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GILEAD SCIENCES INC
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EXAMINER

ART UNIT PAPER NUMBER

DATE MAILED: 01/16/2008

Please find below and/or attached an Office communication concerning this application or proceeding.



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(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

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1375 Broadway, Suite 600
New York, NY 10018

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. 90/008,556.

PATENT NO. 5935946.

ART UNIT 3991.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination

Control No.
90/008,556

Patent Under Reexamination
5935946

Examiner
Dwayne C. Jones

Art Unit
3991

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

- a Responsive to the communication(s) filed on 30 April 2007. b This action is made FINAL.
c A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c)**. If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892. 3. Interview Summary, PTO-474.
2. Information Disclosure Statement, PTO/SB/08. 4. _____

Part II SUMMARY OF ACTION

- 1a. Claims 1-20 are subject to reexamination.
1b. Claims _____ are not subject to reexamination.
2. Claims _____ have been canceled in the present reexamination proceeding.
3. Claims _____ are patentable and/or confirmed.
4. Claims 1- 20 are rejected.
5. Claims _____ are objected to.
6. The drawings, filed on _____ are acceptable.
7. The proposed drawing correction, filed on _____ has been (7a) approved (7b) disapproved.
8. Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some* c) None of the certified copies have
 1 been received.
 2 not been received.
 3 been filed in Application No. _____.
 4 been filed in reexamination Control No. _____.
 5 been received by the International Bureau in PCT application No. _____.
 * See the attached detailed Office action for a list of the certified copies not received.
9. Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. Other: _____

cc: Requester (if third party requester)

DETAILED ACTION

***Ex Parte Reexamination
by
Third Party Requester:***

First Action on the Merits

Procedural Posture

- On 03/23/2007: A Request for *Ex Parte* Reexamination by a Third Party Requester was filed.
- On 04/03/2007: A Notice of Failure to Comply with *Ex Parte* Reexamination Request Filing Requirements (37 CFR 1.510(c)) was mailed.
- On 04/30/2007: A Corrected Request for *Ex Parte* Reexamination by a Third Party Requester was filed for U.S. Patent No. 5,935,946 ('946 Patent) now assigned control number 90/008,556.
- On 07/13/2007: A Determination GRANTING the Request for *Ex Parte* Reexamination by a Third Party Requester was mailed.
- A statement under 37 CFR 1.530 has not been received from the Patent Owner.

Priority

1. The '946 Patent issued to Munger, Jr. et al. on 08/10/1999, which was filed on 07/25/1997 as U.S. Application No. 08/900,752. Therefore, the earliest effective filing date possible for the '946 Patent (patent undergoing reexamination) is 07/25/1997.

References Cited by the Third Party Requester

New References Cited:

1. **Arimilli et al.** of U.S. Patent No. 5,922,695 issued on 07/13/1999, which has priority to 07/26/1996, (hereinafter referred to as **Arimilli et al.**).
2. **Bischofberger et al.**, "Bis(POC)PMPA, an Orally Bioavailable Prodrug of the Antiretroviral agent PMPA," *Conference on Retroviruses and Opportunistic Infections*, 4th:104 (abstract no. 214, January 22-26, 1997, (hereinafter referred to as **Bischofberger et al.**).
3. **Gould, P. L.** "Salt Selection for Basic Drugs," *International Journal of Pharmaceutics*, 33:201-271, 1986. (hereinafter referred to as **Gould**).
4. **Takashima et al.** of EP 0206459 B1, published on 01/04/1985, (hereinafter referred to as **Takashima et al.**).

Legal Standards

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

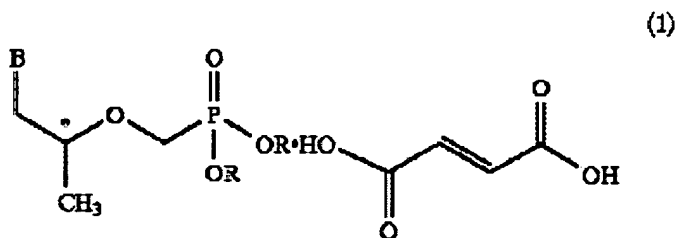
Claim Rejections - 35 USC § 102

4. Claims 1-15, 19, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Arimilli et al. (*U.S. Patent No. 5,922,695*) as evidenced by the Patent Owner's Admission in U.S. Patent No. 5,935,946 (*patent undergoing reexamination*).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

A) Independent claim 1 is anticipated.

1. A composition of formula (1)



wherein B is adenin-9-yl and R independently is —H or —CH₂—O—C(O)—O—CH(CH₃)₂, but at least one R is —CH₂—O—C(O)—O—CH(CH₃)₂.

Regarding claim 1, the Arimilli et al. invention discloses the antiviral phosphonmethoxy nucleotide compounds and compositions of formula (1a) and formula (1)

(See column 1, lines 29-45; column 2, lines 1-45; from column 35, line 21 to column 38, line 41). Arimilli et al. expressly disclosed bis(POC)PMPA fumarate (See column 44, line 65).

B) Dependent claims 2-6 and 9 are anticipated.

Regarding claim 2, Arimilli et al. expressly disclosed bis(POC)PMPA fumarate (See column 44, line 65). Moreover, the Arimilli et al. disclosure of the antiviral phosphonmethoxy nucleotide compounds and compositions of formula (1a) and formula (1) did not exclude both R variables from being $\text{CH}_2\text{-O-C(O)-O-CH(CH}_3\text{)}_2$.

Regarding claim 3, Arimilli et al. expressly disclosed bis(POC)PMPA fumarate as a crystalline solid (See column 44, line 65; column 45, lines 50-65).

Regarding claim 4, Arimilli et al. expressly disclosed "compounds of this invention are optionally enriched or resolved at the carbon atom chiral center" (See column 6, lines 46-47).

Regarding claim 5, Arimilli et al. disclose bis(POC)PMPA fumarate as a crystalline solid (See column 44, line 65; column 45, lines 50-65).

Regarding the recitation that the composition of claim 1 has *an X-ray powder diffraction spectrum peak using Cu-K α radiation, expressed in degrees 2 θ at about 25.0*, the prior art reference of Arimilli et al. inherently meets this claim recitation.

