprising a water insoluble anticancer agent and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises albumin, wherein the ratio (w/w) of albumin to the anticancer agent in the pharmaceutical composition is 1:1 to 9:1, wherein the pharmaceutical composition comprises nanoparticles comprising the water insoluble anticancer agent and albumin, and wherein the nanoparticles have a particle size of less than 200 nm.

Claims 2 to 12 are dependent on claim 1.

3. A representation by way of opposition u/s 25(1) of the Patents Act, 1970 was filed by M/s Natco Pharma Ltd., Hyderabad on 09/09/2008. The said representation was forwarded to the applicant on 10/10/2008. The applicant submitted reply statement u/r 55(4) of the Patents Rules, 2003 on 09/01/2009. Hearing u/s 14 and u/r 55 of the Patents Act and Rules was held with both the parties on 09/04/2009.
After perusing through all the documents submitted by both the parties and the arguments made by them during the hearing, the claims were found not to fulfill the patentability criteria u/s 2(1)(j), u/s 3(e) and u/s 10 of the Patents Act, 1970 and therefore the instant application was refused u/s 15 for grant of patent. Detailed decision was issued on 24/07/2009 to both the parties.

4. The applicant filed an appeal (M.P.NO. 57/2010 IN OA/3/2010/PT/DEL and OA/3/2010/PT/DEL) in 'Intellectual Property Appellate Board' (IPAB) against the said decision. The Hon'ble IPAB vide its decision dated 20/01/2014 (Order No. 9 of 2014) set aside the said controller's order dated 24/07/2009 and remanded the matter to the Assistant Controller for fresh consideration by affording opportunity to both sides. The Hon'ble IPAB also directed the Assistant Controller to serve the copy of the affidavit filed by the applicant through Dr Anindhya Sircar, to the opponent.

5. As per directions of the Hon'ble IPAB, a copy of the affidavit dated 08/04/2009 filed by the applicant through by Dr Anindhya Sircar was forwarded to the opponent on 07/03/2014. The opponent submitted affidavit by Dr Shashank Shridhar Apte on 28/03/2014 in response to the affidavit filed by the applicant. The applicant filed another affidavit by Dr Neil Desai on 11/04/2014. Hearing was held on 01/04/2014 and 02/04/2014 with both the parties.

6. The opponent filed a fresh representation u/s 25(1) on 28/03/2014 under the grounds of section 25(1)(g) and 25(1)(f) limited to section 3(d). The said representation was forwarded to the applicant. The applicant filed reply statement on 15/04/2014. The hearing on the fresh representation was held on 17/04/2014.

7. All the submissions and evidences put forward by both the parties have been taken on record and duly considered. For the sake of brevity and to avoid repetition and conciseness of the decision, the detailed contentions taken in the representations u/s 25(1) filed by the opponent and reply statement's of the applicant has not been reproduced here. The main contentions raised by both the parties during hearing have been noted below.

On maintainability of the second representation filed on 28/03/2014

8. The opponent submitted that the Hon'ble IPAB in its Order No. 9 of 2014 has held that '….*the Assistant Controller of Patents has formulated an additional ground on "insufficiency" and rendered a finding in the absence of any specific plea taken by the 4th respondent*". Therefore, the opponent is precluded from agitating the question of 'insufficiency' in the hearing of the original representation. The opponent submitted that the original representation was filed on the basis of the claims which were then on record and known to the opponent. The amended set of claims filed on 08/04/2009 (a day before the hearing) which altered the scope of the invention, were not known to the opponent. Since the insufficiency still stares in the specification, the opponent has preferred to file the said fresh representation.
The opponent cited case laws and literature in support of their arguments which have not been reproduced here.

9. The applicant submitted that the second representation is a case of 'serial opposition' and the amended set of claims 1 to 12 existed in the original set of claims 1 to 93.
The applicant cited case laws and literature in support of their arguments which have not been reproduced here.

10. I observe that although the amended claims 1 to 12 filed on 08/04/2009 can be mapped from the original PCT claims, but till the date of hearing the opponent was not having the knowledge that the applicant has amended the claims (i.e., elected the said 12 claims from the original 93 claims) one day before the hearing. The said claims were forwarded to the opponent on the hearing day (09/04/2009) itself and on the basis of the said claims the opponent raised the ground of 'insufficiency' during the hearing.

It is observed that the claim 1 as amended makes specific reference to the ratio of albumin to anticancer agent in the range of 1:1 to 9:1 and nanoparticles having particle size of less than 200nm. The said features were not available in original claim 1. Also the reference of 'deferoxamine' has been removed. Therefore, I observe that the scope of amended claim 1 as to the original claim 1 is different and the second representation is aimed to include the ground of insufficiency that stares from the amended claims 1 to 12.

