Paper No.1

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Baxter Healthcare Corp., ApaTech, Inc., and ApaTech Limited,
Petitioners,

v.

Millenium Biologix, LLC,
Patent Owner

Patent No. 6,585,992
Issued: July 1, 2003
Filed: October 4, 2001
Inventors: Sydney M. Pugh, Timothy J. N. Smith,
Michael Sayer, and Sarah Dorthea Langstaff

Title: SYNTHETIC BIOMATERIAL COMPOUND OF CALCIUM PHOSPHATE PHASES PARTICULARLY ADAPTED FOR SUPPORTING BONE CELL ACTIVITY

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*Inter Partes* Review No. 2013-00590

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**PETITION FOR INTER PARTES REVIEW**

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**Attachment A. Proof of Service of the Petition**

**Attachment B. List of Evidence and Exhibits Relied Upon in Petition**

## I. Compliance with Requirements of an *Inter Partes* Review Petition

### A. Certification that the Patent May Be Contested via *Inter Partes* Review by the Petitioner

Petitioner certifies that it is not barred or estopped from requesting *inter partes* review of U.S. Patent No. 6,585,992 (the '992 patent) (Ex. 1001). Neither Petitioner, nor any party in privity with Petitioner: (i) has filed a civil action challenging the validity of any claim of the '992 patent; or (ii) has been served a complaint alleging infringement of the '992 patent more than a year prior to the present date. Also, the '992 patent has not been the subject of a prior *inter partes* review or a finally concluded district court litigation involving Petitioner.

Petitioner also certifies this petition for *inter partes* review is filed in compliance with 35 U.S.C. § 315(b). Baxter Healthcare Corp. and ApaTech, Inc. were served a complaint alleging infringement of the '992 patent on May 13, 2013 and ApaTech Limited agreed to accept service of the same complaint on or about May 28, 2013. That complaint led to Civil Action No. 1:13-CV-3084 in the U.S. District Court for the Northern District of Illinois. *See* Ex. 1123.

### B. Fee for Inter Partes Review (§ 42.15(a))

The Director is authorized to charge the fee specified by 37 CFR § 42.15(a) to Deposit Account No. 50-1597.

## C. Mandatory Notices (37 CFR § 42.8(b))

### 1. Real Party in Interest (§ 42.8(b)(1))

The real parties in interest are: (i) Baxter Healthcare Corp. ("Baxter") located at One Baxter Parkway, Deerfield, Illinois 60015, (ii) ApaTech, Inc. located at 2 Hampshire Street, Suite 103, Foxborough, Massachusetts 02035, and (iii) ApaTech Limited located at 370 Centennial Ave., Centennial Park, Elstree, Hertfordshire, WD6 3TJ, United Kingdom.

### 2. Other Proceedings (§ 42.8(b)(2))

The '992 patent is the subject of litigation in the N.D. of Illinois (Civil Action no. 1:13-cv-03084), which names as defendants Baxter, ApaTech, Inc., and ApaTech Limited. In addition, the '992 patent is the subject of IPR2013-00591, filed concurrently with this petition. U.S. Patent No. RE41,251, which issued from an application to which the '992 patent claims priority, is the subject of IPR2013-00582 and IPR2013-00583 (both filed on September 16, 2013).

### 3. Lead and Backup Lead Counsel (§ 42.8(b)(3))

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### 4. Service Information (§ 42.8(b)(4))

Service on Petitioners may be made by mail or hand delivery to: Sidley

Austin LLP, 1501 K Street, N.W., Washington, D.C. 20005. The fax number for Petitioner's counsel is (202) 736-8711.

### 5. Proof of Service (§§ 42.6(e) and 42.105(a))

Proof of service of this petition is provided in **Attachment A**.

## II. Identification of Claims Being Challenged (§ 42.104(b))

Claims 1, 2, 4, 9, 11, 16-18, 20, 25-26, 36, 38, and 43-44 of the '992 patent are unpatentable as being anticipated under 35 U.S.C. § 102(a) or 35 U.S.C. § 102(b), and/or for being obvious in view of the prior art under 35 U.S.C. § 103. Specifically:

1) Claims 1, 9, and 11 Are Anticipated by WO 97/09286
2) Claims 1, 2, 9, 11, 16, 18, 20, and 25 Would Have Been Obvious Based on WO 97/09286 In View of the '303 Patent
3) Claim 4, 36, and 38 Would Have Been Obvious Based on WO 97/09286 In View of Bioceramics 1993 and Ohgushi 1990
4) Claim 43 Would Have Been Obvious Based on WO 97/09286 In View of Bioceramics 1993 and Ohgushi 1990 In Further View of the '303 Patent
5) Claim 17 Would Have Been Obvious Based on WO 97/09286 In View of Chaki 1994
6) Claims 17 and 26 Would Have Been Obvious Based on WO 97/09286 In View of the '303 Patent In Further View of Chaki 1994
7) Claim 44 Would Have Been Obvious Based on WO 97/09286 In View of Bioceramics 1993 and Oghushi 1990 In Further View of the '303 Patent and Chaki 1994
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11) Claims 17 and 26 Would Have Been Obvious Based on Ruys 1993a In View of the '303 Patent In Further View of Chaki 1994

