NATRAPHARM, INC.
Opposer,

-versus-

SMITHKLINE BEECHAM PLC,
Respondent
x----------x

IPC NO. 14-2006-00024

Opposition to:
Cancellation of Patent No.
1-1996-52993
(Issued On: 5 May 2005)

TM: "Method of Treatment"

Decision No. 2007-61

DECISION

For decision is a Petition for Cancellation of Letters Patent No. 1-1996-52993 dated 5 May 2005 for "Method of Treatment" issued in the name of Smithkline Beecham PLC, respondent, with office at New Horizons Court, Brentford, Middlesex TW8 9EP United Kingdom filed by Natrapharm, Inc., petitioner, a corporation existing under Philippine laws with office at the Patriot Building, Km. 18, West Service Road, South Luzon Expressway, Paranaque City 1700. The petitioner believes that it will be damaged by the registration of the patent and seeks its cancellation based on the following grounds:

a. Subject invention is not patentable for lacking in novelty as defined under either Section 7 and 9, Chapter II of Republic Act No. 165 ("old Patent Law") or under Section 23 and 24.1 Chapter II, Part II of Republic Act No. 8293 ("IP Code") hence, the granting of the letters patent was contrary to law.

b. Subject invention is not patentable for lacking in inventive step under either Section 7 of the old Patent Law, or Section 26 of the IP Code; hence, the granting of the letters patent was contrary to law;

c. Patent documents as well as non-patented documents that were in existence more than one year prior to the priority filing date of the subject invention show that the dosages claimed in the patent are obvious to a person skilled in the art;

d. As there is no significant improvement in the efficacy of the present invention as compared to that of the prior art, the disclosure of the subject patent does not satisfy the requirements for inventive step. Routine experimentation, which appears to be the main factor that contributed to the subject invention, is deemed to be within the knowledge of who possesses ordinary skills in the art at the time of the filing date or priority filing date of its patent application.

e. All the indications and suggestions in the prior arts clearly lead the skilled person to the teaching of the subject invention. There is nothing unexpected or surprising and there is no bar to combine the conventional approaches to arrive at the subject matter of the subject invention. It is obvious to a person of ordinary skill in the art to

develop the dosage form as claimed therein in view of the disclosures suggestions and incentives as earlier mentioned.

f. An examination of the file history to the subject invention shows that once the examiner has made a final determination and after considering that the formality requirements have been met and that corresponding EP and AU applications have been granted patents, a patent has also been granted to the PH application. The present case was filled under the old Patent Law and not under the new IP Code, therefore, it was not appropriate to use as basis for the allow ability of the subject invention as related EP or AU patents, EP or AU patent laws were not similar to our old Patent Law."

In its Answer filed on 6 October 2006, respondent argued that issued letter patents carry a presumption of validity and that clear and convincing evidence is required to support a petition for cancellation. On the allegation that the patent is invalid for lack of novelty, respondent submits:

> "xxx that the phrase in relation to the patent law and the rules, simply put, really meant "anticipation". By way not illustration, "lack of originality", or "lack of priority" or even, the concept of "statutory bar", in the field of patents, can be established only where the prior invention is identical to, or "anticipates", the invention sought to be patented. Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference or embodied in a single prior art device or practice. It means that the elements must either be inherent or disclosed expressly and must be arranged as in the claim. For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field on the invention. It is the claims that define the claimed invention and that which re supposed to be anticipated. 13 (paragraph 20, Verified Answer)

In reply to petitioner's contention that the patent is invalid for lack of inventive step, respondent refers to Section 26 of the Intellectual Property Code. Respondent intimates that this legal issue be resolved through the following determination:

> > "34. Petitioner alleged that the formulations covered by Letters Patent in question "lacks inventive". Respondent submits that the concept of "lack of inventive step" refers to "obviousness". Respondent further submits that the said "lack of inventiveness" or "obviousness" is a question of law and like all legal conclusions it is reached after answers to a series of potential fact questions have been found – and said "conclusion" is reached in the light of those answers. In the ordinary patent case, the trier of fact must answer the Graham inquires relating to (1) the scope and content of the prior art; (2) the difference between the art and the claims at issue; (3) the level of ordinary skill in the art; and (4) whatever objective evidence may be present. xxx" (page 19, 20-21 – Answer)