In UCB Farchim vs Cipla Ltd. And Ors (para 13 page 10) Hon'ble HC held that
'…..this court finds merit in the contention that the pre grant opposition is in fact "in aid of the examination" of the patent application by the controller….'.

In Sami Khatib vs. Optho Remedies Pvt. Ltd. And Anr. dated 29/12/2006, the Hon'ble IPAB held that

'…in the interest of justice and based on the principles of natural justice and on the settled proposition of law laid by various High Courts and Supreme Court, the Assistant Registrar should have considered the documents. On this account, though the Assistant Registrar had committed an error in not considering the documents …'.

In patent application no. 85/DEL/1995, the Assistant Controller considered revised representation in the basis of 49 RPC 565 -
'….the controller is bound in the public interest to consider any alleged prior publication which may be brought to his notice after the hearing and before the issue of his decision'.

The opponent's fresh representation on grounds u/s 25(1)(g) and u/s 25(1)(f) limited to section 3(d) is considered as an aid of the examination of the amended claims 1 to 12 (which were made available to opponent on hearing date 09/04/2009).

The applicant's submission that the same cause of action cannot be vexed twice as per principles of res judicata (Supreme Court judgments: (1995) 6 SCC 733; (1998) 5 SCC 590), I observe that grounds of the second representation are different from the original one. Also the claims (original PCT claims) aimed in the original representation are different from the claim set (amended claims 1 to 12 filed on 08/04/2009) of the second representation. Since the 'cause of action' is entirely different in the second representation, the principle of res judicata shall not be applicable in the instant case.

The second representation is considered as a fresh representation and not a 'serial opposition' because of the circumstances of the instant case wherein the amended claims 1 to 12 were not known to the opponent before the date of hearing. It is to be borne in mind that the original representation was filed before the amendment of the claims and undoubtedly the scope of the amended claims are different from that of the original claims. Therefore, I find no justification in disregarding the second representation. In my opinion the fundamental aim of section 25(1) would be defeated if the second representation filed on 28/03/2014 is not taken on record and therefore the second representation is maintainable.

11. Both the oppositions have been heard together during 01/04/2014, 02/04/2014 and 17/04/2014. The instant decision is the combined decision for both the said representations.

12. The grounds taken in the first representation filed by the opponent are as under –

Ground u/s 25(1)(b) - The claims lack novelty
Ground u/s 25(1)(d)- Claims are in public use/ publicly known
Ground u/s 25(1)(e) -The claims lack inventive step
Ground u/s 25(1)(f) -Claims are not patentable u/s 3(e) of the Patents Act, 1970.
Ground u/s 25(1)(i) – The priority has not been properly claimed.

The grounds of the second representation are as under –

Ground u/s 25(1)(f)- Claims are not patentable u/s 3(d) of the Patents Act, 1970,

Ground u/s 25(1)(g) – Specification does not sufficiently and clearly describe the invention.

The opponent did not raise the grounds u/s 25(1)(c) and 25(1)(i) during the hearing.

13. Ground u/s 25(1)(b) –Lack of novelty

The opponent relied on Annexure V - WO00/71079 (US 6749868) in support of the said ground.

Opponent's arguments on section 25(1)(b) -

13.1 The opponent submitted that object of WO'079 is to deliver pharamacologically active agents (e.g.paclitaxel and the like) in unmodified form in a composition that does not cause allergic reactions due to the presence of added emulsifiers and solubilizing agents, as are currently employed in drug delivery. Further object is to deliver pharmacologically active agents in a composition of microparticles or nanoparticles (page 7 lines 20-25). WO'079 further provides a method for the reproducible formation of unusually small nanoparticles (less than 200 nm diameter) which can be sterile filtered (page 8 lines 25-27). WO'079 further provides a drug delivery system in which part of the molecules of active agent are bound to the protein (e.g. human serum albumin) (page 9 lines 14-16) and particularly "pre-bound" to a protein (through hydrophobic or ionic interactions) prior to administration (page 9 lines 23-26). HAS serves as the structural component of nanoparticles, and also a cryoprotectant and reconstitution aid. The preparation of particles ….produces a sterile solid formulation useful for intravenous injection (page 10 lines 13-18).

13.2 The opponent submitted that example 1 of WO'079 demonstrates preparation of nanoparticles by high pressure homogenization. The opponent has calculated the ratio of the drug to albumin as 1:9. The calculation was made as under.
Weight of paclitaxel – 30 mg;
Volume of human serum albumin – 27 ml(1% w/v);
100 ml has 1 g of albumin;
Similarly, 27 ml has 0.27g of albumin, i.e. 270 mg of albumin;
Hence, the ratio of paclitaxel :albumin is 1:9.