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

Something which is old does not become patentable upon the discovery of a new property. See MPEP 2112, section I.

"Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Patent Owner discloses and/or

claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658, (Fed. Cir. 1990).

Composition claims – if the composition is physically the same, it must have the same properties. See MPEP 2112.01, section II.

The fact that Arimilli et al. never mentions *an X-ray powder diffraction spectrum peak using Cu-K α radiation, expressed in degrees 2 θ at about 25.0* is irrelevant because the *an X-ray powder diffraction spectrum peak using Cu-K α radiation, expressed in degrees 2 θ at about 25.0* is a physical property intrinsic to the bis(POC)PMPA fumarate in crystalline form. Due to the fact that Arimilli et al. disclose the same composition that is instantly claimed, the burden has now shifted to the Patent Owner to show that Arimilli et al.'s composition does not possess the crystal structure as claimed (See MPEP 2112, section V).

As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith.” *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 699 (CCPA 1972).

Furthermore, the Arimilli et al. disclosure of bis(POC)PMPA fumarate crystals did not exclude *an X-ray powder diffraction spectrum peak using Cu-K α radiation, expressed in degrees 2 θ at about 25.0*.

Regarding claim 6, the Arimilli et al. invention discloses the antiviral phosphonomethoxy nucleotide compounds and compositions of formula (1a) and formula (1) together with one or more acceptable carriers (excipients) (See column 1, lines 29-45; column 2, lines 1-45; from column 35, line 21 to column 38, line 41). Arimilli et al. expressly disclosed bis(POC)PMPA fumarate (See column 44, line 65).

The Patent Owner in the '946 Patent (patent undergoing reexamination) in column 5, lines 18-25⁰ equates acceptable carriers with excipients in the following admission:

“[t]he formulations of the present invention comprise BPPF [“bis(POC)PMPA fumarate”], together with one or more pharmaceutically acceptable excipients or carriers (“acceptable excipients”). . . . The carrier(s) must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient.”

Accordingly, the claimed limitation directed to a *composition comprising the composition of claim 1 and an acceptable excipient* is necessarily met by Arimilli et al. as combined with the Patent Owner’s admission.

Regarding claim 9, Arimilli et al. expressly teach various methods (i.e., oral) of administering bis(POC)PMPA fumarate to treat man or animals with viral infections (See column 34, lines 42-66; from column 35, line 21 to column 36, line 12).

C) Independent claim 7 is anticipated.

7. A composition comprising a lithium alkoxide and a 9-(2-hydroxypropyl)adenine solution.

Regarding claim 7, Arimilli et al. expressly disclose a composition comprising lithium alkoxide (lithium t-butoxide) and 9-(2-hydroxypropyl)adenine in solution (See column 42, lines 32-44; column 40; lines 53-54; and column 39, lines 56-62). A species will anticipate a claim to a genus. See MPEP 2131.02.

D) Independent claim 8 is anticipated.

8. A composition comprising an (R,S)-PMPA solution at a pH of about 2.7–3.5 wherein the solution has less than about 0.1 g/mL (R,S)-PMPA and wherein about 90–94% of the PMPA is in the (R) configuration.

Regarding claim 8, PMPA refers to (R)-9-[2-(Phosphonomethoxy)propyl]adenine. Arimilli et al. expressly teach PMPA (See columns 43-44). Arimilli et al. expressly disclose that the compounds of their invention will be in the (R) configuration and will be substantially free of

the (S) enantiomer (See column 6, lines 46-51). Arimilli et al. also disclose that at least about 90% of the compound is in the (R) configuration at the R¹ site (See column 61, lines 12-13).

Arimilli et al. also teach that the pH of the solution is adjusted to about 2.6 – 3.0 and 3.1- 3.3 (See column 43).

As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith.” *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 699 (CCPA 1972).

In addition, the Arimilli et al. disclosure did not exclude an *(R,S)*-PMPA solution at a pH of about 2.7-3.5 wherein the solution has less than about 0.1 g/mL *(R,S)*-PMPA and wherein about 90-94% of the PMPA is in the (R) configuration.

E) Independent claim 10 is anticipated.

10. A method comprising contacting bis(POC)PMPA with fumaric acid.

Regarding claim 10, Arimilli et al. expressly taught contacting bis(POC)PMPA with fumaric acid (See column 3, line 48; column 34, lines 38-41; columns 38-40 for Example 1; column 45, lines 34-36, 46-47, and 64).

F) Dependent claim 11 is anticipated.

Regarding claim 11, Arimilli et al. expressly taught fumaric acid is dissolved in 2-propanol (See column 45, lines 34-37).

G) Independent claim 12 is anticipated.

12. A method comprising mixing a lithium alkoxide with a 9-(2-hydroxypropyl)adenine solution.

Regarding claim 12, Arimilli et al. expressly disclose a composition comprising mixing lithium t-butoxide (lithium alkoxide) and 9-(2-hydroxypropyl)adenine in solution (See column 42, lines 32-44; column 40; lines 53-54; and column 39, lines 56-62). A species will anticipate a claim to a genus. See MPEP 2131.02.

H) Dependent claims 13-14 are anticipated.

Regarding claims 13-14, Arimilli et al. specifically teach that the lithium alkoxide embraces alkyl groups with 1-6 carbon atoms, e.g., n-hexoxide, n-pentoxide, n-butoxide, i-butoxide, t-butoxide, n-propoxide, i-propoxide, ethoxide, methoxide (See column 39, lines 55-59). See MPEP 2131.02.

I) Independent claim 15 is anticipated.

15. A method comprising adjusting the pH of a solution comprising less than about 0.08 g/mL (R,S)-PMPA wherein about 90-94% of the PMPA is in the (R) configuration to a pH of about 2.7-3.5.

Regarding claim 15, PMPA refers to (R)-9-[2-(Phosphonomethoxy)propyl]adenine.

Arimilli et al. expressly teach PMPA (See columns 43-44). Arimilli et al. expressly disclose that the compounds of their invention will be in the (R) configuration and will be substantially free of the (S) enantiomer (See column 6, lines 46-51). Arimilli et al. also disclose that at least about 90% of the compound is in the (R) configuration at the R¹ site (See column 61, lines 12-13). Arimilli et al. also teach that the pH of the solution is adjusted to about 2.6 – 3.0 and 3.1- 3.3 (See column 43).