35. Respondent submits and defer to the ruling that "The timing of the inquiry is crucial. The analytical focus is upon the state of knowledge at the time the invention was made. Thus, the obvious test CANNOT INCLUDE A REQUIREMENT THAT THE INVENTION DEMONSTRATE UNUSUAL OR SURPISING RESULTS OR HAVE AN EFFECT GREATER THAN THE PRIOR ART, SINCE THIS WOULD FOCUS ON FACTS DETERMINABLE ONLY AFTER THE INVENTION MADE. xxx

38. Stated otherwise, the test for obviousness is what the combined teachings of the references, taken as a whole, would have suggested to one of ordinary skill in the art. It is generally held that the focus should not be merely on the differences between the claimed invention and the prior art before a claimed invention can be considered to possess and inventive step. Xxx" (page 21)

The main issues to be considered in resolving this cancellation case is whether the subject patent is invalid for lack of novelty and lack of inventive step. Has the petitioner successfully discharged the burden of proving that the patent's invalidity on the aforementioned grounds?

The challenged patent having been applied for, prosecuted and granted under the provision of Republic Act 165, this petition for cancellation shall be decided based on the provisions of old patent law then existing.

Section 28 of Republic Act 165 provides:

"Sec. 28. General grounds for cancellation. Any person may on payment of the required fee petition the Director within three years from the date of publication of the issued of the patent in the Official Gazette, to cancel the patent or any claim thereof, on any of the following grounds:

(a) That the invention is not new or patentable in accordance with sections seven, eight, and nine, or that the design or utility model in not a new or patentable under section fifty-five hereof;

(b) That the specification in the case of an invention does not comply with the requirement of section fourteen, Chapter III, hereof; or

(c) That the person to whom the patent was issued was not the true and actual inventor, designer or author of the utility model."

In comparison, Republic Act 8293, the IP Code provides:

SEC 61. Cancellation of Patents: 61.1. Any interested person may, upon payment of the required fee, petition to cancel the patent or any claim thereof, or parts of the claim, on any of the following grounds:

(a) That what is claimed as the invention is not new or patentable;

(b) That the patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art; or

(c) That the patent is contrary to public order or morality. Xxx

In either case, a patent may be cancelled on the ground of lack of novelty or lack of inventive step under section 28 (a) of Republic Act 165, the old patent law and Sec. 61 (a) of the IP Code.

The claims of Letters Patent 1-1996-52993 reads as follows:

"Claims"

1. A method of treating bacterial infections in pediatric patients in need thereof an antibacterially effective amount of a formulation comprising amoxycllin trihydrate and potassium clavulanate in combination, in a weight ratio 7:1, the weights being expressed as the free parent acids amoxycllin and clavulanic acid, the formulation being administered twice daily (bid), at a dosage of between 20 and 70 mg/kg/day of amoxycllin and a pro rate amount of clavulanic acid.

2. A method as claimed in claim 1 in which the dosage regimen is 70 ± 10% mg/kg/day amoxycillin in combination with 10 ± 10% mg/kg/day clavulanic acid.

3. A method as claimed in claim 1 in which the dosage regime is 45 ± 10% mg/kg/day amoxycillin in combination with 6.4 ± 10% mg/kg/day clavulanic acid.

4. A method as claimed in claim 1 in which the dosage regime is 35 ± 10% mg/kg/day amoxycillin in combination with 5 ± 10% mg/kg/day clavulanic acid.

5. A method as claimed in claim 1 in which the dosage regime is 25 ± 10% mg/kg/day amoxycillin in combination with 3.6 ± 10% mg/kg/day clavulanic acid.

6. A method as claimed in claim 1 for treating acute otitis media.

7. A pediatric pharmaceutical formulation in the form of a dry powder which is reconstitute into a multiple dosage suspension with water or other suitable aqueous media, comprising amoxycillin trhydrate and potassium clavulanate in combination, in weight ration of 7:1, the weights being expressed as the free parent acids amoxycillin and clavulanic acid, which formulation, when reconstituted, comprise amoxycillin in an amount of from 150 to 450 mg/5ml of liquid aqueous suspension and clavulanic acid in an amount of from 25 to 75 mg/5ml of liquid aqueous suspension.