13.3 The opponent submitted that it is nowhere disclosed that the ratio of the drug to albumin would increase due to the drug loss while undergoing the various process steps. Examples 6 and 7 clearly state that the paclitaxel recovery is between 70 to 100% depending upon the filtration and purification steps. Therefore, the resultant composition can have the same ratio of paclitaxel to albumin as the starting ratio of paclitaxel to albumin.

The opponent cited case laws and literature in support of their arguments which have not been reproduced here.

Applicant's arguments on section 25(1)(b)

13.4 The applicant submitted that the ratio as provided in example 1 of WO'079 is the 'starting ratio' of the composition and the ratio in the final product will be much higher than the starting

ratio. Example 1 of WO'113 is identical to example 1 of WO'079. WO' 113 on page 36 demonstrates that during the manufacturing process the starting ratio of albumin to drug always increased in the final resultant composition, the final ratio is 13.3:1 when starting ratio is 9:1. The calculation is as under –
Amount of HAS – 400 mg
Amount of paclitaxel – 30 mg
Ratio of HAS to paclitaxel – 400/30= 13.3:1

13.5 The applicant submitted that Dr Neil Desai's affidavit states that example 1 of WO'079 discloses a lab scale preparation method of nanoparticle albumin bound paclitaxel composition. The starting albumin/ paclitaxel ratio was subsequently changed during the scaling up process, from laboratory to plant scale. Examples 6 and 7 of WO'079 which disclose a larger preparation, discloses the starting ratio of albumin to paclitaxel as 13:1. Exhibits 1 and 2 of Dr Neil Desai's affidavit shows starting ratio as 13:1 and 19:1 respectively which was used in the clinical studies. The new formulation having ratio of 9:1 is referred to as AB1007.

The applicant cited case laws and literature in support of their arguments which have not been reproduced here.

Decision on section 25(1)(b)

13.6 I observe that example 1 of WO'079 employs 30 mg paclitaxel and 27.0 ml of HSA. Examples 6 and 7 of WO'079 employ 225 mg paclitaxel and 97 ml of HSA. Going by the calculations provided by both the parties, it is seen that WO'079 discloses ratio range from 9:1 to 13.3:1 and not the claimed range of 1:1 to 9:1 of albumin: paclitaxel. Since WO'079 does not disclose each and every element of the instant claimed composition (i.e. fails to disclose the ratio range as claimed in the instant application), therefore the claims 1 to 12 do not lack novelty in view of WO'079.

The ground taken by the opponent u/s 25(1)(b) is dismissed.

14. Ground u/s 25(1)(d)- Claims are in public use/ publicly known

Opponents arguments on section 25(1)(d)

14.1 The opponent submitted that since WO '079 (Annexure V) was available to the public at large before the priority date of the instant application, thus the said document constitutes prior public knowledge.

Applicant's arguments on section 25(1)(d)

14.2 The applicant submitted that no material facts have been pleaded and no evidence in support of this ground has been adduced by the opponent.
The applicant cited case laws and literature in support of their arguments which have not been reproduced here.

Decision on section 25(1)(d)

14.3 It is observed that the opponent has relied upon WO'079 in support of this ground. As discussed in above para 13.6, WO'079 does not disclose the composition as claimed fully, therefore through the said reference the instant claimed composition was not available to the public before the priority date of the instant application.
Furthermore, the pleadings in relation to this ground are deficient as material facts have not been pleaded and also the opponent has failed to adduce any evidence in support.

Therefore, the ground taken by the opponent u/s 25(1)(d) is dismissed.

15. Ground u/s 25(1)(e) -The claims lack inventive step

The opponent cited the following references in support –

Annexure III -US5439686
Annexure IV – US 6096331
Annexure V – US 6749868
Annexure VII – Articles and abstracts of the literature disclosing antimicrobial and antioxidant effects of deferoxamine

Opponent's arguments on section 25(1)(e)

15.1 The opponent submitted that the examples of the specification showing the enhanced efficacy (reduction of side effects or inducing greater stability) of the claimed composition are all compared to the compositions comprising cremophor and paclitaxel and not with prior art compositions comprising paclitaxel and albumin without cremaphor.

15.2 The opponent submitted that the US'686 (Annexure III) provided suggestions to use nanoparticles in order for a better delivery of the active, albumin being a preferred protein carriers and a albumin to drug ratio of 11.5 to 1.