As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith.” *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 699 (CCPA 1972).

In addition, the Arimilli et al. disclosure did not exclude an *(R,S)*-PMPA solution at a pH of about 2.7-3.5 wherein the solution has less than about 0.1 g/mL *(R,S)*-PMPA and wherein about 90-94% of the PMPA is in the *(R)* configuration.

J) Independent claim 19 is anticipated.

19. A product produced by the process of preparing wet granules from a mixture comprising a liquid, 9-[2-(R)-[[bis [[(isopropoxycarbonyl)oxy]methoxy]phosphinoyl] methoxy]propyl]-adenine.fumaric acid (1:1) and a pharmaceutically acceptable excipient.

Regarding claim 19, this claim is defined as a product-by-process claim.

“[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1984).

Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. See MPEP 2113.

Arimilli et al. disclose the antiviral phosphonmethoxy nucleotide compounds and compositions of formula (1a) and formula (1) (See column 1, lines 29-45; column 2, lines 1-45; from column 35, line 21 to column 38, line 41). Arimilli et al. expressly disclosed bis(POC)PMPA fumarate with acceptable carriers (See column 44, line 65).

In addition, Arimilli et al. teach that formulations are prepared by any of the methods well known in the art of pharmacy and these methods include the step of bringing into association the active ingredient with a carrier (excipient) (See column 35, lines 49-59).

As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith.” *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 699 (CCPA 1972).

Accordingly, the invention disclosed by Arimilli et al. anticipates the product-by-process as defined in **claim 19**.

The use of 35 U.S.C. 102/103 rejections for product-by-process claims has been approved by the courts. See MPEP 2113.

K) Dependent claim 20 is anticipated.

Regarding claim 20, this claim depends on the product-by-process defined in **claim 19**.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1984).

Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. See MPEP 2113.

Arimilli et al. disclose the antiviral phosphonmethoxy nucleotide compounds and compositions of formula (1a) and formula (1) (See column 1, lines 29-45; column 2, lines 1-45; from column 35, line 21 to column 38, line 41). Arimilli et al. expressly disclosed bis(POC)PMPA fumarate (See column 44, line 65).

In addition, Arimilli et al. teach that formulations are prepared by any of the methods well known in the art of pharmacy and these methods include the step of bringing into association the active ingredient with a carrier (excipient) (See column 35, lines 49-59). Arimilli et al. disclose oral formulations, such as tablets, powder or granules (See column 35, lines 59-62). Arimilli et al. disclose bis(POC)PMPA fumarate as a crystalline solid that was dried (See column 44, line 65; column 45, lines 50-65). Arimilli et al. also disclose that water is used in the process of making bis(POC)PMPA fumarate products (See columns 35-59). The teachings of

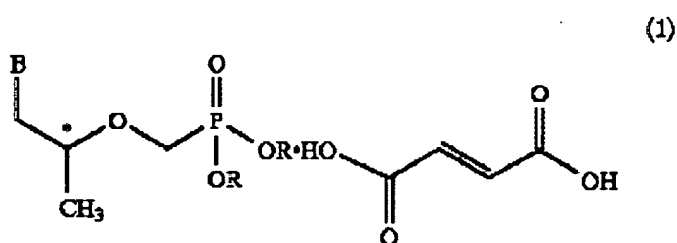
Arimilli et al. show dry forms (tablets, powder or granules) of the active ingredient, bis(POC)PMPA fumarate and thus anticipate the product-by-process as recited in claim 20.

Claim Rejections - 35 USC § 103

5. Claims 1-6, 8-10, 15, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bischofberger et al. ("*Bis(POC)PMPA, an Orally Bioavailable Prodrug of the Antiretroviral agent PMPA,*" *Conference on Retroviruses and Opportunistic Infections, 4th:104* (abstract no. 214, January 22-26, 1997) or Patent Owner's Admission (in the '946 Patent) in view of Gould ("*Salt Selection for Basic Drugs,*" *International Journal of Pharmaceutics,*, 33:201-271, 1986.) and in further view of Takashima et al. (EP 0206459 B1, published on 01/04/1985).

A) Independent claim 1 is rendered obvious.

1. A composition of formula (1)



wherein B is adenin-9-yl and R independently is —H or —CH₂—O—C(O)—O—CH(CH₃)₂, but at least one R is —CH₂—O—C(O)—O—CH(CH₃)₂.

Regarding claim 1, Bischofberger et al. teach bis(POC)PMPA (See Abstract).

The claimed subject matter differs from the teachings of Bischofberger et al. by requiring the bis(POC)PMPA to be present with the fumarate salt. However, Bischofberger et al. teach the oral administration of bis(POC)PMPA, and that bis(POC)PMPA is a promising agent for the treatment of HIV infections (See Abstract).

The Patent Owner in the '946 Patent (patent undergoing reexamination) in column 4, lines 50-58 makes the following admission:

“PMPA and bis(POC)PMPA are known to be useful in the treatment . . . of one or more viral infections in man or animals, including particularly retroviruses, HIV, SIV. . . .”

Accordingly, the Patent Owner admits that PMPA and bis(POC)PMPA are well known in the art to treat retrovirus, in particular HIV.

Gould teaches on page 202, 1st column that:

“It would seem sensible that any acid relating to normal metabolism, or present in food and drink can be regarded as a suitable candidate for preparing salts.”

In fact, Gould specifically discloses that fumarate was a suitable candidate for preparing salts for drugs (See Table 1, page 202). Thus, it was well known in the art that fumaric acid was a good candidate for pharmaceutical salt formation.

The claimed subject matter differs from the teachings of Bischofberger et al. or Patent Owner's Admission in view of Gould by requiring the bis(POC)PMPA to be present along with the fumarate salt. However, Bischofberger et al. teach the oral administration of bis(POC)PMPA, and that bis(POC)PMPA is a promising agent for the treatment of HIV infections, and Patent Owner admits that bis(POC)PMPA are well known in the art to treat HIV and the prior art reference of Gould teaches that fumarate was a suitable candidate for preparing salts for drugs.