8. A formulation as claimed in claim 7 which when reconstituted comprises 200 ± 10% mg/5ml amoxycillin and 28.5 ± 10% mg/5ml clavulanic acid, or 400 ± 10% mg/5ml amoxycillin and 57 ± 10% mg/5ml clavulanic acid.

9. A multiple dosage pharmaceutical formulation in the form of a liquid aqueous suspension comprising 200 ± 10% mg of amoxycillin and 28.5 ± 10% mg/5ml clavulanic acid/5ml suspension, or 400 ± 10% mg amoxycillin and 57 ± 10% mg/ clavulanic acid/5ml suspension (the weights being expressed as the free parent acids amoxycillin and clavulanic acid), in a nominal ratio of 7:1.

10. A formulation having a composition within ± 10% of the formulate listed below, expressed as mg/5ml dose of reconstitutes aqueous suspension:

Ingredient	Mg/5ml	Mg/5ml
Amoxycillin trihydrate	408.0	204.0
Potassium clavulanate	61.56	30.78
Xanthan gum	12.5	12.5
Collodial silica	25.0	25.0
Succinic acid	0.84	0.84
Orange flavour	26.25	26.25
Golden syrup flavour	23.75	23.75
Aspartame	12.5	12.5
Hydroxypropylmethycellulose	79.65	79.65
Silicon dioxide	to 885.5	to 537.5

Respondent submits that the essential features of the patent are as follows:

29.1 The methods of the invention are for treating bacterial infections in paediatric patients and the compositions are for paediatric use.

29.2 The formulations are either in the form of a liquid oral suspension or as a dry powder or granule formulation for reconstitution into a liquid aqueous suspension.

29.3 The composition comprise a combination of amoxicillin and clauvinic acid at a ratio 7:1.

29.4 The dosage to be administered is from 20 to 70 mg/kg/day of amoxicillin and pro rate amounts of clavulanic acid.

29.5 The methods of the invention are directed to administration of the formulations twice daily (bid)".

Novelty is a requirement in determining the patentability of an invention. Section 7 and Section 9 of Republic Act 165 provide:

"Sec. 7. Inventions patentable. Any invention of a new and useful machine, manufactured product or substance, process or improvement of any of the foregoing, shall be patentable."

> "Sec. 9. Invention not considered new or patentable. – An invention shall not be considered new or capable of being patented if it was known or used by others in the Philippines before the invention thereof by the inventor named in an application for patent for the invention, or if it was patented or described in any printed publication in the Philippines or any foreign country more than one year before the application for a patent therefore; or if it had been in public use or sale in the Philippines for more than one year before the application for a patent therefore; or if it had been in public use or on sale on in the Philippines for more than one year before the application for a patent therefore; or if it is a subject matter of a validly issued patent in the Philippines granted on an application filed before the filling of the application for patent therefore".

An invention is not patentable if it is no longer new. An invention shall not be considered new if its subject matter had already been patented or if such invention has already been described in any printed publication in the Philippines or any foreign country more than one year before the application for a patent in the Philippines.

In accord with jurisprudential precedents, the Bureau rules that in order that prior art anticipate an invention, all elements of the claim must be contained or found in one single prior art reference or device. Respondent avers that petitioner failed to adduce a single reference that covers all the elements of claims of the patent.