15.3 The opponent submitted that US'331 (Annexure IV) teaches a formulation of paclitaxel (CAPXOL) comprising unmodified paclitaxel and HSA wherein the preferred size range of the collodial suspension is about 20-400 nm. US'331 teaches that the basis for the localization within certain tissues could be a result of the particle size of the formulation (20-400 nm), or the presence the protein albumin in the formulation. Examples 2 and 6 of US'331 exemplify the preparation of polymeric shells containing dissolved Taxol and solid Taxol, where the ratio of Taxol to albumin is 1:11.5. Examples 10 to 19 shows the efficacy and toxicity studies of Capxol formulation compared to TAXOL ®, therefore the examples of the present specification which shows similar studies is of no avail. Example 16 of the US'331 mentions two capxol formulations, VR-3 or VR-4, thus clearly indicating that Capxol formulation is not limited to any particular ratio.

15.4 The opponent submitted that WO'079 (Annexure V) teaches sterile compositions comprising nanoparticles (particularly less than 200 nm diameter), of pharmaceutically active agents (particularly taxanes which are water insoluble) along with proteins such as HSA/albumin, where the ratio of drug is to albumin includes a ratio of 1:9 as exemplified in the examples. Example 2 exemplifies the preparation of nanoparticles by sonication. The paclitaxel to HSA ratio is 1:10. Examples 5, 6 and 7 exemplify preparation of less than 200 nm sterile-filterable nanoparticles having paclitaxel to HSA ratio of 1:9.8, 1:12.9, and 1:12.9 respectively. The examples 6 and 7 state that the amount of paclitaxel recovered varies between 70 to 100%. The opponent submitted that it is an indication that the ratio in the final product can stay the same as the starting ratio depending on the filtration and purification steps. Examples 15, 20, 22, 27, 31, 38, 40 to 51 demonstrate the efficacy of the composition.

15.5 The opponent submitted that Annexures VII and VIII teach use of deferoxamine for inhibitin microbial growth and prevent oxidative damage.

15.6 The opponent submitted that it is a constant endeavor in the field of drug discovery to improve existing formulations. The applicant at the oral proceedings referred to the present composition (Abraxane) as the new formulation and that of WO'079 as the old formulation. The applicants have performed mere optimization to arrive at the said ratio range.

15.7 The opponent submitted that Dr. Voung Trieu's affidavit filed by the applicant makes no mention of the ratios disclosed in prior art, i.e. drug to albumin ratios of 1:11.5. 1:9, and 1:13.3. Such ratios are covered by the impugned application and there is no clarification as to how the present is superior to these ratios.

15.8 The opponent submitted that example 46 of the specification demonstrates that 'lower amounts of albumin in the inventive pharmaceutical composition results in stable compositions'. Examples 47, 48 and 49 of the specification demonstrates a pharmaceutical composition comprising albumin and paclitaxel having a high (27:1), low (4.5:1), and intermediate (10:1) albumin to paclitaxel ratio respectively. The opponent submitted that there is no indication in the examples of the ratio which amounts to a high ratio and what constitutes a low ratio as paragraph [0041] states an exemplary range of 0.01:1 to about 100:1. The opponent submitted that even on assuming that low ratio is a drug to albumin ratio of 1:4.5 and high is 1:27, the obligation of the applicant to compare the composition with the closest prior art, namely, the WO'079 remains.

15.9 The opponent submitted that Dr. Sircar's affidavit filed by the applicant provided data pertaining to clinical study, where a ratio of 20:1 albumin to paclitaxel (old formulation) was compared to 9:1 (new formulation). The opponent submitted that this is an unfair comparison as ratios less than 1:20 was also known.

15.10 The opponent submitted that exhibit 4 of Dr Neil Desai's affidavit filed by the applicant shows an
inflexion point at a albumin to drug concentration of 9:1 ratio. There is no indication in the specification that such surprising findings are associated with the said ratio range. The opponent submitted that exhibit 7 compares ABI-007 with that of standardized paclitaxel. The ratio of the

composition was not mentioned anywhere and the WO'079 also exemplify such ABI-007 formulation.

The opponent cited case laws and literature in support of their arguments which have not been reproduced here.

Applicant arguments on section 25(1)(e)

15.11 The applicant submitted that there is no teaching in the cited references to even look into the ratio of albumin to paclitaxel. Based on the common general knowledge, a person skilled in the art would be motivated to increase the ratio of albumin to paclitaxel and not reduce the ratio as high content of albumin is necessary to maintain the drug in nanoparticle form. Albumin being a macromolecule in nature has a negative charge and an increase in amount of albumin would lead to higher viscosity, an increased steric and electrostatic intermolecular repulsion is a favorable environment for nanoparticles.

