

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT NO.: 5,935,946
ISSUED: Aug. 10, 1999
TO: Munger, Jr. et al.
FOR: NUCLEOTIDE ANALOG COMPOSITION
AND SYNTHESIS METHOD

ATTACHMENT TO FORM PTO-1465,
REQUEST FOR *EX PARTE* REEXAMINATION

SIR:

The Public Patent Foundation (“PUBPAT”), a not-for-profit public service organization that works to protect the public from the harms caused by undeserved patents and unsound patent policy, respectfully requests *ex parte* reexamination under 35 U.S.C. §§ 302 – 307 and 37 C.F.R. § 1.510 of every claim of United States Patent No. 5,935,946 issued August 10, 1999, to Munger, Jr. et al. and assigned to Gilead Sciences, Inc. (“the '946 patent”) because they are all invalid under 35 U.S.C. §§ 102 and 103 and their existence is causing significant public harm.¹

¹ A copy of the '946 patent is attached hereto as Appendix A.

THE '946 PATENT IS CAUSING SIGNIFICANT PUBLIC HARM

HIV/AIDS is one of the greatest threats to public health faced by the world today. As of November 2006, roughly 40 million people worldwide were living with HIV/AIDS, including more than 1.2 million Americans.² Every person afflicted with HIV/AIDS has the right to obtain the best medical treatment available, without any improper obstacles placed in their way. More specifically, American men, women and children suffering from HIV/AIDS are entitled to access the best pharmaceutical treatments available without undeserved patents making those treatments either too expensive or too limited in supply.

Tenofovir disoproxil fumarate (also referred to as “TDF”, “bis(POC)PMPA fumarate” or “BPPF”) is a nucleotide analogue reverse transcriptase inhibitor (“NtRTI”) that is a significant treatment for HIV/AIDS. The '946 patent claims TDF, methods of making TDF and tablets containing TDF. Gilead is using the '946 patent – and three other patents for which requests for reexamination are being filed concurrently herewith – to prevent anyone else from offering TDF to HIV/AIDS patients in the United States.³ Not only is the '946 patent being used to deny American HIV/AIDS patients fair access to the medical treatment that they need and deserve, it is also a barrier to further research on TDF here in the United States because there is no exception to patent infringement for such research. In these ways, the '946 patent is unquestionably causing

² *HIV/AIDS Policy Fact Sheets*, The Henry J. Kaiser Family Foundation, November 2006, available from <http://www.kff.org/hiv/aids/index.cfm>.

³ Approved Drug Products with Therapeutic Equivalence Evaluations, Food and Drug Administration (“Orange Book”).

significant public harm to the American people.

Although these issues are not grounds to grant this request for reexamination, PUBPAT respectfully requests that they be considered when determining whether the validity of the '946 patent merits review by your office.

THE SUBSTANTIAL NEW QUESTIONS OF PATENTABILITY

The substantial new questions of patentability raised by this request are the following:

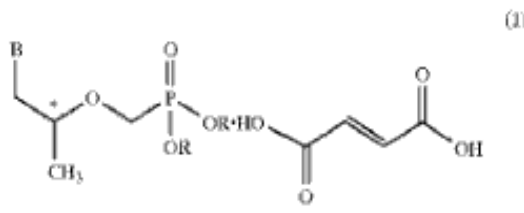
1. Whether claims 1 – 20 of the '946 patent were anticipated by U.S. Patent No. 5,922,695 issued to Arimilli et al. on July 13, 1999 (“Arimilli”); and
2. Whether claims 1 – 20 of the '946 patent were rendered obvious by Bischofberger et al., “Bis(POC)PMPA, an Orally Bioavailable Prodrug of the Antiretroviral Agent PMPA,” *Conference on Retroviruses and Opportunistic Infections*, 4th:104 (abstract no. 214) (January 22-26, 1997) (“Bischofberger”), in light of Gould, “Salt Selection for Basic Drugs,” *International Journal of Pharmaceutics*, 33:201-271 (1986) (“Gould”), and EP 0632048 to Takashima et al. published January 4, 1995 (“Takashima”).

These are new questions because Arimilli was not addressed and neither Bischofberger, Gould nor Takashima were of record during prosecution of the '946 patent application. A detailed explanation of the pertinency and manner of applying the cited patents and publications to the claims of the '946 patent is set forth below.⁴

⁴ Appendix B contains a copy of the cited patents and publications.