To belie respondent's defense, petitioner's presented several references consisting of Exhibits "A" to "G" of petitioner's reply to support its contention that respondent's patents are no longer novel. These consist of patent documents, publications dated earlier than April 30, 1996, the filing date of respondent's application for patent. GB 2 005 538 A (Beecham group ltd) dated April 25, 1979 (Exhibit "A") describes a paediatric aqueous liquid suspension formulations comprising with a weight ratio of 1; 1 to 6:1.; US 4 537 887 (Exhibit "C"); WO 91/15197 (Exhibit "B") are patent documents which are formulations comprising amoxyxillin hydrate in conjunction with clavulanic acid which filing dates are October 5, 1983 and 2 April 1991 respectively. EUR J. Pediatr (Exhibit "D") is a publication dated December 1986 with an article on the use of amoxicillin (only) twice daily in treatment of acute otitis media in infants and children. Exhibit "E" is a publication dated January 1989 discussing the treatment of acute otitis media infants using an amoxicillin – clavulanic acid formulation (in the form of oral suspension for pediatric use); Exhibit "F" is the use of the amoxicillin – clavulanic acid suspension for children in the treatment of bronchopulmonary infections). Exhibit "G" is a copy of European journal of clinical microbiology and infectous diseases dated May 1993 where an article discussed the evaluation of amoxicillin clavulanate twice daily versus thrice daily in the treatment of otitis media in children. Exhibit "H" is a copy of the Canadian Medical Association Journal dated January 15, 1990 with an article on "twice – daily antibiotics in the treatment of acute otitis media: trimethroprim-sulfamethoxazole versus amoxicillin-clavulanate" and Exhibit "I" is a copy of the Journal of International Medical Research dated 1989 with an article on Amoxycillin and clavulanic acid in the treatment of urinary tract infection in children.

The Supreme Court in Angelita Manzano v. Court of Appeals and Melecia Madolaria, G.R. No. 113388. September 5, 1997 held:

"It is relevant and material to state that in determining whether novelty or newness is negatived by and prior art, only one item of the prior art may be use at a time. For anticipation to occur, the prior must show that each element is found either expressly or described or under principles of inherency in a single prior art reference or that the claimed invention was probably known in a single prior art device or practice. (Kalman v. Kimberly Clark, 218 USPQ 781, 789)."

Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference (In re Spada, 911 F .2d 705, 15 USPQ2d 1655, Fed. Cir. 1900), or embodied in a single prior art device or practice (Minnesota Min. & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc., 976 F .2d 1226, 9 USPQ2d 1913, Fed. Cir. 1989). Those elements must either be inherent or disclosed expressly and must be arranged as in the claim (Consultant v. Micro-Devices, Inc., 848 F2d 1560, 7 USPQ2d 1057, Fed. Cir. 1986).

Applying the foregoing precepts to the instant case and after thorough review of the references, we find no single reference that expressly describes the art as expressed in the patent document. However, we concede that all elements are inherently described in patent document WO91/15197 (Exhibit "B") and US Patent 4,537,887 (Exhibit "C") which filing dates are October 5, 1983 and April 2, 1991, respectively.

With regard to US Patent 4,537,887 (Exhibit "C"), respondent admits that this prior art contains all elements except that it is in tablet form. The use of amoxycillin with oral dosage unit of 20 to 1500 mg and clavulanic acid of 20 to 500 mg at weight ratios 12:1 and 1:1, preferably 8:1. The process of preparation of this composition was suggested in tablet form. In WO 91/15197 (Exhibit "B"). The 7:1 weight ratio of Amoxycillin at various illustrations was between 125 to 3000 mg with clavulanic acid 31.25 to 250 mg. The combination of amoxycillin and clavulanic acid was also suggested in suspension form.

The patent document reads as follows:

"PHARMACEUTICAL FORMULATIONS"

The present invention relates to pharmaceutical compositions for oral administration in the treatment of bacterial infections.

In some clinical situations, to improve patient compliance, it is desirable to administer medicaments orally in liquid form as suspensions or solutions."

Thus, Patent No. 1-1996-52993 lacks novelty because its subject matter is inherently contained in a single prior reference which ante dates the filing date of the Patent No. 1-1996-52993, contrary to Section 7, Republic Act 165.

Anticipation of a patented method is shown by knowledge of the method, and its use with operative success, although without full and precise knowledge of the scientific principles involved, as outlined in the patent. In determining anticipation of a patented method it is immaterial that the structure employed in the earlier use was neither the best

possible nor as skillfully designed or used as that later employed by the patentee. (Smith, Executor v. Hall, et. Al. Supreme Court of the United States, 301 U.S. 216, 57 S. Ct. 711, 81 L. Ed. 1049, April 26, 1937.)