12) Claim 44 Would Have Been Obvious Based on Ruys 1993a In View of Bioceramics 1993 and Oghushi 1990 In Further View of the '303 Patent and Chaki 1994

13) Claim 1, 2, 9, 11, 16, 18, 20, and 25 Would Have Been Obvious Based on Ruys 1993b In View of the '303 Patent

14) Claim 4, 36, and 38 Would Have Been Obvious Based on Ruys 1993b In View of Bioceramics 1993 and Ohgushi 1990

15) Claim 43 Would Have Been Obvious Based on Ruys 1993b In View Bioceramics 1993 and Oghushi 1990 In Further View of the '303 Patent

16) Claims 17 and 26 Would Have Been Obvious Based on Ruys 1993b In View of the '303 Patent In Further View of Chaki 1994

17) Claim 44 Would Have Been Obvious Based on Ruys 1993b In View of Bioceramics 1993 and Oghushi 1990 In Further View of the '303 Patent and Chaki 1994

Petitioner's proposed construction of the claims, the evidence relied upon, and the precise reasons why the claims are unpatentable are provided in § IV, below. A list of evidence relied upon in support of this petition is set forth in Attachment B.

## III. Relevant Information Concerning the Contested Patent

The '992 patent indicates it is directed to a "synthetic biomaterial

compound" based on an allegedly new "stabilized" calcium phosphate (Ca-P) material, which the patent says "may be referred to as Skelite™." Ex. 1001 at col. 1:17-21. In fact, the '992 patent equates the term Skelite™ with "Si-TCP" (*id*. at col. 9:58-59), which the patent states is a "new biomaterial compound, [formed] by substitution of silicon at phosphorous sites" within TCP (tricalcium phosphate or $Ca_3(PO_4)_2$). *Id*. at col. 16:63-67; Ex. 1003 at ¶¶ 191-197.

The '992 patent discloses two methods for producing Si-TCP (silicon substituted-TCP): one using quartz as the source of silicon to make a thin-film (Example 3); the other involves using an organo-silicate as the silicon source (Example 5). Ex. 1003 at ¶¶ 223-226. Both processes start with the known Ca-P material hydroxyapatite (HA), $Ca_5(PO_4)_3(OH)$ or $Ca_{10}(PO_4)_6(OH)_2$, and, following a "sintering" step, result in the formation of a multi-phasic mixture that contains both HA and Si-TCP. *See* Ex. 1001 at Examples 1-3, 5; Ex. 1003 at ¶¶ 223-226.

### A. Prosecution History and Effective Filing Date of the '992 Patent

The '992 patent issued from U.S. Application No. 09/971,148 ('148 application), filed on October 4, 2001. Ex. 1003 at ¶ 240. It claims the benefit as a divisional of U.S. Application No. 09/044,749 ('749 application), which issued as U.S. Patent No. 6,323,146, and reissued as RE41,251 ('251 patent). *Id.* The '749 application, in turn, filed on March 19, 1998, claims benefit as a C-I-P to U.S. Application No. 09/029,872, the national phase of PCT/CA96/00585, filed on

August 30, 1996, which was published as WO 97/09286. *Id.* at ¶¶ 242, 246. The '872 application, in turn, claims benefit as a C-I-P to 08/576,238 filed on December 21, 1995. The '872 application claims priority to 60/003,157, filed September 1, 1995. *Id.*

### 1. Prosecution of U.S. Application No. 09/971,148

The '992 patent issued on July 1, 2003 from the '148 application. A preliminary amendment was filed on October 4, 2011. *Id.* at ¶ 243. With the amendment, Patent Owner stated that the new claims "present method claims that *parallel the allowed claims in the parent application…*" (*i.e.*, the '749 application that resulted in the '146 patent (and later reissued as the '251 patent)). *Id.* In allowing the claims, the Examiner stated: "All method claims contained in the instant case contain *all limitations of the composition found allowable in U.S. Patent 6,323,146* ('146 patent); therefore, the methods of using this novel composition are also deemed allowable." *Id.* at ¶ 244. The Examiner thus expressly conditioned allowance of the claims on the belief that the claims of the '146 patent defined a patentable new compound. *See id.*