ARIMILLI ANTICIPATED THE '946 PATENT

The '946 patent was filed July 25, 1997. Since Arimilli claims priority to an application filed July 26, 1996, Arimilli is prior art to the '946 patent under 35 U.S.C. § 102(e). The chart below sets forth an element-by-element comparison of all 20 claims of the '946 patent to the teachings of Arimilli. In essence, every element of each claim of the '946 patent was anticipated by Arimilli. As such, each claim of the '946 patent is invalid and should be canceled.

| '946 Patent | Arimilli |
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| <p>1. A composition of formula (1)</p>  <p>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.</p> | <p>The '946 patent defines “formula (1)” as “bis(POC)PMPA fumarate.” '946 patent, 1:29-45. Arimilli expressly disclosed bis(POC)PMPA fumarate. Arimilli, 44:65 – 45:66.</p> |
| <p>2. The composition of claim 1 wherein both R are --CH₂ --O--C(O)--O--CH(CH₃)₂.</p> | <p>Arimilli's teaching of bis(POC)PMPA fumarate did not exclude both R's from being --CH₂ --O--C(O)--O--CH(CH₃)₂.</p> |

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| <p>3. The composition of claim 1 wherein the composition is a crystalline solid.</p> | <p>Arimilli expressly taught bis(POC)PMPA fumarate as a crystalline solid. 45:50-65 (“The filter cake, which is at no more than 40° C., is dried in vacuo for about 1 to 3 days and the dried product is optionally milled (Fitzmill M5A fitted with a 0.050" screen), affording bis(POC)PMPA fumarate as white, fine, powder-like crystals of about 97.0 to 99.5% purity.”).</p> |
| <p>4. The composition of claim 1 wherein the compound is enriched or resolved at the carbon atom chiral center (*).</p> | <p>Arimilli expressly taught “compounds ... optionally enriched or resolved at the carbon atom chiral center.” 6:46-65.</p> |
| <p>5. The composition of claim 1 having an X-ray powder diffraction spectrum peak using Cu-Kα radiation, expressed in degrees 2Θ at about 25.0.</p> | <p>Arimilli's teaching did not exclude bis(POC)PMPA fumarate having an X-ray powder diffraction spectrum peak using Cu-Kα radiation, expressed in degrees 2Θ at about 25.0. Further, this is merely a descriptive attribute with no functional effect.</p> |
| <p>6. A composition comprising the composition of claim 1 and an acceptable excipient.</p> | <p>The '946 patent defines “excipient” to be synonymous with “carrier.” '946 patent, 5:19-25 (“The formulations of the present invention comprise BPPF, together with one or more pharmaceutically acceptable excipients or carriers ('acceptable excipients')). Arimilli expressly taught pharmaceutical formulations of bis(POC)PMPA fumarate “compris[ing] at least one active ingredient ... together with one or more acceptable carriers.” 35:37-44.</p> |
| <p>7. A composition comprising a lithium alkoxide and a 9-(2-hydroxypropyl)adenine solution.</p> | <p>Arimilli expressly taught a composition comprising a lithium alkoxide and a 9-(2-hydroxypropyl)adenine solution. 40:53-54 and 42:32-44.</p> |

