IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Neil P. DESAI et al.

Application No.: 11/520,479 Confirmation No.: 8972

Filed: September 12, 2006 Art Unit: 1611

For: NOVEL FORMULATIONS OF PHARMACOLOGICAL AGENTS, METHODS FOR THE PREPARATION THEREOF AND METHODS FOR THE USE THEREOF Examiner: T. Love

DECLARATION OF NEIL P. DESAI PURSUANT TO 37 C.F.R § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Neil P. Desai, declare as follows:

1. I was formerly Senior Vice President of Global Research and Development at Abraxis BioScience, LLC ("Abraxis"), assignee of the above-referenced patent application, and am currently Vice President at Celgene Corporation, which acquired Abraxis. A copy of my biography is attached hereto as Exhibit 1.

2. I have more than 20 years of experience in the research and development of drug delivery systems and biocompatible polymers. I was one of the individuals responsible for the development of Abraxis' nanoparticle-albumin bound (nab™) drug delivery platform and its

product Abraxane®, one of the leading drugs for treating metastatic breast cancer in the United States.

3. I am one of the named inventors of the above-referenced patent application and am familiar with the technical features of the invention and the claims proposed to be amended.

4. I have reviewed the Office Action dated December 29, 2010. I understand that claims in the present patent application are rejected as being obvious over one of Abraxis' earlier patents, U.S. Pat. No. 5,439,686 ("Desai"), for which I am also a named inventor, in view of U.S. Pat. No. 5,407,683 ("Shively").

5. The claims as amended recite a pharmaceutical formulation comprising: paclitaxel at a concentration between 5 mg/ml and 15 mg/ml, wherein the pharmaceutical formulation is an aqueous suspension that is stable for at least 3 days under at least one of room temperature or refrigerated conditions, wherein the pharmaceutical formulation comprises nanoparticles comprising a solid core of paclitaxel and an albumin coating, and wherein the size of the nanoparticles in the composition is less than 400 nm. In the paragraphs below, I discuss stability considerations for nanoparticle formulations, the Shively and the Desai references, and the advantageous stability of the nanoparticle formulations recited in the amended claims.

Stability considerations for nanoparticle formulations and the cited references

6. Physical stability is a key consideration for ensuring safety and efficacy of nanoparticle drug products. Precipitation and particle size increase (for example by aggregation) are key parameters for evaluating physical stability of a nanoparticle formulation. Precipitation of drug nanoparticles in an aqueous suspension could decrease the effective amount of drugs being administered to a patient. The presence of large particles in an intravenously administered nanoparticle product could lead to capillary blockage and embolism.

7. The tendency of nanoparticles to precipitate and increase in size (for example by aggregation) increases as the drug concentration increases. Specifically, an increase in the concentration of drug in the nanoparticle formulation could increase the size of the particles, the

density of the particles, and/or the number of particles per volume in a suspension. Under the well-known Stoke's law, the settling velocity of a particle composition is proportionally related to the size and density of the particles. An increase in particle size and/or density could thus increase the tendency of the particles to precipitate. Further, an increase in the number of particles per unit volume could increase the collision of the particles and thus increase the tendency of the particles to increase in size and/or precipitate. It would therefore have been expected that a nanoparticle formulation having a solid core of paclitaxel and an albumin coating would be unstable at a high paclitaxel concentration, for example between 5 mg/ml and 15 mg/ml.

8. Shively does not teach a nanoparticle formulation comprising a solid core of paclitaxel and an albumin coating having a paclitaxel concentration of between 5 mg/ml and 15 mg/ml. Shively states that "[f]or therapeutic use, emulsions containing between about 0.5 and about 5 mg/ml [paclitaxel] are prepared by the foregoing methods and administered orally or intravenously." Column 9, lines 51-54. Shively thus teaches emulsions instead of solid nanoparticles.

9. In Shively's emulsions, the paclitaxel is dissolved in oil droplets suspended in an aqueous solution rather than in a solid core of albumin-coated nanoparticles. Such oil droplets are different from the solid nanoparticles in terms of composition, density, and buoyancy, and involve different stability considerations. For example, oil droplets, which have a lower density than that of water, would tend to float rather than precipitate. Thus, Shively's teaching of 5 mg/ml paclitaxel in an oil-in-water emulsion formulation provides no suggestion that a nanoparticle formulation having a solid core of paclitaxel and an albumin coating would be stable at paclitaxel concentration of between 5 mg/ml and 15 mg/ml.