### 2. Issuance and Reissuance of the '146 Patent

In the '146 patent which served as the basis of the Examiner's belief that the '992 patent defined allowable subject matter, Patent Owner originally pursued claims to a "bioresorbable biomaterial compound comprising calcium, oxygen, and

phosphorous wherein at least one of said elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1 Å." Ex. 1009 at 62; *see also id*. at 195-96, 269-71. Claims of this form, however, were rejected over a variety of references as being anticipated by or obvious in view of the prior art. For example, the Examiner found that two PCT applications (WO 94/26872 and WO 97/09286) disclosed the *same compounds*. With respect to WO 94/26872, the Examiner found that "[s]ince applicants *admit the compounds taught in this application are identical to the claimed composition*…the taught composition would inherently have the claimed properties." *Id.* at 261-62 (emphasis added). With respect to WO 97/09286, the Examiner found "…the taught *process is identical to applicants' disclosed process*. When the prior art and applicant both describe processes which are indistinguishable, then the products may also be assumed to be inherently indistinguishable." *Id*. at 265 (emphasis added).

Despite the fact that WO 97/26872 was in the chain of priority of the '749 application (as a C-I-P of the national stage of WO 97/26872), Patent Owner *did not dispute that the published PCT application was prior art*. Instead, Patent Owner conceded that the multi-phasic Ca-P mixtures disclosed in the PCT application was the same as the multi-phasic mixtures being claimed. To distinguish the claims, Patent Owner added the word "isolated" to the claims and argued that the claims were distinguishable over WO 97/09286 because the

inventors had "isolated therefrom" the compound that was the alleged invention. Ex. 1003 at ¶¶ 257-265 (citing Ex. 1009 at 202). The term "isolated" was omitted from the '992 patent claims.

On January 30, 2008, Patent Owner sought reissue of the '146 patent to address "a defect in the specification, which fails to identify the priority claim to PCT Application No. PCT/CA98/00046." *Id.* at ¶ 266 (citing Ex. 1002 at 7). PCT/CA98/00046 was filed January 29, 1998. *Id.* at ¶ 267. The claims in the reissue (*i.e.*, the original claims of the '146 patent), however, were rejected as anticipated by Ruys 1993b (Ex. 1014), which the Examiner stated taught "an isolated bioresorbable biomaterial compound" wherein "silicon substituted for a portion of the phosphorous atoms in the compound." Ex. 1003 at ¶¶ 268-269 (citing Ex. 1002 at 138). Patent Owner did not dispute the Examiner's characterization of Ruys 1993b. *Id.* at ¶¶ 270-271. Instead, it amended claim 1 to "incorporate the features of claim 5," adding the phrase "wherein said compound has a microporous structure." *Id.* (citing Ex. 1002 at 154-58). Patent Owner also replaced the phrase "an element having an ionic radius of approximately 0.1 to 0.6 Å" with the word "$Si^{4+}$." *Id.* (citing Ex. 1002 at 154). Finally, Patent Owner cancelled claims 2, 4, 5 and 14. *Id.* (citing Ex. 1002 at 154-55). The Examiner subsequently allowed the claims, and the '251 reissue patent issued on April 20, 2010. *Id.* The claims of the '992 patent do not contain the limitation added to

claim 1 of the ’251 reissue patent that the “biomaterial compound” exhibit a “microporous structure.” *Id*. at ¶ 272; *see also* ¶¶ 53-60. Nor do the independent claims of the ’992 patent limit the compound to one substituted with $Si^{4+}$ as found in the claims of the ’251 patent. *Id.* at ¶¶ 53-60. Dependent claims 11, 20, and 38 of the ’992 patent, however, require the “element” substituting to be “silicon.” *Id*.

### 3. Effective Filing Date of the Claims

The effective filing date of claims 1, 2, 4, 9, 11, 16-18, 20, 25-26, 36, 38, and 43-44 of the ’992 patent is no earlier than March 19, 1998, the filing date of the ’749 application. *Id.* at ¶¶ 315-316. Applications filed prior to March 19, 1998 to which the ’992 patent claims benefit or priority do not provide an adequate written description corresponding to the full scope of the subject matter encompassed by the claims under 35 U.S.C. § 112, first paragraph. *Id.* at ¶¶ 316-317. In particular, the claims require that at least one of calcium, oxygen, and phosphorous be “*substituted*” with an element having an ionic radius of approximately 0.1 to 0.6 Å. Ex. 1001 at col. 33:59-col. 38:24. Applications filed prior to March 19, 1998, however, do not establish that the inventors had possession of the concept of “substitution.” Ex. 1003 at ¶¶ 314-331. Instead, the earlier filed applications describe the effect of adding an element such as silicon to a Ca-P compound as being “stabilization.” *Id.* at ¶ 317. In fact, Patent Owner *expressly admitted* during examination of the ’749 application that its pre-March

1998 applications did not describe the concept of "substitution." *See, e.g.*, Ex. 1009 at 202 (stating WO 97/09286 "does not teach or suggest the 'substitution' of at least calcium, oxygen and phosphorous by an element, but rather teaches stabilization…."); Ex. 1003 at ¶¶ 323-325. WO 97/09286 is the international publication of PCT/CA1996/000585 (filed in the national phase as Application No. 09/029,872) to which the '992 patent claims benefit. *See supra*, at § III.A.