Takashima et al. teach the formation of pharmaceutically acceptable acid salts for orally administered phosphonate-nucleotide esters that have effective anti-HIV activity. Specifically, Takashima et al. teach using fumarate in the formation of such salts in order to achieve superior oral administration characteristics (See page 2, lines 5-30; page 4, lines 41, 42, and 46; page 77, lines 1-11). Although Takashima et al. may not have specifically disclosed PMPA, it nonetheless provided sufficient motivation and a reasonable expectation of success to apply its teachings regarding the formation of a phosphonate-nucleotide fumaric salt in order to produce a compound with superior physical properties. At the time of the invention, one having ordinary skill in the art would have found it obvious to combine the bis(POC)PMPA as disclosed by Bischofberger et al. or the Patent Owner's admission both in view of the general teachings of Gould regarding the benefits of using fumarate to form compounds with superior pharmaceutical characteristics and further in view of Takashima's teaching of using fumaric acid to form anti-HIV phosphonate-nucleotide salts tablets thus arriving at the instantly claimed invention.

B) Dependent claims 2-6 and 9 are rendered obvious.

Regarding claim 2, Bischofberger et al. expressly disclosed bis(POC)PMPA (See column 44, line 65).

Regarding claim 3, it is inherent in Takashima's teaching of the phosphonate-nucleotide fumaric salt compounds as tablets and other products that the composition could be crystalline form (See page 77, lines 10-11). In addition, Takashima et al. teach that phosphonate-nucleotide ester derivatives of general formula (I) may be separated and purified by properly selecting conventional means for separation and purification for nucleotide, for example, recrystallization

(See from page 2, line 31 to page 3, line 24; page 76, lines 45-47), thus meeting the *crystalline solid* limitation.

Regarding claim 4, the compounds of the prior art of record would embrace the stereoisomers of these phosphonate-nucleotide compounds. One having ordinary skill in the art at the time of the invention would have known that stereoisomers of a racemic compound, such as bis(POC)PMPA, would exhibit different biological (pharmaceutical) activities. In addition, isomers of a racemic compound are expected to have different activities, where one stereoisomer is expected to be more active than the other.

“[T]he physiological properties of two antipodes [stereo-isomers] can differ considerably,” giving as examples several pairs of optical isomers which differ substantially in their physiological effects. “The cause of the different physiological behavior,” it is said, “lies in the fact that many constituents of cells within the organism with which the substrates react are themselves asymmetric.” *In re Adamson and Duffin*, 275 F.2d 952, 124 USPQ 233-235 (CCPA 1960).

In the absence of evidence to the contrary, one having ordinary skill in the art would have recognized that enantiomeric (optical isomer) separation (enrichment) of a particular enantiomer is regarded as a routine separation procedure, thus allowing the skilled artisan with the necessary motivation to obtain (resolve) the enantiomeric compound of **claim 4** that *is enriched or resolved at the carbon atom chiral center (*)*. In addition, pharmacological (biological) testing of the claimed compound would have been well within the purview of the skilled artisan, and as such the skilled artisan would have a reasonable expectation of success that the biological activities of the enantiomers of bis(POC)PMPA will vary in treating viruses due to the presence of an asymmetric (chiral) center on the bis(POC)PMPA compound. Furthermore, the combined teachings of Bischofberger et al., Gould, and Takashima et al., which rendered bis(POC)PMPA

fumarate obvious, did not exclude compounds optionally enriched or resolved at the carbon atom chiral center.

Regarding claim 5, the recitation that the composition of claim 1 has *an X-ray powder diffraction spectrum peak using Cu-K α radiation, expressed in degrees 2 θ at about 25.0* is inherently met by the combined teachings of Bischofberger et al., Gould, and Takashima et al., which rendered bis(POC)PMPA fumarate obvious as stated *supra*.

“[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.” *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

Something which is old does not become patentable upon the discovery of a new property. See MPEP 2112, section I.

“Products of identical chemical composition can not have mutually exclusive properties.” A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Patent Owner discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658, (Fed. Cir. 1990).

Composition claims – if the composition is physically the same, it must have the same properties. See MPEP 2112.01, section II.

The fact that the combined teachings of Bischofberger et al., Gould, and Takashima et al. never mention *an X-ray powder diffraction spectrum peak using Cu-K α radiation, expressed in degrees 2 θ at about 25.0* is irrelevant because *an X-ray powder diffraction spectrum peak using Cu-K α radiation, expressed in degrees 2 θ at about 25.0* is a physical property intrinsic to the bis(POC)PMPA fumarate in crystalline form. Due to the fact that the combined teachings of Bischofberger et al., Gould, and Takashima et al., which rendered bis(POC)PMPA fumarate obvious, the burden has now shifted to the Patent Owner to show that the combined teachings of

Bischofberger et al., Gould, and Takashima et al. do not possess the crystal structure as claimed (See MPEP 2112, section V).

As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith.” *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 699 (CCPA 1972).

Furthermore, the combined teachings of Bischofberger et al., Gould, and Takashima et al., which rendered bis(POC)PMPA fumarate obvious, did not exclude bis(POC)PMPA fumarate having an X-ray powder diffraction spectrum peak using Cu-K α radiation, expressed in degrees 2θ at about 25.0.

Regarding claim 6, Takashima et al. expressly teach producing compositions with acceptable excipients (See page 77, lines 4-11).

Regarding claim 9, Takashima et al. expressly taught that phosphonate-nucleotide fumaric salt compounds for the treatment of HIV could be orally administered to a human patient (See page 2, lines 11-16; page 77, line 1).

C) Independent claim 8 is rendered obvious.

8. A composition comprising an (R,S)-PMPA solution at a pH of about 2.7–3.5 wherein the solution has less than about 0.1 g/mL (R,S)-PMPA and wherein about 90–94% of the PMPA is in the (R) configuration.

Regarding claim 8, PMPA refers to (R)-9-[2-(Phosphonomethoxy)propyl]adenine.

Bischofberger’s teaching of bis(POC)PMPA would embrace the stereoisomers, in particular (R,S)-PMPA.

The Patent Owner in the ‘946 Patent (patent undergoing reexamination) in column 4, lines 50-58 makes the following admission:

“PMPA and bis(POC)PMPA are known to be useful in the treatment . . . of one or more viral infections in man or animals, including particularly retroviruses, HIV, SIV. . . .”

