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FSG: SRV: 2899/DELNP/2005

January 6, 2009

**THE CONTROLLER OF PATENTS**
**THE PATENT OFFICE**
**DELHI**

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16/01/09

**Attention: Dr. ARCHANA GUPTA**

**VERY URGENT**

**FINAL DATE FOR ALLOWANCE: January 7, 2009**

Dear Sir,

re: **Abraxis BioScience, LLC**
**Indian [National Phase] Patent Application No. 2899/DELNP/2005**
**Filed: June 29, 2005**
**Out of International Appln. No. PCT/US2003/038941 dated December 9, 2003**
**Priority date: December 9, 2002 – United States Application No. 60/432,317**
**December 3, 2003 – United States Application No. 60/526544**
**December 4, 2003 – United States Application No. 60/526773**
**December 5, 2003 – United States Application No. 60/527177**

This response is made to the objections raised in the first examination report (FER).

As a preliminary point, the applicants respectfully submit that the claims on file have been revised and amended to address each of the Examiner's objections in the first examination report as well as the points marked by her in pencil on the original claims. The amendments to the claims have necessitated re-typing pages 47 to 56 as fresh pages 47 to 49 which are submitted herewith in duplicate together with the corresponding pages which have been cancelled over our signature.

Each of the objections is dealt with hereafter either individually or together with the other cognate objections.

**Objections 1, 14 and 15:**

With respect, the applicants submit that the claims as amended are novel and inventive over the prior art documents cited in the International Search Report and relied upon by the Examiner and thus, qualify as an invention.

As revised, claim 1 recites a sterile pharmaceutical composition comprising a water insoluble pharmaceutical agent and albumin, wherein the ratio (w/w) of albumin to pharmaceutical agent in the 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.

It is the applicants' respectful submission that there is no teaching in the cited references that would lead to the claimed combination of the recited ingredients in the stated ratio in a sterile nanoparticle pharmaceutical composition. In the prior art, the focus was on using albumin to stabilize the water insoluble pharmaceutical agent in a nanoparticle composition and to avoid side effects caused by the administration of the water insoluble pharmaceutical agent. Because albumin is a macromolecule in nature and has a net negative charge, an increase in the amount of albumin would lead to higher viscosity and increased steric and electrostatic intermolecular repulsion – a favorable environment for nanoparticles. It was thus generally believed that a higher amount of albumin is desirable in order to keep the water insoluble pharmaceutical agent in a nanoparticle form. It was unexpected that a lower albumin/drug ratio (namely, 1:1 to 9:1) would maintain the water insoluble drug in a nanoparticle pharmaceutical composition, maintaining the many advantages of a nanoparticle pharmaceutical composition.

Albumin to drug ratio of 1:1 to 9:1 is more advantageous because it leads to enhanced cellular transport of the water insoluble pharmaceutical agent and reduces the adverse effects of albumin on the pharmacological activity of the water insoluble pharmaceutical agent, both of which would lead to improved therapeutic efficacy. A lower ratio is also important because it reduces safety risks caused by the administration of albumin. Not only that, a lower albumin/drug ratio is also economically significant because less albumin is needed in the formulation. Furthermore, a lower albumin/drug ratio provides manufacture efficiency because it reduces the viscosity problem during the large scale manufacturing process.

Each citation is individually discussed hereafter:

**WO 92/07259 (D1):**

This reference discloses a pharmaceutical composition comprising a covalent adduct of deferoxamine, ferric iron, and polymer (such as albumin) for imaging enhancement. The reference does not disclose water insoluble drugs or nanoparticles comprising water insoluble pharmaceutical agent and albumin. Furthermore, D1 does not disclose an albumin/drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

**Meijs (D2):**

This reference discloses albumin-desferal conjugates for labeling protein with ion isotopes. D2 does not disclose water insoluble drugs or nanoparticles comprising water insoluble pharmaceutical agent and albumin. Furthermore, D2 does not disclose an albumin/drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

**US 4,425,319 (D3):**

D3 discloses radioactive diagnostic agent comprising deferoxamine, a physiologically active compound (such as albumin), and a radioactive metallic element chemically connected thereto. It nowhere discloses water insoluble drugs or nanoparticles comprising water insoluble pharmaceutical agent and albumin. Furthermore, D3 does not disclose an albumin/drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

**US 5,990,153 (D4):**

D4 discloses micelles of lipid-soluble antioxidants and lipoic acid in aqueous solutions (such as albumin solutions), which may also contain antioxidants and/or metal chelators (such as deferoxamine). However, it does not disclose nanoparticles comprising water insoluble pharmaceutical agent and albumin. Furthermore, D4 does not disclose an albumin/drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

**WO 2004/007520 (D5):**

This reference was cited in the International Search Report as only a "E" reference *[Earlier document but published on or after the international filing date]*. D5, therefore, does not qualify as valid prior art. In any event, this reference was cited against only former claims 37 to 50 directed to a method of inhibiting microbial growth or inhibiting oxidation by adding deferoxamine, and not as being relevant to the subject matter currently in the main composition claim. This reference discloses a method of preventing oxidative damage to proteins (such as albumin). D5 does not disclose nanoparticles comprising water insoluble pharmaceutical agent and albumin. Furthermore, D5 does not disclose an albumin/drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