Patent Owner's admission that WO 97/09286 does not "describe or teach the concept of 'substitution'" demonstrates the '872 application does not contain a written description that establishes possession of the concept of a substituted Ca-P compound, which is an essential element of the claims. *See* Ex. 1003 at ¶¶ 323-325 (citing Ex. 1009 at 202). Consequently, claims 1, 2, 4, 9, 11, 16-18, 20, 25-26, 36, 38, and 43-44, are not entitled to § 120 benefit of the '872 application, meaning the '992 patent claims cannot have an effective filing date earlier than March 19, 1998. *See generally, id.* at ¶¶ 314-332.

### B. Person of Ordinary Skill in the Art

The person of ordinary skill in the art is a biomaterials scientist who has at least a bachelor's degree, and potentially some advanced schooling, in chemistry, chemical engineering, biomedical engineering, or a related discipline (*e.g.*, materials science/engineering) with some specialized training or education in the biomaterials field in the case of an individual with an advanced degree, or

approximately 1-2 years of additional training and experience in the biomaterials field in the case of an individual with a bachelor's degree. *Id*. at ¶ 51.

### C. Construction of Terms Used in the Claims

In an IPR, claims must be given their broadest reasonable construction in light of the specification. *See* 37 CFR 42.100(b); M.P.E.P. § 2111.01.

#### 1. "biomaterial"

The specification of the '992 patent shows that the inventors had a specific definition in mind for the term "biomaterial." Specifically, at column 9, the patent states that the "compound of the present invention is herein referred to as a *biomaterial* compound due to its bioactive nature in both in vitro and in vivo systems. *Bioactivity* refers to the ability of the biomaterial compound to support osteoclast and osteoblast activity and the ability to be assimilated with natural bone by the activity of these cells." Ex. 1001 (U.S. Patent No. 6,585,992) at col. 9:36-41 (emphasis added). The broadest reasonable construction of the term "biomaterial" should employ this definition of the term in the specification. Ex. 1003 at ¶ 276.

#### 2. "compound"

The broadest reasonable construction of the term "compound" encompasses a multi-phasic mixture having as a component substituted-TCP. Ex. 1003 at ¶¶ 294-296. This definition includes, for example, a compound that is a multi-phasic mixture containing the allegedly novel component of the invention, Si-TCP. *Id*.;

*see also id.* at ¶¶ 198-218.[1] This conclusion is compelled by the disclosure of the '992 patent, and is reinforced by statements made by the Patent Owner during examination of the '146 patent. *See id.* at ¶¶ 277-301.

Indeed, the '992 patent uses the term "compound" to refer to what are, in fact, mixtures of two or more distinct, solid and stable Ca-P phases. *Id.* at ¶ 280. Specifically, the '992 patent refers to mixtures of (i) a substituted-TCP phase, particularly Si-TCP, together with (ii) an un-substituted HA phase, as being "compounds" of the invention. *Id*. at ¶¶ 198-218, 286-298. That multiple Ca-P phases often co-exist within a polycrystalline lattice structure in this manner was well known before March of 1998. *Id*. at ¶ 285.

The use of the term "compound" to refer to materials that contain multiple, distinct Ca-P phases occurs throughout the '992 patent. *Id*. at ¶¶ 198-218, 286-298. The title of the '992 patent indicates that the "compounds" of the invention

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[1] While the ordinary meaning of this phrase may also include single phase substituted-TCP, the patent did not describe methods for separating the phases of multi-phase mixtures created by the methods of the invention (*e.g.*, bi-phasic HA/Si-TCP). *E.g.*, Ex. 1003 at ¶¶ 207-210, 293. Whether the claims are construed to also include single phase materials, however, is irrelevant to the invalidity of the claims based on the art cited herein.

contain multiple, distinct Ca-P phases. *See* Ex. 1001 at col. 1:1-4 ("Synthetic biomaterial *compound* of calcium *phosphate phases* …") (emphasis added). Similarly, the '992 specification indicates the field of the invention is "a synthetic biomaterial *compound* based on stabilized *calcium phosphates*." Ex. 1001 at col. 1:17-18 (emphasis added).