Accordingly, the Patent Owner admits that PMPA and bis(POC)PMPA are well known in the art to treat retrovirus, in particular HIV.

One having ordinary skill in the art at the time of the invention would have known that stereoisomers of a racemic compound, such as bis(POC)PMPA, would exhibit different biological (pharmaceutical) activities. In addition, isomers of a racemic compound are expected to have different activities, where one stereoisomer is expected to be more active than the other.

“[T]he physiological properties of two antipodes [stereo-isomers] can differ considerably,” giving as examples several pairs of optical isomers which differ substantially in their physiological effects. “The cause of the different physiological behavior,” it is said, “lies in the fact that many constituents of cells within the organism with which the substrates react are themselves asymmetric.” *In re Adamson and Duffin*, 275 F.2d 952, 124 USPQ 233-235 (CCPA 1960).

In the absence of evidence to the contrary, one having ordinary skill in the art would have recognized that enantiomeric (optical isomer) separation (enrichment) of a particular enantiomer is regarded as a routine separation procedure, thus allowing the skilled artisan with the necessary motivation to obtain (resolve) the enantiomeric compound of **claim 8** in enriched amounts. Pharmacological (biological) testing of the claimed compound would have been well within the purview of the skilled artisan, and as such the skilled artisan would have a reasonable expectation of success that the biological activities of the enantiomers of (R,S)-PMPA will vary in treating viruses due to the presence of an asymmetric (chiral) center on the bis(POC)PMPA compound.

The prior art of record is silent to the claim limitations that the (R,S)-PMPA solution has *a pH of about 2.7-3.5 wherein the solution has less than about 0.1 g/mL (R,S)-PMPA*. However,

it is well within the level of the skilled artisan to measure and manipulate general parameters and conditions (pH and solubility) of a product (solution).

“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Optimization Within Prior Art Conditions or Through Routine Experimentation. See MPEP 2144.05, section II, A.

Furthermore, the combined teachings of Bischofberger et al. or Patent Owner’s Admission, Gould, and Takashima et al., which rendered bis(POC)PMPA fumarate obvious, did not exclude an *(R,S)-PMPA solution at a pH of about 2.7-3.5 wherein the solution has less than about 0.1 g/mL (R,S)-PMPA and wherein about 90-94% of the PMPA is in the (R) configuration.* Accordingly, the claim limitations of **claim 8** are rendered obvious.

D) Independent claim 10 is rendered obvious.

10. A method comprising contacting bis(POC)PMPA with fumaric acid.

Regarding claim 10, Bischofberger et al. teach bis(POC)PMPA (See Abstract).

The Patent Owner in the ‘946 Patent (patent undergoing reexamination) in column 4, lines 50-58 makes the following admission:

“PMPA and bis(POC)PMPA are known to be useful in the treatment . . . of one or more viral infections in man or animals, including particularly retroviruses, HIV, SIV. . . .”

Accordingly, the Patent Owner admits that PMPA and bis(POC)PMPA are well known in the art to treat retrovirus, in particular HIV.

Gould teaches on page 202, 1st column that:

“It would seem sensible that any acid relating to normal metabolism, or present in food and drink can be regarded as a suitable candidate for preparing salts.”

Takashima et al. provide the motivation to combine Bischofberger et al. with Gould by teaching the creation of phosphonate-nucleotide fumaric salt compounds having superior oral administration characteristics in treating HIV (See page 2, lines 5-30; page 4, lines 41, 42, and 46; page 77, lines 1-11).

At the time of the invention, one having ordinary skill in the art would have found it obvious and motivated to combine the bis(POC)PMPA as disclosed by Bischofberger et al. or the Patent Owner's admission both in view of the general teachings of Gould regarding the benefits of using fumarate to form compounds with superior pharmaceutical characteristics and further in view of Takashima's teaching of using fumaric acid to form anti-HIV phosphonate-nucleotide salts tablets in order to arrive at the instantly claimed invention.

E) Independent claim 15 is rendered obvious.

15. A method comprising adjusting the pH of a solution comprising less than about 0.08 g/mL (R,S)-PMPA wherein about 90-94% of the PMPA is in the (R) configuration to a pH of about 2.7-3.5.

Regarding claim 15, PMPA refers to (R)-9-[2-(Phosphonomethoxy)propyl]adenine.

Bischofberger's teaching of bis(POC)PMPA would embrace the stereoisomers, in particular (R,S)-PMPA.

The Patent Owner in the '946 Patent (patent undergoing reexamination) in column 4, lines 50-58 makes the following admission:

“PMPA and bis(POC)PMPA are known to be useful in the treatment . . . of one or more viral infections in man or animals, including particularly retroviruses, HIV, SIV. . . .”

Accordingly, the Patent Owner admits that PMPA and bis(POC)PMPA are well known in the art to treat retrovirus, in particular HIV.

One having ordinary skill in the art at the time of the invention would have known that stereoisomers of a racemic compound, such as bis(POC)PMPA, would exhibit different biological (pharmaceutical) activities. In addition, isomers of a racemic compound are expected to have different activities, where one stereoisomer is expected to be more active than the other.

“[T]he physiological properties of two antipodes [stereo-isomers] can differ considerably,” giving as examples several pairs of optical isomers which differ substantially in their physiological effects. “The cause of the different physiological behavior,” it is said, “lies in the fact that many constituents of cells within the organism with which the substrates react are themselves asymmetric.” *In re Adamson and Duffin*, 275 F.2d 952, 124 USPQ 233-235 (CCPA 1960).

In the absence of evidence to the contrary, one having ordinary skill in the art would have recognized that enantiomeric (optical isomer) separation (enrichment) of a particular enantiomer is regarded as a routine separation procedure, thus allowing the skilled artisan with the necessary motivation to obtain (resolve) the enantiomeric compound of **claim 15** in enriched amounts. In addition, pharmacological (biological) testing of the claimed compound would have been well within the purview of the skilled artisan, and as such the skilled artisan would have a reasonable expectation of success that the biological activities of the enantiomers of (R,S)-PMPA will vary in treating viruses due to the presence of an asymmetric (chiral) center on the bis(POC)PMPA compound.