Respondent's invention is non-patentable because it lacks an inventive step. The law provides:

> "Sec. 7. Inventions patentable. Any invention of a new and useful machine, manufactures product or substance, process or improvement of any of the foregoing, shall be patentable."
>
> "Sec. 8. Inventions not patentable. – An invention shall not be patentable if it is contrary to public orders or morals, or to public health or welfare, or if it constitutes a mere idea, scientific principle or abstract thereon not embodied in an invention as specified in section 7 thereof, or any process not directed to the making or improving of a commercial product."

In the instant case, obviousness was established by petitioner though clear and convincing evidence. The references before the examiner during prosecution taught the principle used by persons of ordinary skill in the art to address the problem of providing treatment of acute otitis media in children.

Evidence show that GB 2 005 538 A (Exhibit "A") (Beecham group ltd) dated April 25, 1979 describes a paediatric aqueous liquid suspension formulations composition of comprising with a weight ratio of 1;1 to 6:1 of amoxycillin trihydrate, 20 mg to 500 mg of potassium clavulanate. The patent reads:

> "Accordingly the present invention provides a dry unit-dose pharmaceutical composition suitable for oral administration which composition comprise 20 mg to 1500 of amoxycillin trihydrate, 20 mg to 500 mg of potassium clavulanate and a pharmaceutically acceptable carrier with the provision that the weight ration of amoxycillin trihydrate to potassium clavulanate is from 6:1 to 1:1
>
> In general the oral dosage unit of this invention will contain from 125 mg to 1250 mg of amoxycillin trihydrate for example it may contain about 50, 60, 75, 100, 120, 125, 150, 200, 240, 250 or 300 mg of potassium clavulanate.
> The oral dosage unit of this invention may be in the form of a tablet, capsule, syrup powder or granulate for reconstitution presented in a sachet or the like. Shaped forms of the composition such as tablets or capsules are particularly suitable."

WO 91/15197 (Exhibited "B") suggests oral administration of the same composition in liquid form as suspensions. The preferred ratio of 7:1 amoxicillin trihydrate and clavulanic acid was also claimed. The amount of amoxycillin will depend on the infection to be treated typically in 3000 or 125 or an Intermediate dose. Therefore, encompassing the dose as claimed in the challenged patent.

The same teaching is present in US Patent 4,573,887 (Exhibit "C") which states:

"I claim:

1. A pharmaceutical composition in unit dose table form suitable for oral administration to humans and animals which comprises amoxicillin trihydrate equivalent to 20 mg to 1500 mg of amoxicillin, potassium clavulanate equivalent to 20 mg to 500 mg of clavulanic acid, the weight ratio of amoxicillin to clavulanic acid being in the range of from 12:1 to 1:1, xxx

2. A composition according to claim 1 wherein the ratio of amoxicillin to clavulanic acid is from 8:1, 4:1 or 2:1 xxx

3. A composition according to claim, which contains amoxicillin trihydrate equivalent to 125-500 mg of amoxicillin. Xxx"

Eur J Pediatr (Exhibit "D") dated December 1986 had already discussed the treatment regimen of twice daily dosing of amoxicillin for otitis media in infants and children.

Ann Pediatr, dated January 1989 (Exhibit "E") has already taught amoxicillin-clavulanic suspension formulation for treatment of acute otitis media in infants.

In European Journal of Clinical Microbiology & Infectious Diseases date May 1993 (Exhibited "G"), an effective clinical assessment was noted for 50 mg/ml amoxicillin + 12.5 mg/ml clavulanic acid the given b.i.d in the treatment of Otitis Media in children.

As just discussed, prior art already taught the use of amoxicillin and clavulanic acid in specific ranges that effectively treat acute otitis media in children in infants at particular weight rations. Formulation in suspension form has also been seen in prior art and b.i.d dosing has also been used. As in the instant case, evidence show prior art contain sufficient reference, teaching and suggestion to formulate the invention.

It has been a basic principle of patent law, subject to minor exceptions, that prior art is technology already available to the public, it is available in legal theory at least, when it is described in the world's accessible literature, including patents, or has been publicly known or in public use of sale "in this country". That is the real meaning of "prior art" in legal theory –it is knowledge that us available, including what would be obvious form it, at a given time, to a person of ordinary skill in the art. (Oddzon Products, Inc. v. Just Toys, Inc. Lisco Inc. and Spalding & Evenflo Companies, Inc., United States Court of Appeals for the Federal Circuit, August 8, 1997).