15.12 The applicant submitted that affidavit of Dr Neil Desai states that ratio of albumin to paclitaxel in 1:1 to 9:1 unexpectedly shows increased cellular binding, higher therapeutic efficacy and reduced toxicity compared to old formulation. Low ratio involves a technical advancement because high albumin drug ratio not only affects transfer but leads to an increased local concentration of albumin at the tumor site which will negatively affect the pharmacological activity of the active.

15.13 The applicant submitted that the old formulation is disclosed in WO'079 in example 16. Example 1 was on a very small lab scale and there was not sufficient nanoparticle composition made that could be used for clinical studies. The applicant submitted that sufficient comparative studies have been provided to demonstrate that the new formulation (now marketed under brand name ABRAXANE) is better than the old formulation.

The applicant cited case laws and literature in support of their arguments which have not been reproduced here.

Decision on section 25(1)(e)

15.14 I observe that WO'079 teaches all aspects of the instant composition except the claimed range of 1:1 to 9:1 of albumin:paclitaxel. However WO'079 does teach ranges from 9:1 to 20:1. Dr Trieu's affidavit (para 4) submitted by the applicant states that person skilled in the art generally believe that a higher amount of albumin is desirable in order to keep the water insoluble pharmaceutical agent in nanoparticle form. However in the present invention, the inventor has discovered the lowering of ratio of albumin in the range of 1:1 to 9:1 shows unexpectedly better results.

15.15 I observe that example 4 of US'686 and example 1 of WO'079 teach compositions having albumin and paclitaxel in ratio of 11.5:1 and 9:1, respectively. The reduction of albumin and improvement in properties of the composition is taught in the prior art. Therefore, a person having ordinary skill in the art would be motivated with reasonable

expectation of success by teachings of the said references to further reduce the ratio of albumin to obtain desired results. I observe that the applicant's argument that there is motivation to increase the amount of albumin and not to reduce it, is not agreeable.

15.16 During the hearing and through the affidavit of Dr Neil Desai, the applicant referred to new formulation (9:1 as claimed) and old formulation (20:1) and provided comparative data showing efficacy of the new formulation over the old formulation. I observe that at the time of filing the application the ratio of 13.3:1 and 11.5:1 was known through the disclosure of US'331 and US'686, respectively. But the applicant did not show any comparison of the claimed composition with the said closest known ratio's.

15.17 I observe that the comparative results for showing improved composition submitted through affidavit by Dr Anindhya Sircar are in between 9:1 and 20:1. This comparison is not convincing for the reason that the cited references show that the ratio 20:1 is not the closest prior art. To assess technical advancement, the comparison with the closest prior art as known at the time of filing of the instant application should have been made. The ratio selected by the applicant lies within the general teaching of the prior art and no technical effect other than what has already been taught by the cited references has been shown to be associated with the selected ratio range. In absence of such comparative data, any improvement whatsoever cannot be adjudged.

15.18 I observe that the applicant has failed to provide any evidence of improved unexpected properties of the claimed composition. Moreover the specification does not demonstrate betterment of properties of the claimed composition with the lower amount of albumin (4.5:1-albumin: active) as against the high amount of albumin (27:1 or 18:1 – albumin: active). Going through the teachings of the cited references, a person having ordinary skill in the art would have sufficient teachings/ suggestions and motivation to reach at each and every element of the claimed composition.
Therefore, the amended claims 1 to 12 lack inventive step.

15.19 I observe that in Case Number: T 0059/04 - 3.3.02 (Date of decision: 23 November 2006), the EPO Board of Appeals held that

'It is true that the patent in suit contains comparative tests (clinical trial A) which demonstrate a lower incidence of diarrhoea for the ratio 7:1, but as the opposition division had already correctly pointed out in the decision under appeal, these tests cannot be taken into consideration, as the comparison was made with a 4:1 t.i.d. regimen which does not represent the closest prior art. In this context, it is emphasized that it has been established case law at the EPO that if comparative tests are chosen to demonstrate an inventive step on the basis of an improved effect, the nature of the comparison with the closest state of the art must be such that the said effect is convincingly shown to have its origin in the distinguishing feature of the invention (T 197/86, OJ 1989, 371).

10.1.5 In the assessment of inventive step, it appears appropriate in this case to evaluate as a next step whether the person skilled in the art, starting from the b.i.d. regimen of (D2), had any motivation to look for alternatives.

10.1.6 In the last step it has to be determined whether the solution of the problem, i.e. the selection of a 7:1 ratio, was obvious.
It stands to reason that a higher concentration of active agent causes more severe side effects. There is no evidence at all that the same results would have been obtained by using equal amounts of active agent in both regimens. An additional complication is the fact that the results of one set of tests were combined with the results of a different set of tests where different conditions prevailed so that it is next to impossible to draw even qualitative conclusions. As a consequence, in the absence of any direct comparative tests between b.i.d. 7:1 and b.i.d. 4:1, the board cannot discern any improvement over the closest prior art in the assessment of inventive step.'