The prior art of record is silent with respect to the claim limitations that the (R,S)-PMPA solution has a pH of about 2.7-3.5 wherein the solution has less than about 0.1 g/mL (R,S)-PMPA. The step of adjusting the pH of a solution, such as a solution containing (R,S)-PMPA, is regarded as an optimization and well within the level of the skilled artisan. However, it is well within the level of the skilled artisan to measure and manipulate general parameters and conditions (pH and solubility) of a product (solution).

“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Optimization Within Prior Art Conditions or Through Routine Experimentation. See MPEP 2144.05, section II, A.

Furthermore, the combined teachings of Bischofberger et al. or Patent Owner's Admission, Gould, and Takashima et al., which rendered bis(POC)PMPA fumarate obvious, did not exclude an (R,S)-PMPA solution at a pH of about 2.7-3.5 wherein the solution has less than about 0.1 g/mL (R,S)-PMPA and wherein about 90-94% of the PMPA is in the (R) configuration. Accordingly, the claim limitations of claim 15 are rendered obvious.

F) Independent claim 19 is rendered obvious.

19. A product produced by the process of preparing wet granules from a mixture comprising a liquid, 9-[2-(R)-[[bis [[(isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]-adenine.fumaric acid (1:1) and a pharmaceutically acceptable excipient.

Regarding claim 19, this claim is defined as a product-by-process claim.

“[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is

unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1984).

Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. See MPEP 2113.

Bischofberger et al. teach bis(POC)PMPA (See Abstract).

The Patent Owner in the '946 Patent (patent undergoing reexamination) in column 4, lines 50-58 makes the following admission:

"PMPA and bis(POC)PMPA are known to be useful in the treatment . . . of one or more viral infections in man or animals, including particularly retroviruses, HIV, SIV. . . ."

Accordingly, the Patent Owner admits that PMPA and bis(POC)PMPA are well known in the art to treat retrovirus, in particular HIV.

Gould teaches on page 202, 1st column that:

"It would seem sensible that any acid relating to normal metabolism, or present in food and drink can be regarded as a suitable candidate for preparing salts."

Takashima et al. provide the motivation to combine Bischofberger et al. or Patent Owner's Admission with Gould by teaching the creation of phosphonate-nucleotide fumaric salt compounds having superior oral administration characteristics in treating HIV (See page 2, lines 5-30; page 4, lines 41, 42, and 46; page 77, lines 1-11). In addition, Takashima et al. expressly teach that various conventional pharmaceutically acceptable carriers and excipients are included, and that various dosage forms may be employed when preparing pharmaceuticals. In fact, Takashima et al. teach that tablets and powders are used when a solid carrier is used, and that syrups, soft gelatin capsules, and gels when a liquid carrier is used (See page 77, lines 1-11).

The determination of a dosage as well as processes of making pharmaceuticals (i.e., *preparing wet granules from a mixture comprising a liquid*) having the optimum therapeutic

index is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts, acceptable carriers and excipients, as well as preparation steps to get the maximum effect of the drug while minimizing adverse and/or unwanted side-effects. At the time of the invention, one having ordinary skill in the art would have found it obvious and motivated to combine the bis(POC)PMPA as disclosed by Bischofberger et al. or the Patent Owner's admission both in view of the general teachings of Gould regarding the benefits of using fumarate to form compounds with superior pharmaceutical characteristics and further in view of Takashima's teaching of using fumaric acid to form anti-HIV phosphonate-nucleotide salts tablets in order to arrive at the instantly claimed invention.

As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 699 (CCPA 1972).

Accordingly, the combined teachings of Bischofberger et al. or Patent Owner's Admission, Gould, and Takashima et al., which rendered bis(POC)PMPA fumarate obvious, also render the product-by-process as defined in **claim 19** obvious to one having ordinary skill in the art.

G) Dependent claim 20 is rendered obvious.

Regarding claim 20, this claim depends on the product-by-process defined in **claim 19**.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1984).

Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. See MPEP 2113.

Takashima et al. expressly teach that various conventional pharmaceutically acceptable carriers and excipients are included, and that various dosage forms may be employed when preparing pharmaceuticals. Takashima et al. also teach that tablets and powders are used when a solid carrier is used, and that syrups, soft gelatin capsules, and gels when a liquid carrier is used (See page 77, lines 1-11). In particular, Takashima et al. expressly teach the use of water when making pharmaceutical preparations of phosphonate-nucleotide fumaric salt compounds (See page 77, line 9).

The determination of a dosage as well as processes of making pharmaceuticals having the optimum therapeutic index is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts, acceptable carriers and excipients, as well as preparation steps to get the maximum effect of the drug while minimizing adverse and/or unwanted side-effects. At the time of the invention, one having ordinary skill in the art would have found it obvious and would have been motivated to combine the bis(POC)PMPA as disclosed by Bischofberger et al. or the Patent Owner's admission both in view of the general teachings of Gould regarding the benefits of using fumarate to form compounds with superior pharmaceutical characteristics and further in view of Takashima's teaching of using fumaric acid to form anti-HIV phosphonate-nucleotide salts tablets and preparation of drying wet granules from the pharmaceutical composition in order to arrive at the instantly claimed invention. Thus, the teachings of Bischofberger et al. or the Patent Owner's admission in view of Gould and Takashima et al. show dry forms (tablets, powder or granules) of the active ingredient,

bis(POC)PMPA fumarate, and render the product-by-process as defined in **claim 20** obvious to one having ordinary skill in the art.

6. **Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arimilli et al. (U.S. Patent No. 5,922,695) in view of PHARMACEUTICAL EXCIPIENTS (Handbook of PHARMACEUTICAL EXCIPIENTS, pages 153-162, 296-297, 1986), Remington's Pharmaceutical Sciences (Osol et al., Editor, Remington's Pharmaceutical Sciences, Sixteenth Edition, pages 1554-1557, 1980), and MARTINDALE (MARTINDALE, The Extra Pharmacopoeia, Twenty-eighth Edition, pages 950-951, 1982).**

A) Independent claim 16 is rendered obvious.

16. A composition comprising a tablet containing 9-[2-(R)-[[bis[[isopropoxycarbonyl]oxy]methoxy]phosphinoyl]methoxy]propyl]-adenine.fumaric acid (1:1), pregelatinized starch, croscarmellose sodium, lactose monohydrate and magnesium stearate.