**EP 0227593 (D6):**

This reference was cited against only former claims 37 to 50 directed to a method of inhibiting microbial growth or inhibiting oxidation by adding deferoxamine, and not as being relevant to the subject matter currently in the main composition claim. This reference discloses a method for treating cancer by administering iron chelating agents (such as deferoxamine) and a cytostatic agent. D6 does not disclose albumin or nanoparticles comprising water insoluble pharmaceutical agent and albumin. Furthermore, D6 does not disclose an albumin/drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

**FR 2775900 (D7):**

This reference was cited against only former claims 37 to 50 directed to a method of inhibiting microbial growth or inhibiting oxidation by adding deferoxamine, and not as being relevant to the subject matter currently in the main composition claim. D7 teaches the use of deferoxamine to prevent haematopoiteic and tissue toxicity of anthracyclines. It does not disclose albumin. Furthermore, D7 does not disclose an albumin/drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

**US 4,645,660 (D8):**

This reference was cited against only former claims 37 to 50 directed to a method of inhibiting microbial growth or inhibiting oxidation by adding deferoxamine, and not as being relevant to the subject matter currently in the main composition claim. D8 discloses non-radioactive carrier for increasing labeling efficiency of radioactive diagnostic agent comprising a carrier substance having a chelate-forming property (such as deferoxamine) and optionally a physiologically active substance chemically bonded thereto (such as albumin). D8 does not disclose nanoparticles comprising water insoluble pharmaceutical agent and albumin. Furthermore, D8 does not disclose an albumin/drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

**Halliwell (D9):**

This reference was cited in the International Search Report as only a "A" reference relevant only to claims 37 to 50 directed to a method of inhibiting microbial growth or inhibiting oxidation by adding deferoxamine, and not as being relevant to the subject matter currently in the main composition claim. This reference is only a category "A" citation, which implies that this document defines merely the general state of art but is not considered to be of particular relevance. D9 discloses the use of deferoxamine as an inhibitor of iron-dependent free radical reactions. It does not disclose water insoluble drugs or nanoparticles comprising water insoluble pharmaceutical agent and albumin. Furthermore, D9 does not disclose an albumin/drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

**Chuang (D10):**

D10 is a review article which discusses different methodologies of using albumin for drug delivery. Although D10 generally discloses microspheres, it does not disclose an albumin/drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1 in a sterile nanoparticle pharmaceutical composition.

**US 5,916,596 (D11):**

D11 is a patent owned by Abraxis BioScience, LLC, the applicant of the instant case. This reference reflects Applicants' prior effort in formulating water insoluble pharamceutical agents by eliminating physiologically harmful organic solvents. This reference does not disclose a sterile nanoparticle pharmaceutical composition having an albumin to drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

**US 5,439,686 (D12):**

D12 is a patent owned by Abraxis BioScience, LLC, the applicant of the instant case. This reference reflects Applicants' prior effort in formulating water insoluble pharamceutical agents by eliminating physiologically harmful organic solvents. This reference does not disclose a sterile nanoparticle pharmaceutical composition having an albumin to drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

**WO 00/23117 (D13):**

D13 discloses a conjugate (a single component) of photosensitizer and a targeting moiety (moiety can be "aggregated albumin", or albumin). It, however, does not disclose nanoparticles comprising water insoluble pharmaceutical agent and albumin. Furthermore, D13 does not disclose an albumin/drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

**EP 0544292 (D14):**

D14 discloses a non-covalent complex of nucleic acid and protein for delivery of nucleic acid. It does not disclose the use of water insoluble drugs and/or albumin. Furthermore, it does not teach nanoparticles comprising water insoluble pharmaceutical agent and albumin.

**US 6310039 (D15):**

D15 discloses a single pharmaceutical agent, namely, a conjugate of a cytostatic compound (such as paclitaxel) and albumin. It does not disclose nanoparticles comprising water insoluble pharmaceutical agent and albumin. Nor does the reference disclose a combination of a water insoluble pharamceutical agent and a pharamceutically acceptable carrier comprising albumin.

**US 6204054 (D16):**

D16 discloses transcytosis vehicles and enhancers (such as albumin) capable of delivering and enhancing drug transport via GP60. The drugs exemplified in the description of this reference are all water soluble drugs. According to D16, a composition can be formulated into microcapsules of 2-5 microns. D16 does not disclose nanoparticles having a particle size of less than 200 nm. Nor does it disclose an albumin/drug ratio as claimed, viz. albumin to drug ratio of 1:1 to 9:1.

To anticipate a patent, a prior publication must contain the whole of the invention impugned, i.e. all the features by which the claims in question are limited. It is clear from the foregoing discussion that none of the cited references discloses the claimed combination of the recited ingredients in the stated ratio in a sterile pharmaceutical composition. Thus, the present claims are not anticipated by the cited prior art.

The applicants further submit that claims as amended are inventive over the cited references. In order to uphold a finding of lack of inventiveness, there must be some teaching, suggestion or incentive for doing what the applicants have done. Typically, both the suggestion and the expectation of success must be found in the prior art, not in the applicants' disclosure. A prima facie case of obviousness can be established only by showing some objective teaching in the prior art or by proving that knowledge generally available to a person skilled in the relevant art would lead the individual to combine relevant teachings of the prior references.

As stated above, claims have been amended to recite a sterile pharmaceutical composition comprising a water insoluble pharmaceutical agent and albumin,

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