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| <p>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.</p> | <p>Arimilli's teaching 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. Further, Arimilli expressly taught a composition with about 90-94% of the PMPA in the (R) configuration. 6:50-52 and 61:12-13.</p> |
| <p>9. A method comprising orally administering to a patient infected with virus or at risk to viral infection a therapeutically effective amount of a composition of claim 1.</p> | <p>Arimilli expressly taught orally administering bis(POC)PMPA fumarate to treat viral infections in man or animals. 32:41-45 and 34:43-50 and 62-67.</p> |
| <p>10. A method comprising contacting bis(POC)PMPA with fumaric acid.</p> | <p>Arimilli expressly taught contacting bis(POC)PMPA with fumaric acid. 3:48, 34:38-41, 38-39:Example 1 and 45:34-36.</p> |
| <p>11. The method of claim 10 wherein the fumaric acid is dissolved in 2-propanol.</p> | <p>Arimilli expressly taught fumaric acid dissolved in 2-propanol. 45:34-37.</p> |
| <p>12. A method comprising mixing a lithium alkoxide with a 9-(2-hydroxypropyl)adenine solution.</p> | <p>Arimilli expressly taught mixing a lithium alkoxide and a 9-(2-hydroxypropyl)adenine solution. 40:53-54 and 42:32-44.</p> |
| <p>13. The method of claim 12 wherein the lithium alkoxide is an alkoxide selected from the group consisting of methoxide, ethoxide, n-propoxide, i-propoxide, n-butoxide, i-butoxide, t-butoxide, neopentoxide, n-pentoxide, i-pentoxide or n-hexoxide, n-heptoxide, 2-heptoxide, n-octoxide, 2-octoxide, typically t-butoxide or i-propoxide.</p> | <p>Arimilli expressly taught lithium alkoxide included "alkyl containing 1, 2, 3, 4, 5 or 6 carbon atoms, e.g., n-hexoxide, n-pentoxide, n-butoxide, i-butoxide, t-butoxide, n-propoxide, i-propoxide, ethoxide, methoxide." 39:56-59.</p> |
| <p>14. The method of claim 13 wherein the lithium alkoxide is lithium t-butoxide or lithium i-propoxide.</p> | <p>Arimilli expressly taught lithium alkoxide could be "t-butoxide [or] i-propoxide." 39:56-59.</p> |

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| <p>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.</p> | <p>Arimilli's teaching did not exclude 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. Further, Arimilli expressly taught a composition with about 90-94% of the PMPA in the (R) configuration. 6:50-52 and 61:12-13.</p> |
| <p>16. A composition comprising a tablet containing 9-[2-(R)-[[bis[[isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]-adenine.fumaric acid (1:1),</p> | <p>The '946 patent defines "9-[2-(R)-[[bis[[isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]-adenine.fumaric acid (1:1)" as "bis(POC)PMPA fumarate." '946 patent, 1:29-45. Arimilli expressly taught that formulations of bis(POC)PMPA fumarate could be presented as "capsules, cachets or tablets." 35:59-62.</p> |
| <p>pregelatinized starch, croscarmellose sodium, lactose monohydrate and magnesium stearate.</p> | <p>Arimilli expressly taught 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." 35:37-44. Arimilli continued to teach that "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." 38:15-19. Pregelatinized starch, croscarmellose sodium, lactose monohydrate and magnesium stearate were well know by those of ordinary skill in the art at the time the application for the '946 patent was filed to be acceptable carriers and agents for oral administration tablets.</p> |

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| <p>17. The composition of claim 16 wherein the 9-[2-(R)-[[bis[[isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]-adenine.fumaric acid (1:1) is crystalline.</p> | <p>Arimilli expressly taught bis(POC)PMPA fumarate as a crystalline solid. 45:50-65 (“The filter cake, which is at no more than 40° C., is dried in vacuo for about 1 to 3 days and the dried product is optionally milled (Fitzmill M5A fitted with a 0.050" screen), affording bis(POC)PMPA fumarate as white, fine, powder-like crystals of about 97.0 to 99.5% purity.”).</p> |
| <p>18. The composition of claim 16 wherein the tablet contains 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.</p> | <p>Arimilli's teaching of bis(POC)PMPA fumarate tablets did not exclude those containing 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.</p> |
| <p>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.</p> | <p>Arimilli's expressly taught making bis(POC)PMPA fumarate products with acceptable excipients (“carriers”). Specifically, Arimilli taught “[t]he formulations ... are prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.” 35:49-59.</p> |
| <p>20. The product of claim 19 wherein the liquid is water and the process optionally further comprises drying the wet granules.</p> | <p>It is inherent in Arimilli's teachings that the liquid could be water and that the process could include drying the wet granules.</p> |

**BISCHOFBERGER, IN LIGHT OF GOULD AND TAKASHIMA,
RENDERED THE '946 PATENT OBVIOUS**

In addition to being anticipated by Arimilli, the '946 patent was also obvious in light of other prior art teachings that PMPA and bis(POC)PMPA were strong treatments for HIV and that bis(POC)PMPA fumarate would have been expected to have superior properties over free base bis(POC)PMPA.