When obviousness is based on a particular prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference. This suggestion or motivation need not be expressly stated. (B.F. Goodrich Company v. Aircraft Braking Systems Corporation and Allied – Signal Incorporated, United States Court of Appeals for the Federal Circuit, January 4, 1996.)

It is well established that before a conclusion of obviousness may be based on a combination of references, there must have been a reason, suggestion or motivation to lead an inventor to combine those references Inventors strive to improve that which already exists. The law sets the dividing line between patentability and unpatentability at what would have been obvious to one having ordinary skill in the art to which the invention pertains. If one prior art reference describes the claimed invention, it is worse than obvious in terms of patentability, it lacks novelty. If the inventions is different from what is disclosed in one reference, but the differences are such that combination with another reference would lead to what is claimed, the obviousness question then requires inquiry into whether there is reason, suggestion, or motivation to make that combination. Such a suggestion may come expressly from the references themselves. It may come from knowledge of those skilled in the art that certain reference, or disclosures in the references, are known to be of special interest or importance in a particular field. (Pro-Mold and Tool Company, Inc. v. Great Lakes Plastics, Inc. Unites States Court of Appeals for the Federal Circuit, February 7, 1996)

Accordingly, the teachings of these prior art references, to one skilled in the art direct that the same combination may be formulated as pediatric suspension and weight ratio of 7:1 claimed as novel in the challenged patent is obtainable by mere mathematical calculation. Besides, prosecution history show the 7:1 ration at b.i.d. dosing was available in Italy and Spain as per respondent's own patent application documents. To elaborate this point, we quote the testimony of petitioner's witness, Agnes Casiding.

In the direct examination of Ms. Agnes Casiding on June 13, 2006 in the Civil Case No. 06-373 pending in the Regional Trial Court of Makati, Branch 149 she testified thus:

(TSN page 49-50, Exhibit "J")

Q: Meaning to say madam witness when you came up with the 7:1 ratio, it just a pure mathematical computation involving the factors of weight of the child?

A: yes sir.

Q: What about the severity of the dosage?

A: So we have arranged, do we get the highest weight of the child then we computer it then we got around 400 ml so we round if off also to 400 for easier computation, for easier administration so if its 200 to 400 and we just get the ratio equivalent of potassium clavulanate which is 7 amoxicillin and 1 clavulanic acid and the formulation is based also on our own existing pediatric suspension which is the 4:1 combination"

On June 26, 2006, the same witness testified in Civil Case No. 06-373; Smithkline Beecham, p.l.c. et. al. vs. Natrapharm, Inc.; Regional Trial Court of Makati Branch 149, as follows: (Transcript of Stenographic notes June 26, 2006 p.9-10, 11)

Atty. Pinoy: I understand Ms. Casiding that this product Coamoxiclav has a weight ratio of 125 mg and 31.25 mg. I understand also that when you subdivide 125 by 31.25 you come up with the ration of 4:1?

Agnes P. Casiding: Yes, sir.
(Witness)

xxx

Atty. Pinoy: Do you have another document?

A: I have also the formulation of the product that is the 7:1 ratio we submitted to BFAD.

Atty. Pinoy: Witness handed over to me a document entitled Lloyd Laboratories Inc. Annex A for Incoming Initial/Monitored Realease/Monitored Release Extension Registration dated August 6, 2004 addressed to one professor Leticia Barbara B. Gutierrez, which is a notarized document referring to a product called Co-Amoxiclav for Natravox, 200 mg/28.5 mg. per 5ml powder for suspension which I request to be marked as Exhibit N and witness handed over to me another document entitle Llyod laboratories, Inc. Annex A for Incoming/Monitored Release/ Monitored Extension Registration date 6 August 2004 addressed to one Professor Leticia Barbara Gutierrez referring to a product called Co-Amoxiclav Natravox 400 mg/57 mg per 5 ml which I request to be marked as exhibit O.

xxx

(page 13-15)

Q: With regards to this specific product Co-Amoxiclav 400 and 200 formulations Ms. Casiding it's not quite for me to assume that it was actually Lloyd Laboratories who brought this product to the Philippines?