10. The Examiner relies on Example 5 of Desai as teaching that "the composition of Desai is stable for 27 days at temperatures of 4°C, 25°C, and 38°C (see Example 5)." Page 4 of the Office Action. Example 5 of Desai refers to the stability of polymeric shells containing buoyant soybean oil. No drug was present within the polymeric shell. Like the oil droplets in Shively, the

oil-containing polymeric shells in Example 5 of Desai are different from the solid nanoparticles in terms of composition, density, and buoyancy. The stability of the oil-containing polymeric shells discussed in Example 5 of Desai thus provides no suggestion that a nanoparticle formulation comprising a solid core of paclitaxel and an albumin coating would be stable at paclitaxel concentration of between 5 mg/ml and 15 mg/ml.

11. The Examiner also points to Example 4 of Desai as teaching that "a higher loading of taxol can be achieved by utilizing an additional solvent such as ethyl acetate, which is removed." Pages 3-4 of the Office Action. As the Examiner himself acknowledges, "[s]aid taxol suspension is taught as being protein walled polymeric shells enclosing an oil/taxol solution." Page 4 of the Office Action. As discussed above, such oil-containing polymeric shells are different from the solid nanoparticles in terms of composition, density, and buoyancy, and involve different stability considerations. Furthermore, an increase in loading of paclitaxel (taxol) within the polymeric shells as taught in Desai would be expected to increase the particle size and/or the density of the particles, which in turn could increase the tendency of the particles to precipitate.

12. The Examiner also states that "the preferred particle radii for the invention of Desai are 0.1 to 5 microns (100-5000 nm), which overlaps the instant [particle size] range." Page 5 of the Office Action. Example 2 of Desai shows that the protein shells have a size range of 1.35±0.73 microns (1350±730 nm). The wide size range taught in Desai would be expected to lead to further instability. Specifically, according to the well-known phenomenon of Ostwald ripening, when both small and large particles are present (such as the compositions disclosed in Desai), smaller particles tend to dissolve, and the larger particles tend to increase in size. *See* Yao et al., Theory and Simulation of Ostwald Ripening, Physical Review B, 1993)(Exhibit 2). Given the wide size range of the particles in Desai and the increased tendency of the particles to precipitate as the paclitaxel concentration increases, one would not reasonably have expected that the nanoparticle formulation of paclitaxel disclosed in Desai could be obtained at a concentration between 5 mg/ml to 15 mg/ml, without causing precipitation and compromising the stability of the composition.

13. Thus, neither Shively nor Desai suggests that a nanoparticle formulation comprising a solid core of paclitaxel and an albumin coating would be stable at a paclitaxel concentration of between 5mg/ml and 15 mg/ml.

The advantageous stability of the nanoparticle formulations recited in the amended claims

14. Example 37 of the present application has shown, unexpectedly, that a pharmaceutical composition with nanoparticles having a size of less than 400 nm and having a solid core of paclitaxel and an albumin coating can be reconstituted to a paclitaxel concentration between 5 mg/ml and 15 mg/ml without compromising the stability of the composition. As shown in Example 37, the lyophilized composition was reconstituted to 5, 10, and 15 mg/ml and stored at room temperature and under refrigerated conditions. The suspensions were found to be homogeneous for at least three days under these conditions. Particle size measurements performed at several time points indicated no change in size distribution. No precipitation was observed under these conditions.

15. The advantageous properties of the nanoparticles recited in the amended claims is further demonstrated in a subsequent experiment which compared the physical stability of two pharmaceutical compositions containing nanoparticles comprising a solid core of paclitaxel and an albumin coating. In Composition 1, there was no detectable percentage of nanoparticles that have a size above 400 nm. In Composition 2, by contrast, at least 10% of the nanoparticles in the composition had a particle size that is above 400 nm.[1]

16. Exhibit 3 shows photographs of vials containing Composition 1 and two lots of Composition 2 stored at 40°C for 24 hours at the concentration of about 5 mg/ml. The vials were inverted at the end of the storage period to show the sedimentation of the particles at the bottom of the vials. As shown in Exhibit 3, upon storage at 40 °C for 24 hours,[2] there was a distinctly visible

[1] Size determined by disc centrifugation method immediately after reconstitution of the compositions at about 5 mg/ml.
[2] Storage at 40 °C for 24 hours is equivalent to storage at room temperature for at least three days.

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