PMPA and bis(POC)PMPA Were Well Known Treatments for HIV

The '946 patent concedes that “PMPA and bis(POC)PMPA were known to be useful in the treatment [of] viral infections, ... including particularly ... HIV.” '946 patent, 4:50-54. Several references confirm this concession regarding the advanced state of the art relating to PMPA and bis(POC)PMPA as treatments for HIV/AIDS before the filing of the '946 patent application.

For example, 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) (“Bischofberger”) is prior art to the '946 patent under 35 U.S.C. § 102(a). Bischofberger taught bis(POC)PMPA that was “chemically stable in solution over a broad pH range.” Bischofberger further taught that “oral administration of bis(POC)PMPA resulted in significantly delayed tumor appearance.” Bischofberger concluded that “bis(POC)PMPA is a promising agent for the treatment and prophylaxis of HIV infections.”

Since PMPA and bis(POC)PMP were already well known, the '946 patent application directed itself to the purported invention of bis(POC)PMPA fumarate (“BPPF”) and

claimed that making a fumaric salt from bis(POC)PMPA was an advance worthy of patenting because “[c]rystalline BPPF has an unexpectedly superior combination of physico-chemical properties compared to the free base and other salts.” '946 patent, 3:21-23. As a result, the claims of the '946 patent are directed to (i) bis(POC)PMPA fumarate (“BPPF”), (ii) a method of making BPPF by “contacting bis(POC)PMPA with fumaric acid,” and (iii) tablets or products containing BPPF.

One of Ordinary Skill in the Art Would Have Expected BPPF to Have Superior Properties

While it is true that BPPF is superior to either the free base or other salts of PMPA or bis(POC)PMPA, contrary to the '946 patent's assertions, this was not a surprising result. In fact, it would have been obvious to one of ordinary skill in the art at the time the '946 patent application was filed that the formation of pharmaceutically acceptable salts of compounds and their crystalline form – such as the preparation of fumaric acid salts for phosphonate nucleotide esters like bis(POC)PMPA as claimed in the '946 patent – would achieve superior results. This knowledge and expectation of superior results would provide the necessary motivation to one of ordinary skill in the art to combine the prior art teachings of PMPA and bis(POC)PMPA with other prior art teachings of pharmaceutical salt selection, including specifically the following references.

Gould, "Salt Selection for Basic Drugs," *International Journal of Pharmaceutics*, 33:201-271 (1986) (“Gould”) is prior art to the '946 patent under 35 U.S.C. § 102(b). Gould expressly taught that “[i]t would seem sensible that any acid relating to normal metabolism, or

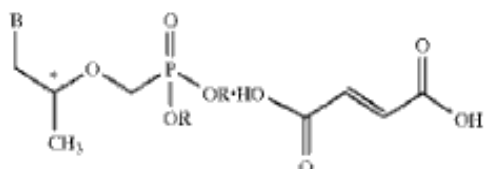
present in food and drink can be regarded as a suitable candidate for preparing salts.” 202. Gould then continued in Table 1 to provide a list of such acids, where he specifically identified “fumarate.” Thus, it was well known that fumaric acid was a good candidate for pharmaceutical salt formation.

This general understanding was confirmed to have specific applicability to phosphonate-nucleotide esters by EP 0632048 to Takashima et al. published January 4, 1995 (“Takashima”), which is prior art to the '946 patent under 35 U.S.C. § 102(b). Takashima taught the formation of pharmaceutically acceptable acid salts for phosphonate-nucleotide esters that have effective anti-HIV activity. 1:11-16 and 4:40-41. Specifically, Takashima taught the use of fumarate in the formation of such salts in order to achieve superior oral administration characteristics. 4:46 and 77:1-3. Therefore, although Takashima may not have specifically disclosed PMPA, it nonetheless provided more than sufficient motivation and 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 over a free base phosphonate-nucleotide ester form.

Further, with respect the claims of the '946 patent relating to excipients, Takashima expressly taught the creation of phosphonate-nucleotide fumaric salt compounds with pharmaceutically acceptable carriers. 77:4-9. Takashima also expressly taught producing such compositions as tablets and other products. 77:10-11. Methods for obtaining a crystalline form of a

salt was also well known in the art at the time the application for the '946 patent was filed.