The '992 patent also presents experimental data documenting properties of multi-phasic Ca-P materials as evidence of the properties of the "compound" of the invention. For example, the '992 patent refers to test results shown in Figures 11(b) and 22, stating these figures "illustrate osteoclast resorption pits on ceramic pellet and thin film formats of the Si-TCP *compound*." Ex. 1001 at col. 16:30-32 (emphasis added); Ex. 1003 at ¶ 290. Both figures, however, describe experimental results from testing of samples of a multi-phasic mixture of Si-TCP and HA. Ex. 1003 at ¶¶ 198-218. Specifically, Figure 11(b) presents an x-ray crystallographic analysis of a sample of "Si-mHA," which the '992 patent indicates is Si-TCP and HA. Ex. 1001 at col. 16:30-32, 8:37-44, 10:22-23, Fig. 11(b); Ex. 1003 at ¶¶ 198-218. Figure 22, similarly, presents results of an SEM analysis of a sample of a multi-phasic mixture of Si-TCP and HA. Ex. 1003 at ¶¶ 198-218.

The '992 patent also equates the "compound" of the invention with a commercial product termed "Skelite™." *See, e.g.*, Ex. 1001 at col. 1:17-24 ("This compound which in the alternative may be referred to as Skelite™."); *id*. at col.

10:14-16 ("[t]hese studies . . . led to the characterization of the new compound, an additive stabilized calcium phosphate compound, Skelite™."); *see also* Ex. 1003 at ¶¶ 191-197. The commercially marketed Skelite™ product is a multi-phasic mixture containing ~ 67% Si-TCP and ~ 33% HA. *Id.* The '992 patent reports the same multi-phasic proportions of Si-TCP and HA for Skelite™. Figure 9 reports x-ray crystallographic data showing the compound of the invention is made up of ~ 67% Si-TCP and ~ 33 % HA. *Id.* at ¶ 194.

The way the '992 patent uses the term "compound" to refer to multi-phasic Ca-P mixtures, and its reliance on data characterizing multi-phasic materials to define the "novel" compound of the invention, compel the conclusion that the broadest reasonable construction of the phrase "compound" as used in the claims must encompass multi-phasic Ca-P mixtures, particularly those containing a substituted-TCP phase, which are the focus of all of the working examples in the '992 patent. *See generally, id*. at ¶¶ 191-239, 277-301.

**3. "comprising calcium, oxygen and phosphorous wherein a portion of at least one of said elements is substituted with an element having an ionic radius of approximately 0.1 to 0.6 Å"**

The broadest reasonable construction of the term "compound" necessarily encompasses multi-phasic Ca-P compounds containing at least a substituted-TCP phase. *See supra* § III.C.2; Ex. 1003 at ¶¶ 277-301. The specification makes clear that the inventors believed their critical contribution was the determination that a

particular substituted-TCP component, Si-TCP, was present within these multi-phasic compounds. *Id*. at ¶¶ 191-218, 302.

The next phrase in claim 1 specifies the "compound" contains "calcium, oxygen and phosphorous" that has been "substituted with an element having an ionic radius of approximately 0.1 to 0.6 Å" *Id*. at ¶ 303. An "element" is a pure chemical substance consisting of one type of atom, which is distinguished by its atomic number on the periodic table. *Id*. at ¶ 304. A person of ordinary skill would understand this phrase to be indicating that at least one of the three specified elements in a component molecule of the multi-phasic compound (*i.e.*, Ca, O, or P) has been replaced with an element having the specified ionic radius. *Id*.[2]

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[2] While the ordinary meaning of "comprising" could theoretically encompass any substituted Ca-P compound that contains Ca, O, and P, such a construction would encompass compounds not described in the '992 patent. *See* Ex. 1003 at ¶¶ 191-218. The '992 disclosure and prosecution history are replete with statements that the "novel compound" contains a particular, new substituted-TCP phase termed "Si-TCP." *Id.*; *see also* ¶¶ 245-265, 277-301. Whether the claims are construed to encompass substituted Ca-P materials other than substituted-TCP, however, is irrelevant to the invalidity of the claims based on the art cited herein.

The claim also includes the phrase "a portion of at least one of said elements," which means that not all the elements within the substituted component phase in the polycrystalline lattice structure of the compound (*i.e.*, some of Ca, or some of O, or some of P in TCP) are required to undergo "substitution." *Id*. at ¶ 305.