Regarding claim 16, bis(POC)PMPA represents

9-[2-(R)-[[bis[[isopropoxycarbonyl]oxy]methoxy]phosphinoyl]methoxy]propyl]adenine fumarate and that fumarate is the conjugate acid of fumaric acid. Arimilli et al. expressly disclose bis(POC)PMPA fumarate (See column 44, line 65). Arimilli et al. expressly teach that formulations of bis(POC)PMPA fumarate can be presented as "capsules, cachet or tablets" (See column 35, lines 59-62). Arimilli et al. teach in column 35, lines 37-44 pharmaceutical formulations of bis(POC)PMPA fumarate:

"compris[ing] at least one active ingredient . . . together with one or more acceptable carriers and optionally other therapeutic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient."

Arimilli et al. further teach in column 38, lines 14-19 that,

“[i]n addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.”

Although Arimilli et al. do not expressly recite the claimed ratio of 1:1, Arimilli et al. teach the presence of bis(POC)PMPA fumarate crystals (See column 45, lines 50-65). In the absence of specifying the ratio amount of bis(POC)PMPA to the fumarate, it is assumed that a ratio of 1:1 is inherently present in Arimilli et al. because Arimilli et al. do in fact teach the generation of a crystal having 1 bis(POC)PMPA to 1 fumarate. Moreover, when a coefficient is absent before a product (compound) or unit the coefficient is regarded as single unitary placeholder, in other words it would represent the number one (1), thus meeting the claimed limitation.

“[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom.” *In re Preda*, 401 F.2d 825, 826, 159 UQPQ 342, 344 (CCPA 1986).

The claimed subject matter differs from the teachings of Arimilli et al. by requiring the bis(POC)PMPA fumaric acid to be present in a tablet containing *pregelatinized starch, croscarmellose sodium, lactose monohydrate and magnesium stearate*. However, Arimilli et al. teach the oral administration of bis(POC)PMPA fumarate (conjugate salt of fumaric acid) as a tablet and further teach to the skilled artisan that formulations may include other conventional agents (carriers, excipients, and diluents) known in the art, which are suitable for oral administration.

PHARMACEUTICAL EXCIPIENTS teach using the excipient of pregelatinized starch in pharmaceutical formulations in amounts (concentration) ranging from 5-20% of the pharmaceutical composition (See pages 296-297, in particular part 17 on page 297).

PHARMACEUTICAL EXCIPIENTS also teach the use of lactose (α -monohydrate lactose) in solid dosage forms (See pages 153, 155, 161, and 162).

Remington's Pharmaceutical Sciences teach that lactose can be present as a pharmaceutically acceptable excipient (diluent or binders) in compressed tablets for a variety of reasons in various quantities for the desired properties. For example, excipients are known to increase the bulk to make a tablet a more practical size for compression when the dose of the active ingredient is small as a diluent; impart a cohesiveness to the tablet formulation which insures the tablet remaining intact after compression, or excipients can improve the free-flowing qualities by formulation of granules of desired hardness and size as a binder (See page 1555). Remington's Pharmaceutical Sciences also teach that magnesium stearate is a commonly used pharmaceutically acceptable excipient in tablet manufacturing, which can be present in amounts ranging from 0.1% to 5% (See page 1556, 1st column).

MARTINDALE teach the use of croscarmellose sodium (carmellose sodium or modified cellulose gum) as a pharmaceutically acceptable excipient (disintegrant or suspending agent), which can be present in amounts ranging from 0.25% to 6% (See pages 950 -951 for compound no. 5411-b).

The determination of a dosage of an active agent or a pharmaceutically acceptable excipient as well as processes of making pharmaceuticals having the optimum therapeutic index are well within the purview of the skilled artisan, and the artisan would be motivated to

determine optimum amounts, acceptable carriers and excipients, in order to get the maximum effect of the drug while minimizing adverse and/or unwanted side-effects. At the time of the invention, one having ordinary skill in the art would have found it obvious to combine the bis(POC)PMPA fumaric acid as disclosed by Arimilli et al. with known conventional agents (carriers, excipients, and diluents) provided that they are pharmaceutically acceptable as exemplified in the PHARMACEUTICAL EXCIPIENTS, Remington's Pharmaceutical Sciences, and MARTINDALE. A person of ordinary skill in the art would have been motivated to use the prior art teachings of PHARMACEUTICAL EXCIPIENTS, Remington's Pharmaceutical Sciences, and MARTINDALE for using conventional pharmaceutically acceptable excipients, in particular *pregelatinized starch, croscarmellose sodium, lactose monohydrate and magnesium stearate*, along with the bis(POC)PMPA fumarate as taught by Arimilli et al. with the expectation of successfully making pharmaceutically acceptable formulations with increased tablet cohesiveness or increased tablet (bulk) size, or even improved free-flowing properties. Thus the combination of these references meet the limitations of **claim 16**.

B) Dependent claims 17-18 are rendered obvious.

Regarding claim 17, Arimilli et al. teaches bis(POC)PMPA as stated *supra*. In addition, Arimilli et al. expressly disclosed bis(POC)PMPA fumarate as a crystalline solid (See column 44, line 65; column 45, lines 50-65).

PHARMACEUTICAL EXCIPIENTS, Remington's Pharmaceutical Sciences, and MARTINDALE teach the pharmaceutically known excipients of *pregelatinized starch, croscarmellose sodium, lactose monohydrate and magnesium stearate* as stated *supra*.

Regarding claim 18, Arimilli et al. teach bis(POC)PMPA fumaric acid as stated *supra*. In addition, Arimilli et al. expressly disclosed bis(POC)PMPA fumarate as a crystalline solid (See column 44, line 65; column 45, lines 50-65). Arimilli et al. expressly teach the administration of 75 mg of PMPA carbonates (See column 52, lines 43-67; column 54, lines 21-23).

PHARMACEUTICAL EXCIPIENTS, Remington's Pharmaceutical Sciences, and MARTINDALE teach the pharmaceutically known excipients of *pregelatinized starch*, *croscarmellose sodium*, *lactose monohydrate* and *magnesium stearate* in various amounts (concentrations) as stated *supra*.