The chart below sets forth an element-by-element comparison of all 20 claims of the '946 patent to the teachings of Bischofberger, in light of Gould and Takashima. In essence, Bischofberger's teaching of bis(POC)PMPA, in light of Gould's general teaching of the benefits of using fumarate to form compounds with superior pharmaceutical characteristics and Takashima's teaching of using fumaric acid to form anti-HIV phosphonate-nucleotide salts tablets that are preferable for oral administration, rendered each of the '946 patent's claims obvious. As such, each claim of the '946 patent is invalid and should be canceled.

| '946 Patent | <i>Bischofberger, with Gould and Takashima</i> |
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| <p>1. A composition of formula (1)</p>  <p>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.</p> | <p>The '946 patent defines “formula (1)” as “bis(POC)PMPA fumarate.” '946 patent, 1:29-45. Bischofberger taught bis(POC)PMPA. Bischofberger, 1. Gould taught that fumarate was a suitable candidate for preparing salts for drugs. Gould, 202. Takashima provided the motivation to combine Bischofberger with Gould by teaching the creation of phosphonate-nucleotide fumaric salt compounds. 77:4-9. Thus, one of ordinary skill in the art would have not only expected to be able to create bis(POC)PMPA fumarate, but would have also been expressly motivated to do so.</p> |

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| <p>2. The composition of claim 1 wherein both R are --CH₂ --O--C(O)--O--CH(CH₃)₂.</p> | <p>Bischofberger's teaching of bis(POC)PMPA did not exclude both R's from being --CH₂ --O--C(O)--O--CH(CH₃)₂.</p> |
| <p>3. The composition of claim 1 wherein the composition is a crystalline solid.</p> | <p>Inherent in Takashima's teaching of phosphonate-nucleotide fumaric salt compounds as tablets and other products is that the composition could be in crystalline form. 77:10-11. Further, methods for obtaining a crystalline form of a salt was also well known in the art at the time the application for the '946 patent was filed.</p> |
| <p>4. The composition of claim 1 wherein the compound is enriched or resolved at the carbon atom chiral center (*).</p> | <p>The combined teachings of Bischofberger, Gould and Takashima, which rendered bis(POC)PMPA fumarate obvious, did not exclude compounds optionally enriched or resolved at the carbon atom chiral center. In fact, one of ordinary skill in the art would have been motivated to create such compounds in order to achieve their expected benefits, which would not have been surprising.</p> |
| <p>5. The composition of claim 1 having an X-ray powder diffraction spectrum peak using Cu-Kα radiation, expressed in degrees 2θ at about 25.0.</p> | <p>The combined teachings of Bischofberger, Gould and Takashima, which rendered bis(POC)PMPA fumarate obvious, did not exclude bis(POC)PMPA fumarate having an X-ray powder diffraction spectrum peak using Cu-Kα radiation, expressed in degrees 2θ at about 25.0. Further, this is merely a descriptive attribute with no functional effect.</p> |
| <p>6. A composition comprising the composition of claim 1 and an acceptable excipient.</p> | <p>Takashima expressly taught producing compositions with acceptable excipients. 77:4-9.</p> |

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| <p>7. A composition comprising a lithium alkoxide and a 9-(2-hydroxypropyl)adenine solution.</p> | <p>Bischofberger's teaching of bis(POC)PMPA inherently discloses compositions comprising PMPA, which the '946 patent concedes is produced through a process which includes a composition comprising a lithium alkoxide and a 9-(2-hydroxypropyl) adenine solution. Bischofberger, 1; '946 patent, 12:13-38. Further, Bischofberger's teaching did not exclude compositions comprising a lithium alkoxide and a 9-(2-hydroxypropyl)adenine solution.</p> |
| <p>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.</p> | <p>Bischofberger's teaching of bis(POC)PMPA inherently discloses compositions comprising PMPA, which the '946 patent concedes is produced through a process which includes 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. Bischofberger, 1; '946 patent, 13:35-53. Further, Bischofberger's teaching did not exclude compositions 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.</p> |
| <p>9. A method comprising orally administering to a patient infected with virus or at risk to viral infection a therapeutically effective amount of a composition of claim 1.</p> | <p>Takashima expressly taught that phosphonate-nucleotide fumaric salt compounds for the treatment of HIV could be orally administered to a human patient. 2:11-16 and 77:1.</p> |