The requirement in the claims for a "substitution" step means the claims are product-by-process claims. *Id*. at ¶ 306. However, in this IPR proceeding, the process elements in the claims are not to be given weight in determining if they encompass compounds in the prior art in the absence of evidence demonstrating the process step recited in the claim imparts features or properties to the claimed compounds that distinguish them from the prior art. *See, e.g.*, Manual of Patent Examining Procedure (MPEP) at § 2113. Consequently, the Board may properly find that compounds within the scope of the claims disclosed in the prior art anticipate or render obvious those claims, regardless of how those prior art compounds have been produced. *See Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1370 (Fed. Cir. 2009).

#### 4. "implanting said biomaterial compound at the site of skeletal surgery"

This phrase, found in claim 1, requires that the biomaterial compound be implanted at the site of skeletal surgery. This phrase would be understood to mean that the biomaterial compound is implanted at the site where bone is being

operated on. Ex. 1003 at ¶ 308; *see also, e.g.*, Ex. 1124 (Steadman's 1990) at 6, 7.

**5. "implanting said biomaterial compound at the site of the segmental skeletal gap or non-union fracture"**

This phrase (used in claim 2) requires the biomaterial compound to be implanted at the site of a segmental skeletal gap or non-union fracture. A segmental skeletal gap would be understood to mean any defect or opening in bone. Ex. 1003 at ¶ 309; *see also, e.g.*, Ex. 1124 (Steadman's 1990) at 3, 6. A non-union fracture would be understood to mean a failure in the normal healing of a fractured bone. Ex. 1003 at ¶ 309; *see also, e.g.*, Ex. 1124 (Steadman's 1990) at 4. Thus, the phrase would be understood to mean that the biomaterial compound is implanted at the site of any opening or defect in a bone or at the site of a fractured bone that has failed to heal normally. Ex. 1003 at ¶ 309.

**6. "wherein such implantation promotes the formation of new bone tissue at the interfaces between said biomaterial compound and said host"**

This phrase, found in claims 1 and 2, requires that the biomaterial compound promote bone tissue formation at the interfaces, or boundary, between the compound and the host. Given that new bone formation was known to occur upon implantation of Ca-P materials, such as TCP, *see, e.g.*, Ex. 1041 (Driskell 1973) at 2, this phrase would be understood to mean that new bone tissue forms at the boundary of the biomaterial compound and the host after implantation. Ex. 1003 at ¶ 310.

#### 7. "the progressive removal of said biomaterial compound primarily through osteoclast activity"

This phrase is used in claims 1 and 2, and requires the biomaterial compound to be removed progressively by osteoclasts. Given that bone regeneration was known to occur incrementally and over the course of time, the term "progressively" would be understood to mean incrementally, or over the course of time. The phrase "removal . . . through osteoclast activity" would be understood to refer to cellular resorption by osteoclasts, which the patent admits is "inherent in the natural bone remodeling process." Ex. 1003 at ¶ 311; Ex. 1001 at col. 34:1-29.

#### 8. "the replacement of that portion of said biomaterial compound removed by further formation of new bone tissue by osteoblast activity"

This phrase is used in claims 1 and 2, and would be understood to refer to replacement of the biomaterial compound with new bone by osteoblasts, which the patent admits is "inherent in the natural bone remodeling process." Ex. 1003 at ¶ 312; Ex. 1001 at col. 34:1-29.

## IV. Precise Reasons for Relief Requested

### A. Claims 1, 2, 4, 9, 11, 16-18, 20, 25-26, 36, 38, and 43-44 Are Unpatentable Over WO 97/09286

As explained above in § III.A.3, claims 1, 2, 4, 9, 11, 16-18, 20, 25-26, 36, 38, and 43-44 are not entitled to an effective filing date prior to March 1998, and in particular, are not entitled to the benefit of U.S. Application No. 09/029,872, which

is the U.S. national phase of WO 97/09286 (Ex. 1017). *See generally* Ex. 1003 §.III.I. Because WO 97/09286 was published on March 13, 1997, it is prior art to the claims under 35 U.S.C. § 102(b). A summary of WO97/09286 is provided in Ex. 1003 at § IV.A.7.

**1. WO 97/09286 Anticipates Claim 1**

WO 97/09286 describes procedures for producing multi-phasic Ca-P materials that are essentially identical to the procedures described in the '992 patent for producing the claimed "biomaterial compound." Ex. 1003 at § IV.A.7. WO 97/09286 describes two methods for making the compounds: one uses quartz as the source of silicon to make a thin-film; the other uses an organo-silicate as the silicon donor. *Id.* at ¶¶ 442-449, 458-460. Both processes are essentially identical to corresponding processes in the '992 patent that yield the Si-TCP/HA "biomaterial compound." *Id.*; *see also id.* at Appendix C.