A: After marketing the first 4 products of Co-Amoxiclav and because of my continuous research on these active pharmaceutical materials and we found out the 7:1 ration is also available I requested Lloyd to develop this new ratio of 7:1 for suspension because they have the facilities, they started developing it using the same formulations as 4:1 and we just adjusted the amount of Sorbitol.

Q: Who did you inform in Lloyd Laboratories that 7:1 ratio was possible?

A: The product development group also of Lloyd.

Q: When did you inform Lloyd Laboratories about your proposal that the ratio 7:1 ratio could be developed or could be manufactured?

A: Around 2003

xxx

(page 19, 20)

Q: You testified during the last hearing that the first step that the first step that you conducted with respect to product development was to review general articles and other documents is that so?

A: Yes.

Q: After reviewing those documents, what did you do?

A: Because this product development with Natrapharm is now partnership with the marketing, with Ms. Ravelo, so she researched on marketing side, I researched on technical side. So when it finished searching all the documents, I finished with the literature survey, I discussed it with Ms. Ravelo to look for possible manufacturer or stores of these finished products, so we tried to contract either abroad or locally.

xxx

(Page 23-24)

Q: Ms. Casiding, did you prepare your alleged mathematical computation to convert the 4:1 ration to 7:1 ratio?

A: I did not bring.

xxx

Q: Or you do not have those documents?

A: I did not bring it but as far as I based it from 30 to 40 mg/kg/dose, so the average body weight of a child is 15.5 lbs. Divided by 2.2 kgs. Approximately, I got 207 mg so I round it off equivalent to 200 mg/5ml, because we have already a 250 Co-amoxiclav suspension in the market so we prepared a 200.

(Page 26-27)

Q: When did you come to know this information that in other countries such as Italy and Spain tablets containing Amoxicillin 878 mg and Potassium Clavulanate 125 mg ratio 7:1 are approved twice daily dosing BID, prior to the time that we sent you that letter. Is the correct?

A: As I mentioned in the last hearing I did a continuous research, in year 2003. I encountered already the journal drugs, it was already mentioned the drugs journal, it was already published 1983 that this dosage is already used in Italy and the

continuous research on the website of PubMed regarding the topic on Co-amoxiclav was already mentioned on the article that I downloaded the 7:1 ratio was already used in other countries.

xxx

(pages 35-37)

Q: Ms. Casiding, just for confirmation the phrase “although in Italy the usual dose is 875/125 mg twice or three times daily depending on the severity of the infection” do you confirm again this statement that this refer to dosage in tablet form?

A: Yes.

Q: Does this particular reference Exhibit P-1 suggest to you that you can give Amoxicillin and Potassium Clavulanate in suspension for children?

Witness: Yes sir.

Atty. Pinoy: Yes?

Witness: Yes because….

Q: On what basis? Mathematical computation?

A: As a pharmacist if we can form a tablet definitely we can form a suspension for pediatrics, so if we know that it is for adult we can adjust the suspension for children and use a formulation for children.

Q: What is your basis for saying that you can transform any form of drug from tablet form to suspension or from suspension to tablet form of medicines indicated for children?

Atty. Poblador: Expert your Honor, she said that she is an expert.

Court: You reform your question.

Atty. Poblador: It’s his opinion which has no basis yet.

Atty. Pinoy: I’d like to think over your Honor. In the course of your employment with Natrapharm, UP, PGH, Nova Chemical Industries, Inc., Pharmatechnica, McGwen Pharmaceutical Laboratories, I suppose you were able to acquire your supposed opinion on whether a medicine or a form of medicine or type of medicine can be transformed from tablet form to suspension form or from suspension form to tablet form?

A: Yes sir.

Q: For pediatric patient is that correct?

A: Yes sir.

Q: That expands a period of what? 1979, 27 years of experiences right?

A: Yes sir.

Q: And this time that you presented as an expert pharmacist is that correct?

A: Yes sir.

Q: Did you come across a publication called Goodman and Gillman?

A: Yes sir.

Q: I understand that it's a standard textbook for pharmacist student?

A: No sir.

Q: It is not a standard reference?