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| <p>10. A method comprising contacting bis(POC)PMPA with fumaric acid.</p> | <p>Bischofberger taught bis(POC)PMPA. Bischofberger, 1. Gould taught that fumarate was a suitable candidate for preparing salts for drugs. Gould, 202. Takashima provided the motivation to combine Bischofberger with Gould by teaching the creation of phosphonate-nucleotide fumaric salt compounds. 77:4-9. Thus, one of ordinary skill in the art would have not only expected to be able to create bis(POC)PMPA fumarate, but would have also been expressly motivated to do so.</p> |
| <p>11. The method of claim 10 wherein the fumaric acid is dissolved in 2-propanol.</p> | <p>It would have been obvious to one of ordinary skill in the art at the time the '946 patent application was filed that, when contacting bis(POC)PMPA with fumaric acid, one could dissolve the fumaric acid in 2-propanol. Further, such dissolution would produce no unexpected superior results.</p> |
| <p>12. A method comprising mixing a lithium alkoxide with a 9-(2-hydroxypropyl)adenine solution.</p> | <p>Bischofberger's teaching of bis(POC)PMPA inherently discloses compositions comprising PMPA, which the '946 patent concedes is produced through a method which includes mixing a lithium alkoxide and a 9-(2-hydroxypropyl) adenine solution. Bischofberger, 1; '946 patent, 12:13-38.</p> |
| <p>13. The method of claim 12 wherein the lithium alkoxide is an alkoxide selected from the group consisting of methoxide, ethoxide, n-propoxide, i-propoxide, n-butoxide, i-butoxide, t-butoxide, neopentoxide, n-pentoxide, i-pentoxide or n-hexoxide, n-heptoxide, 2-heptoxide, n-octoxide, 2-octoxide, typically t-butoxide or i-propoxide.</p> | <p>It is inherent in Bischofberger's teaching that the lithium alkoxide could be an alkoxide selected from the group consisting of methoxide, ethoxide, n-propoxide, i-propoxide, n-butoxide, i-butoxide, t-butoxide, neopentoxide, n-pentoxide, i-pentoxide or n-hexoxide, n-heptoxide, 2-heptoxide, n-octoxide, 2-octoxide, typically t-butoxide or i-propoxide. Further, selection of any of these alkoxides would not produce unexpected superior results.</p> |

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| <p>14. The method of claim 13 wherein the lithium alkoxide is lithium t-butoxide or lithium i-propoxide.</p> | <p>It is inherent in Bischofberger's teaching that the lithium alkoxide could be lithium t-butoxide or lithium i-propoxide. Further, selection of either of those lithium alkoxides would not produce unexpected superior results.</p> |
| <p>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.</p> | <p>Bischofberger's teaching of bis(POC)PMPA inherently discloses compositions comprising PMPA, which the '946 patent concedes is produced through a method that includes the step of 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. Bischofberger, 1; '946 patent, 13:35-53.</p> |
| <p>16. A composition comprising a tablet containing 9-[2-(R)-[[bis[[isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]-adenine.fumaric acid (1:1),</p> | <p>The '946 patent defines “9-[2-(R)-[[bis[[isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]-adenine.fumaric acid (1:1)” as “bis(POC)PMPA fumarate.” '946 patent, 1:29-45. Bischofberger taught bis(POC)PMPA. Bischofberger, 1. Gould taught that fumarate was a suitable candidate for preparing salts for drugs. Gould, 202. Takashima provided the motivation to combine Bischofberger with Gould by teaching the creation of phosphonate-nucleotide fumaric salt compounds. 77:4-9. Thus, one of ordinary skill in the art would have not only expected to be able to create bis(POC)PMPA fumarate, but would have also been expressly motivated to do so.</p> |