15.20 I observe that in Case no. T 0214/04 (Date of decision: 31.7.2007), the EPO Board of Appeals held that

'As outlined above, ratios of antibacterial agent to clavulanate is generally disclosed in document (23) to be from 30:1 to 1:1. Thus, the amount of clavulanate is taught in document (23) to be at most equal to or much lower than the amount of antibacterial agent.
Consequently, the fact that the preferred range disclosed in document (23) for the ratio of amoxycillin to clavulanate has an upper limit of 12:1 cannot be regarded as representing a prejudice that would dissuade the skilled person from applying the more general teaching of document (23).
2.5 Thus, the main and sole request is rejected for lack of inventive step of claim 1 (Articles 52(1) and 56 EPC).'

The ground of section 25(1)(e) is maintained.

16. Ground u/s 25(1)(f) -Claims are not patentable u/s 3(e) and 3(d)

Opponent's arguments on section 25(1)(f)

16.1 The opponent submitted that the composition as claimed is a mere admixture of prior known components which results in no synergistic activity. There is no data in the specification for inferring synergism.

16.2 The opponent submitted that the claimed albumin:paclitaxel ratio of 9: 1 is a specific type of species of a larger group for the reason that examples 1, 2, 5, 6 and 7 of WO'079 teaches nanoparticle paclitaxel compositions having an albumin to paclitaxel ratio of 9:1 to 13:1. The opponent submitted that compositions are substances within the meaning of the Act as understood from Justice Ayyengar report.

16.3 The opponent submitted that the cited references disclose the known efficacy of the albumin Paclitaxel combination with respect to the treatment of breast cancer. Dr. Desai's affidavit itself refers to the prior art composition as the old formulation and the present composition as the new formulation. Therefore, the claimed composition having ratio 1:1 to 9:1 is new form of known substance.

16.4 The opponent submitted that the test of efficacy would depend upon the function, utility or the purpose of the product under consideration. Therefore, in the case of a medicine that claims to cure a disease, the test of efficacy can only be "therapeutic efficacy". The opponent submitted that example 15 of the specification makes reference to albumin Paclitaxel pharmaceutical combination but is silent about albumin and Paclitaxel ratio. Dr. Sircar's affidavit provides comparative data of the 9:1 ratio and 20:1, which is not a proper comparison as the ratios as low as 13.3 :1 was disclosed in prior art.

16.5 The opponent submitted that the needs (to reduce certain undesirable side effects) as stated in the instant application were addressed in the '331 patent and the '079 application. In the instant case, the ratio has been reduced, which is a new dosage form, without any significant difference in the properties with regard to the efficacy.

The opponent cited case laws and literature in support of their arguments which have not been reproduced here.

Applicant's arguments on section 25(1)(f)

16.6 The applicant submitted that no material facts have been pleaded by the opponent. The instant formulation has enhanced efficacy and increased safety profile which is achievable only through a synergistic mechanism.

16.7 The applicant submitted that the specification shows the enhanced cellular binding of the drug to the infirmity site and enhanced cellular transport of the drug to the infirmity site. These are aspects of therapeutic efficacy.

The applicant cited case laws and literature in support of their arguments which have not been reproduced here.

Decision on section 25(1)(f)

16.8 I observe that the applicant has not provided any comparative data in support of the unforeseen effect. The examples of the specification are routine pharmacological study of the composition to know the therapeutic and toxicological effect inside the body, when administered.

16.9 I observe that the 'brief summary of the invention' in page 4 of the specification mentions that by this invention one or more side effects associated with administration of paclitaxel composition are reduced and transport of paclitaxel to the site of infirmity is enhanced. The specification neither indicates any enhanced effect of paclitaxel nor demonstrates any significance of such properties with regard to 'therapeutic efficacy' in view of the known substance.

16.10 Notwithstanding the above said, I observe that examples 15 to 19 of the specification demonstrate preclinical pharmacokinetics and pharmacodynamics of a pharmaceutical composition comprising albumin and paclitaxel, wherein evaluations have been done over

cremaphor-paclitaxel (Taxol) pharmaceutical compositions. However the said examples do not provide the ratio of the albumin and paclitaxel. It is not clear as to for which ratio's the said effects (reduced side effects/ toxicity) is attributed to. I observe that it is not fair to read the data (9:1 compared with 20:1) provided through the affidavit of Dr Anindhya Sircar along with the text of the description because lower ratio of 9:1 to 13.3:1 (as taught by US'686, US'331 and WO'079) was known in the prior art and in this circumstance efficacy of composition having ratio 9:1 cannot be ascertained by comparing the same with a composition having ratio of 20:1. In absence of any therapeutic efficacy of the composition as claimed, the instant amended claims 1 to 12 fall u/s 3(d) of the Patents Act, 1970.