The claimed subject matter is directed to a tablet in the specified amounts of 75 mg 9-[2-(R)-[[bis[[isopropoxycarbonyl]oxy]methoxy]phosphinoyl]methoxy]propyl]adenine · fumaric acid (1.1), 11 mg *pregelatinized starch*, 8.8 mg *croscarmellose sodium*, 123.6 mg *lactose monohydrate* and 2.2 mg *magnesium stearate*. Optimization of the amount is well within the purview of the skilled artisan.

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Optimization Within Prior Art Conditions or Through Routine Experimentation. See MPEP 2144.05, section II, A.

Thus, the amounts listed in **claim 18** are not inventive because one of ordinary skill in the art could, through routine experimentation, adjust the amounts of the excipients relative to the active agent in order to determine the optimal amounts thereof.

Moreover, MPEP 2144.05, section II, B states that a claimed range is not inventive when it comprises a result-effective variables, i.e., variables which achieve a well-recognized result. The determination of an amount or concentration of a pharmaceutically acceptable agent (carrier, excipient, or diluent) is regarded as a being comprised of variables which achieve a well-recognized result that can optimized to produce pharmaceutically acceptable formulations (1) with increased tablet cohesiveness, (2) increased tablet (bulk) size, or (3) even to improve the free-flowing qualities by formulation of granules of desired hardness and size as taught by PHARMACEUTICAL EXCIPIENTS, Remington's Pharmaceutical Sciences, and MARTINDALE. The selection and determination of a dosage (amount) and processes of making pharmaceuticals with conventional excipients having the optimum therapeutic index is well within the skill level of one having ordinary skill in the art. The skilled artisan would be motivated to determine optimum amounts, acceptable carriers and excipients to get the maximum effect of the drug while minimizing adverse and/or unwanted side-effects.

Absent a showing of unexpected results of criticality regarding the specified amounts of the active agent and the claimed pharmaceutically acceptable excipients the skilled artisan would have found it obvious and motivated to optimize the amounts (concentrations) of the active agent and the pharmaceutically acceptable excipients through routine experimentation to arrive at the instant invention by (1) increased tablet cohesiveness, (2) increased tablet (bulk) size, or (3) even to improve the free-flowing qualities by formulation of granules of desired hardness and size. Thus, the claimed amounts are not deemed inventive. It has been held that discovering an optimum value of a result effective variable in a known process involves only

routine skill in the art, *In re Boesch*, 617 F.2d 272, 205, USPQ 215 (CCPA 1980). See MPEP 2144.05, section IIB.

Conclusion

7. Claims 1-20 are pending and undergoing *Ex Parte* Reexamination.
8. Claims 1-20 are rejected.

Extensions of Time

Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that *Ex Parte* reexamination proceedings "will be conducted with special dispatch" (37 CFR 1.550(a)). Extensions of time in *Ex Parte* reexamination proceedings are provided for in 37 CFR 1.550(c).

Future Amendment

Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

In particular, 37 CFR 1.530(i) states: "All amendments must be made relative to the patent specification, including the claims, and drawings, which are in effect as of the date of filing the request for reexamination." As a result each amendment to the claims should be made relative to the originally patented claims and not to the previous amendment. Any changes must include brackets (not strikethroughs) for the matter to be omitted and underlining for added matter (See 37 CFR 1.530(f)(1)(2)). The Patent Owner is directed to MPEP 2250 (IV) containing examples of claim amendments in reexamination proceedings.

Please provide a complete listing of all pending claims and their respective status (i.e., original, cancelled, amended, new) undergoing reexamination that complies with 37 CFR 1.530(d)-(j).

Ongoing Duty to Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 5,935,946 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Service of Papers

After the filing of a request for reexamination by a third party requester, any document filed by either the patent owner or the third party requester must be served on the other party (or parties where two or more third party requester proceedings are merged) in the reexamination proceeding in the manner provided in 37 CFR 1.248 (See 37 CFR 1.550(f)).

NOTICE RE PATENT OWNER'S CORRESPONDENCE ADDRESS

Effective May 16, 2007, 37 CFR 1.33(c) has been revised to provide that:

The patent owner's correspondence address for all communications in an *ex parte* reexamination or an *inter partes* reexamination is designated as the correspondence address of the patent.

Revisions and Technical Corrections Affecting Requirements for Ex Parte and Inter Partes Reexamination, 72 FR 18892 (April 16, 2007)(Final Rule)

The correspondence address for any pending reexamination proceeding not having the same correspondence address as that of the patent is, by way of this revision to 37 CFR 1.33(c), automatically changed to that of the patent file as of the effective date.

This change is effective for any reexamination proceeding which is pending before the Office as of May 16, 2007, including the present reexamination proceeding, and to any reexamination proceeding which is filed after that date.

Parties are to take this change into account when filing papers, and direct communications accordingly.

In the event the patent owner's correspondence address listed in the papers (record) for the present proceeding is different from the correspondence address of the patent, it is strongly encouraged that the patent owner affirmatively file a Notification of Change of Correspondence Address in the reexamination proceeding and/or the patent (depending on which address patent owner desires), to conform the address of the proceeding with that of the patent and to clarify the record as to which address should be used for correspondence.

Telephone Numbers for reexamination inquiries:

| | |
|--|----------------|
| Reexamination and Amendment Practice | (571) 272-7703 |
| Central Reexam Unit (CRU) | (571) 272-7705 |
| Reexamination Facsimile Transmission No. | (571) 273-9900 |

Future Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays-Thursdays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones, may be reached at (571) 272-1535. The official fax No. for the organization where this application is assigned is (571)-273-9900. For status inquiries of a general nature refer to the customer service line at (571) 272-7705.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see <http://pair-direct.uspto.gov> Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 1-866-217-9197 (toll free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

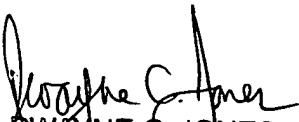
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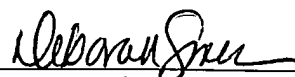
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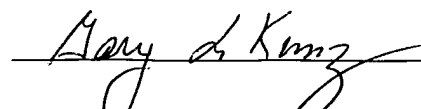
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