Both WO 97/09286 and the '992 patent start with the formation of HA using 4.722 grams of calcium nitrate in water and 1.382 grams of ammonium dihydrogen phosphate. *Id.* at ¶¶ 220, 443; *see also* Appendix C. In the method for making the thin-film, both WO 97/09286 and the '992 patent employ a quartz substrate coated with HA which is sintered at high temperature. *Id.* at ¶¶ 223, 458-459; *see also id.* at Appendix C. In the method involving the use an organo-silicate, both WO 97/09286 and the '992 patent employ tetrapropylorthosilicate (TPOS), which is

added to the HA solution. *Id.* at ¶¶ 225, 445; *see also id.* Appendix C.

The Office recognized during the examination of the '146 patent that the processes described in WO 97/09286 for making "stabilized" compounds *are identical* to those described in the '992 patent for making "substituted" compounds: "one of ordinary skill in the art would expect the stabilizing entities to substitute for at least one of calcium, oxygen and phosphorous in the taught calcium phosphates *because the taught process is identical to applicants' disclosed process*." Ex. 1009 at 264-65 (emphasis added); Ex. 1003 at ¶ 602.

Indeed, at sintering temperatures of ~1000º C, the thin-film process disclosed in WO 97/09286 and the '992 patent each resulted in material containing ~33% HA and ~67% TCP. *Id.* at ¶¶ 459, 593. Further, the '992 patent and WO 97/09286 use the *exact same figures* to describe the activity and morphology of the "products" that result from the thin-film processes disclosed in each document. *Id.* at ¶¶ 461, 594 (citing Ex. 1017 at Figs. 6 and 9; Ex. 1001 at Figs. 20 and 22). Because the methods in WO 97/09286 are the same as those described in the '992 patent, those methods necessarily will produce material that includes at least Si-TCP. *Id.* at ¶¶ 461-462, 594-595. According to the '992 patent, silicon has an ionic radius of 0.40 Å. Ex. 1001 at col. 32:15-45; Ex. 1003 at ¶¶ 601. Thus, the "stabilized compositions" described in WO 97/09286 are inherently the same "biomaterial compounds" that are claimed in claims 1, 2, and 4 (the independent

claims of the '992 patent). Ex. 1003 at ¶¶ 595, 601.

Because the material made in WO 97/09286 is the same as that disclosed in the '992 patent, the properties would also necessarily be the same. *See id.* Later publications by the inventors confirm that the materials made by the processes disclosed in WO 97/09286 included Si-TCP, were bioresorbable and bioactive, and were thus suitable for use as a "biomaterial." *Id.* at ¶¶ 451-457, 559-600.

During examination of the application that resulted in the '146 patent, Patent Owner sought to distinguish the claims over WO 97/09286 by an amendment that specified the compound was "isolated." *Id.* at ¶¶ 257-262, 604. Patent Owner admitted that WO 97/09286 disclosed the same HA/Si-TCP materials being claimed, but argued that the inventors had "isolated therefrom" the novel compound claimed in the application. *Id.* Because the claims of the '992 patent do not include this limitation, Patent Owner has admitted that the biomaterial compound of claim 1 is disclosed in WO 97/09286. *Id.*

In addition to disclosing the same "biomaterial compound" of claim 1, WO 97/09286 states these compounds can be used in a wide range of therapeutic applications, such as implants, as well as for the regeneration and repair of bone tissue, for example, in fractures, among other applications . *Id.* at ¶¶ 474, 606, 663-664. The person of ordinary skill in the art would have recognized that these uses necessarily involve "substituting natural bone at sites of skeletal surgery in human

and animal hosts" comprising the step of "implanting said biomaterial compound at the site of skeletal surgery." *Id.*

The remainder of claim 1 ("such implantation promotes the formation of new bone tissue …the progressive removal of said biomaterial compound primarily through osteoclast activity, and the replacement of that portion of said biomaterial compound …by osteoblast activity…") does not specify any structural feature or chemical component of the "biomaterial compound" used in the method. *Id.* at ¶ 665. Instead, it specifies *inherent functional* properties or capabilities associated with use of the "biomaterial compound" previously disclosed in WO 97/09286. *Id*. In fact, the claims themselves admit these properties are inherent to the biomaterial compound and result from natural processes that occur in the body—"such progressive removal and replacement [are] inherent in the natural bone remodeling process." Ex. 1001 at col. 34:7-9, col. 34:27-29; Ex. 1003 at ¶ 665. A claim that specifies an inherent property of a previously disclosed compound does not render the claim patentably distinct. *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) ("the 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.").

Likewise, the original Examiner imparted no aspect of novelty to the method

steps of the claims ("All method claims contained in the instant case contain all limitations of the composition found allowable in U.S. Patent 6,323,146 ['146 patent]; therefore, the methods of using this novel composition are also deemed allowable."). Ex. 1003 at ¶ 244 (citing Ex. 1002 at 146). While the Examiner's understanding of the composition claims was mistaken (not all limitations of the composition claims were added to the method claims), and the references and arguments herein dictate a different outcome, the Examiner was correct in not resting allowance on the method steps.