16.11 I observe that in the instant application, the amount of albumin has been optimized for better utilization of paclitaxel. In light of the teachings of prior art references, this is a routine experimentation work for a skilled artisan. In absence of any data regarding effects of albumin and paclitaxel in ratio of 1:1 to 9:1, the claimed composition is considered as a mere admixture resulting only in the aggregation of the properties and therefore, the instant amended claims 1 to 12 fall u/s 3(e) of the Patents Act, 1970.

16.12 I observe that in Novartis vs. UOI, the Supreme Court held that

'The ingredients, the active ingredients the solvent and the emulsifier, were known; the process was known, the product was known and the use was known. The plaintiffs were merely camouflaging a substance whose discovery was known through out the world and trying to enfold it in their specification relating to Patent Number 125381. The patent is, therefore, liable to be revoked.…"
163. Now, when all the pharmacological properties of beta crystalline form of Imatinib Mesylate are equally possessed by Imatinib in free base form or its salt, where is the question of the subject product having any enhanced efficacy over the known substance of which it is a new form?.....
171. That being the position, the appellant was obliged to show the enhanced efficacy of the beta crystalline form of Imatinib Mesylate over Imatinib Mesylate (non-crystalline). There is, however, no material in the subject application or in the supporting affidavits to make any comparison of efficacy, or even solubility, between the beta crystalline form of Imatinib Mesylate and Imatinib Mesylate (non-crystalline)……
In this case, there is absolutely nothing on this score apart from the adroit submissions of the counsel. No material has been offered to indicate that the beta crystalline form of Imatinib Mesylate will produce an enhanced or superior efficacy (therapeutic) on molecular basis than what could be achieved with Imatinib free base in vivo animal model….'

The ground u/s 25(1)(f) is maintained.

17. Ground u/s 25(1)(g) – Insufficiency of disclosure

Opponent's arguments on section 25(1)(g)

17.1 The opponent submitted that the specification does discuss ratios in the detailed description and the examples, however there is no indication in the specification, either explicit or implicit, which will lead a person of average skill to comprehend the criticality or significance of the drug to albumin ratio of 1:1 to 1:9 ratio range. In most of the examples, the composition has been compared with prior art compositions containing cremophor (TAXOL®). Example 45 and 46 disclose that increasing amount of albumin can compete with binding of paclitaxel and low amounts of albumin in the composition results in stable composition respectively. The specification fails to define or describe a ratio range constituting the low or the high ratio. Example 47, 48 and 49 demonstrate the toxicity of a high ratio, a low ratio and an intermediate ratio, being 1:27, 1:4.5 and 1:10 respectively. The said examples merely compare the toxicity with TAXOL®, the cremophor containing composition.

The opponent cited case laws and literature in support of their arguments which have not been reproduced here.

Applicant's arguments on section 25(1)(g)

17.2 The applicant submitted that the 'invention' has to be enables and the 'commercial embodiment'. The specification need not provide each and every detail for a layman. A skilled man need not be told what common general knowledge is. The specification need not contain a working example id one skilled in the art is able to perform the invention based on the textual description without undue experimentation. The inventor can choose any method to disclose its best mode. Consequently the failure to provide a specific working example of the best mode, where the inventor has described its best mode in the text of the description will not amount to violation. The specification as a whole has to be considered while determining sufficiency.

The applicant cited case laws and literature in support of their arguments which have not been reproduced here.

Decision on section 25(1)(g)

17.3 I observe that para 41 of the specification discloses the ratio of protein to pharmaceutical agent. The said para states that '*While the ratio of protein to pharmaceutical agent will have to be optimized for different protein and pharmaceutical agent is about 18:1 or less (e.g., about 15:1, about 10:1, about 5:1, or about 3:1). More preferably, the ratio is about 0.2:1 to about 12:1. Most preferably, the ratio is about 1:1 to about 9:1.*'

17.4 Then different ratio's are exemplified through examples 1, 47, 48 and 49 of the specification. Examples 47, 48 and 49 of the specification demonstrate high ratio (27:1), low ratio (4.5:1) and intermediate ratio (10:1) of albumin to paclitaxel, respectively. The said examples investigate if the said ratio's are showing the desired effects or not. The compositions in the examples have been compared to toxicity of paclitaxel dissolved in cremaphore formulations and shown to have substantially lower toxicity. The said examples do not describe the method of preparing the composition.