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| <p>pregelatinized starch, croscarmellose sodium, lactose monohydrate and magnesium stearate.</p> | <p>Takashima expressly taught producing compositions with acceptable excipients. 77:4-9. Pregelatinized starch, croscarmellose sodium, lactose monohydrate and magnesium stearate were well know by those of ordinary skill in the art at the time the application for the '946 patent was filed to be acceptable excipients for oral administration tablets.</p> |
| <p>17. The composition of claim 16 wherein the 9-[2-(R)-[[bis[[isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]-adenine.fumaric acid (1:1) is crystalline.</p> | <p>Inherent in Takashima's teaching of phosphonate-nucleotide fumaric salt compounds as tablets and other products is that the composition could be in crystalline form. 77:10-11. Further, methods for obtaining a crystalline form of a salt was also well known in the art at the time the application for the '946 patent was filed.</p> |
| <p>18. The composition of claim 16 wherein the tablet contains 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.</p> | <p>Takashima expressly taught producing compositions with acceptable excipients. 77:4-9. Pregelatinized starch, croscarmellose sodium, lactose monohydrate and magnesium stearate were well know by those of ordinary skill in the art at the time the application for the '946 patent was filed to be acceptable excipients for oral administration tablets. Determining satisfactory ratios of such excipients to the quantity of drug was within the skill of an ordinary pharmaceutical scientist and these particular rations do not produce unexpectedly superior results.</p> |

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| <p>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.</p> | <p>The '946 patent defines “9-[2-(R)-[[bis[[isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]-adenine.fumaric acid (1:1)” as “bis(POC)PMPA fumarate.” '946 patent, 1:29-45. Bischofberger taught bis(POC)PMPA. Bischofberger, 1. Gould taught that fumarate was a suitable candidate for preparing salts for drugs. Gould, 202. Takashima provided the motivation to combine Bischofberger with Gould by teaching the creation of phosphonate-nucleotide fumaric salt compounds. 77:4-9. Thus, one of ordinary skill in the art would have not only expected to be able to create bis(POC)PMPA fumarate, but would have also been expressly motivated to do so.</p> <p>Further, inherent in Takashima's teaching of phosphonate-nucleotide fumaric salt compounds being produced as tablets and other products is that such tablets or products could be made through a process that includes preparing wet granules. 77:10-11. Lastly, Takashima expressly taught producing compositions with acceptable excipients. 77:4-9.</p> |
| <p>20. The product of claim 19 wherein the liquid is water and the process optionally further comprises drying the wet granules.</p> | <p>It is inherent in Takashima's teachings that the liquid could be water and that the process could include drying the wet granules.</p> |

The '946 Patent's Flimsy Evidence of "Unexpected Superiority" is Scientifically Unsound

The only evidence offered by the '946 patent to support its argument that the superiority of BPPF was "unexpected" is a mere single comparison of bis(POC)PMPA-fumarate to bis(POC)PMPA-citrate. 19:6-29 ("Example 3"). Specifically, the '946 patent said:

The solid state chemical stability of cBPPF and bis(POC)PMPA-citrate salt was compared by analyzing each compound after storage under different conditions. The results showed that BPPF powder was unexpectedly more stable to storage at elevated temperature and relative humidity.

The '946 patent applicant also specifically relied on this argument during prosecution of the '946 patent to overcome the Examiner's rejection. *Response Under 37 C.F.R. 1.111*, pp. 2-3, September 16, 1998 (Paper # 10).

However, Gould taught that "low solubility and low hygroscopicity can contribute significantly to the stability of a salt form," and it is generally known, that fumaric acid is a high melting solid with low hygroscopicity and that it has significantly less solubility in water than citric acid, which is known to be a highly soluble salt. 209; Merck Index, 13th Ed. (2001) (showing that citric acid is roughly 68 times more soluble in water than fumaric acid). Further, Gould taught that to increase stability, one should "reduce hygroscopicity by increasing hydrophobicity of acid." 211, Fig. 5. Since fumaric acid is much more hydrophobic than citric acid, this is even more evidence that one of ordinary skill in the art would have expected bis(POC)PMPA fumarate to have superior solid state chemical stability over bis(POC)PMPA citrate.

For these reasons, Bischofberger, in light of Gould and Takashima, rendered every claim of the '946 patent obvious. As such, each claim of the '946 patent is invalid and should be canceled.

CONCLUSION

For the reasons set forth above, each of the claims of the '946 patent are invalid. As such, PUBPAT respectfully requests that they be reexamined *ex parte* and ultimately canceled.

April 30, 2007

Date

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of this Request for *Ex Parte* Reexamination in its entirety, including all accompanying documents, is being deposited with the U.S. Postal Service as First Class Mail on the date of the signature below in an envelope addressed to the attorney of record for the assignee of U.S. Patent No. 5,935,946 as provided for in 37 C.F.R. § 1.33(c):

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