A: Our standard reference is from pharmaceutical sciences. That is a reference only for Pharmacology for medical students.

Q: What is Goodman and Gillman then?

A: It's a book for Pharmacology.

Q: But you use it?

A: When I was a student.

Q: You said when you were a student?

A: Yes, as a reference.

Q: When you were an undergraduate student I suppose?

A: Yes.

Q. As well as when you were an undergraduate student?

A: Yes sir.

Q: When you were working you did not use it as a reference anymore?

A: One of the references.

Q: But it could have been helpful right?

A: Not so for formulation.

Q: Not so for formulation. This is Goodman and Gillman's, the Pharmacological basis and Therapeutics. I'm sure you come across this reference right?

Atty. Poblador: Already answered. She said that she has encountered that in her student days.

Court: Yes.

Atty. Pinoy: Yes, your Honor, I will have this photocopy of this reference your Honor only the cover, the title page to be marked in evidence as Exhibit Q. I refer you to page 123 column 2 lines 9 to 11 of Goodman and Gillman. Do you agree with the statement here of Goodman and Gillman as an expect pharmacist, that I quote, "there are no reliable, broadly applicable principles or formulas for converting doses of drugs used in adults to doses that are safe and effective in children". Do you agree with this statement?

A: Yes sir because that is a general statement.

Q: There are no broadly applicable principles or formulas for converting doses of drug used in adults to doses that are safe and effective in children? Did you consider this when you did product development of Co-Amoxiclav by converting 4:1 to 7:1?

A: Yes I considered that but as I have told you I did several researches, several journals, several books and that is a general statement. The conversion is depend upon the active pharmaceutical ingredients, for example, amlo…. I forgot the pharmacological…, because there are product listed by the WHO wherein this products you have to conduct a study if you have to convert it to pediatric from adult or from adult to pediatric, but regarding Co-Amoxiclav it is very …. The Co-Amoxicillin.

Q: I'm sorry?

A: The Pharmacokinetics, the distribution of source of elimination excretion of these products is the same for both adult and children.

Q: Do you have basis for your statement?

A: I can bring it.

Q: I'll bring your attention to page 126 column 2, last paragraph line 1 to 8. Do you agree with the statement of Goodman and Gillman and I quote, "that data from the association of drug levels with efficacy and toxicity must be interpreted in the context of the pharmacodynamic variability and the tabulation. The plasma concentration of Phenobarbital required control … For example, is higher in children than in adults. Variability in pharmacodynamic response can result from any of the factors responsible for authoring drug effect that include genetics, age, disease and other drug". Do you agree with this statement?

A: Yes sir because it is general statement, example Phenobarbital, other cardio drug for heart diseases, anti-psychotic drugs, that is a general statement sir.

Q: So on the basis of your other references you were able to make a mathematical computation of converting the dosage for Co-Amoxiclav to children at 7:1 at 400 and 200 mg of Amoxicillin for twice daily dosing is that correct?

A: Yes sir.

Q: What is you basis that the conversion for children and adults are the same?

A: One is the information coming from the pediatrician that they add more amoxicillin, excuse me, one of the bases is the…

Q: Take your time Ms. Casiding.

A: Can you repeat your questions?

Q: What is your basis for saying that conversion of dosage in adult form to children is the same?

A: Safe only for certain products.

Q: And for other products?

A: No.

Upon review of the record and the evidence, as well as the record of testimony that transpired in the civil court. This Bureau concludes that there is substantial evidence to prove that the claimed subject matter is not new and is obvious to a person of ordinary skill in the art at the time the invention was made, hence not patentable.

WHEREFORE, premises considered the instant PETITION FOR CANCELLATION is hereby GRANTED. Accordingly, Letters Patent No. 1-1966-52993 filed on 30 April 1996 and issued on 5 May 2005 for "Method of Treatment" issued in the name of Smithkline Beecham PLC, respondent, is as it is hereby CANCELLED and is declared NULL and VOID.

Let a copy of this decision be forwarded to the Bureau of Patents for appropriate action in accordance with this Decision.

SO ORDERED.

31 May 2007.

ESTRELLITA BELTRAN -ABELARDO
Director, Bureau of Legal Affairs