17.5 Only example 1 demonstrates the preparation of pharmaceutical compositions comprising paclitaxel and albumin, wherein the ratio is calculated to 18:1 of albumin to paclitaxel.

17.6 Affidavit of Dr Neil Desai dated 11/04/2014 states that '*The starting albumin/ paclitaxel ratio was subsequently changed duruing the scaling up process* (para 7)…. *To make a nanoparticle albumin bound paclitaxel formulation having a desired albumin/ paclitaxel ratio, one can use routine methods and experimentation to determine the starting ratio of albumin and paclitaxel needed for the process, by taking into account the percentage of paclitaxel loss during the manufacturing process* (para 11).' I observe that para 7 states that process conditions and processing time affect the final product but para 11 states that by routine experimentation a skilled artisan can determine the starting ratio of albumin and paclitaxel. I observe that the said two para's teaches away from each other and therefore the said affidavit failed to provide the ratio of albumin and paclitaxel in both the starting and final product. Going through the example 1, a person having ordinary skill in the art will not know what amount of paclitaxel and albumin should be taken in order to obtain a composition with 1:9 (w/w) of Paclitaxel to albumin.

17.7 I observe that the main technical feature of the claimed composition lies in the ratio of albumin to paclitaxel as 1:1 to 9:1. But the specification does not demonstrate that the said ratio range shall show unexpected improved properties. Even if the clinical studies and comparative data provided by the applicant though the affidavit of Dr Anindhya Sircar is read along with the specification, then also I observe that the said data's do not suffice the sufficiency requirements of the claimed ratio range for the reason that Dr Sircar's affidavit compares the composition having 9:1 with 20:1. In the present case, this comparison is not considerable because much closer ratio ranges were known at the priority date of the instant application. Moreover in view of examples 5 and 6 of WO'079 which teaches that the recovery of paclitaxel may vary between 70% and 100% depending on the recovery/purification steps; a person of average skill will not be able to calculate the starting ratio of albumin and paclitaxel in order to obtain a final ratio of 1:9.

17.8 In the amended set of claims the drug to albumin ratio has been limited to 1:1 to 1:9. The specification does not disclose any example or working demonstration for the said ratio range. Examples 47, 48 and 49 of the specification demonstrates high, low and intermediate ratio ranges of albumin to paclitaxel ratio, respectively. However para's 154, 157 and 160 of the specification show that same effects (lower toxicity when compared to cremaphore containing paclitaxel formulation) have been reported for all the said ratio's. Therefore, the description is totally insufficient to teach the preparation of the composition which shall have 9:1 ratio of albumin to paclitaxel in the final product and also insufficient to prove the improved efficacy arising out by lowering the amounts of albumin.

17.9 I observe that in patent application no. IN/PCT/2001/1052/CHE, the controller held that

'The patent law debars an applicant a grant for belated discovery of a new thing which is not disclosed which may or may not be pivotal in determining patentability. Thus, the appellant is

not entitled to make out a case for patent in its favor by importing a new matter in the specification which was later on discovered /established. The patentability, therefore, if any, will have to be established on the basis of original disclosure contained in the specification.'

17.10 I observe that in case no. T 0491/08 (21/10/2010), the EPO Board of Appeals held that

The Board observes that it is settled law that the disclosure in post-published might only be taken into account for the question of sufficiency of disclosure if it was used to backup the findings in the patent application and not to establish sufficiency of disclosure on its own.

17.11 I observe that in case no. T654/90-3.3.1, the EPO Board of Appeals held that

'2.5. Therefore, in the absence of any disclosure in the disputed patent indicating how the equivalent weight of alkylolated melamines may be determined and the inability of the skilled person's common general knowledge to cure this deficiency, the disclosure of the patent in suit is insufficient.'

17.12 I observe that in case no. T 0538/10 () of 11.6.2013 the EPO Board of Appeals held that

'2.7 Even when the patent in suit provides three examples showing the preparation of products as claimed (examples I, IV and V), in view of the fact that two of the five examples performed according to the teaching of the patent in suit lead to products outside claim 1, this is not sufficient to support a general guidance of how reliably to prepare the claimed products.'

The ground of section 25(1)(g) is maintained.

Final conclusion

18. In light of the aforesaid, it is concluded that amended claims 1 to 12 lack inventive step and do not constitute an invention u/s 2(1)(j) of the Patents act, 1970. Also the said claims fall u/s 3(d) and 3(e) of the Patents Act, 1970. The specification is also insufficient u/s 10 of the Patents Act, 1970.
The instant application is refused for grant of patent.

19. No order for cost.

Date – 18/06/2014

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(Dr NILANJANA MUKHERJEE)
Assistant Controller of Patents and Designs