In any event, these properties were known to be associated with Ca-P materials, such as TCP and HA. *See generally* Ex. 1003 at §§ II.E.1 and II.E.5. Specifically, Ca-P implant material such as TCP and HA were reported to promote the formation of new bone, and exhibit characteristics consistent with the progressive removal of the biomaterial through osteoclast activity, and the replacement of the biomaterial by further formation of new bone tissue. *Id.* at ¶¶ 76-79, 90-91. WO 97/09286 also expressly teaches that the Si-TCP/HA materials described in it have many of these properties. *See* Ex. 1003 at ¶¶ 450, 666 (citing Ex. 1017 at 29) ("the present invention promotes both osteoconduction and resorption so that normal tissue healing and regeneration can occur while simultaneously allowing the artificial material to be resorbed in the process of normal bone tissue remodeling.") *See* Ex. 1003 at ¶¶ 601, 667-668; *see also*

*generally* Ex. 1003 at §§ IV.A.7, IV.B.1.a, IV.B.2.a. WO 97/09286 therefore anticipates claim 1 under 35 U.S.C. § 102(b).

### 2. Claim 1 Would Have Been Obvious Based on WO 97/09286 In View of the '303 Patent

WO 97/09286 indicates the compounds made by the processes disclosed in it are useful as bone implant materials. Ex. 1003 at ¶¶ 474, 663. Any assertion by the Patent Owner that WO 97/09286 does not describe "implanting said biomaterial compound at the site of skeletal surgery," would be baseless as there is no other way to implant Ca-P materials other than at the site of skeletal surgery. *Id.* at ¶ 668. In any event, claim 1 would nevertheless have been unpatentable, as the claimed method of implanting the biomaterial compound would have been obvious to a person of ordinary skill in the art based on WO 97/09286 in view of the '303 patent (Ex. 1026), which is prior art under 35 U.S.C. §§ 102(b). *See generally id.* at § IV.B.2.b.

A summary of the '303 patent is provided in Ex. 1003 at § IV.A.16. The '303 patent describes a method of inducing bone growth by implanting a resorbable Ca-P ceramic. *Id.* at ¶ 552. The patent states that "[e]specially preferred are … sintered ceramic comprised of 60% hydroxyapatite and 40% β-tricalcium phosphate." *Id.* at ¶ 554 (citing Ex. 1026 at col. 1:64-68). A person of ordinary skill would have considered WO 97/09286 in conjunction with the '303 patent, as each is directed to the development and use of Ca-P materials suitable

for use as bone implants. *Id.* at ¶ 673.

The '303 patent states that it is "known that ceramics, especially calcium hydroxyapatite and other calcium phosphates and mixtures thereof, are osteoconductive (*i.e.*, when placed next to viable bone they provide a framework for the rapid incorporation of connective tissue and subsequent bone growth."). *Id.* at ¶ 552 (citing Ex. 1026 at col 1:14-19). Indeed, the use of Ca-P materials in bone implant applications was well known. *See generally id.* at §§ II.E.1 and II.E.5. Bioceramics 1993, for example, states that HA has been used in various clinical applications that include: the repair of bony defects in dental and orthopedic applications, the augmentation of alveolar ridge, as an adjuvant to the placement of metal implants, the enhancement of guided tissue regeneration, maxillo-facial reconstruction, middle ear reconstruction, and plasma sprayed coatings for dental and orthopedic implants. *Id.* at ¶¶ 511-516; Ex. 1021 at 97.

Bioceramics 1993 also states that HA bone implants "have undergone major clinical trials." Ex. 1003 at ¶ 512 (citing Ex. 1021 at 120). Bioceramics 1993 discusses a study in which 46 patients with traumatic bone defects underwent reconstruction with porous HA. *Id.* at ¶ 514. An illustrative case is discussed in which a radius fracture in the forearm of a patient was treated with an HA implant. *Id.* Specifically, the reference indicates that "a segment of cortical bone was missing which was grafted with a block of porous hydroxyapatite." *Id.* at ¶ 515

(citing Ex. 1021 at 122). According to the publication, "[f]racture union was achieved in all cases." *Id.*

Heise 1990 discloses the use of hydroxyapatite ceramic in a variety of surgical bone implant applications. *Id.* at ¶ 565. In total, operations were performed on 44 patients. *Id.* at ¶ 566. The bone implant applications included the use of a HA composition for "bridging the gap in both the radius and ulna" in a patient who had lost bone fragment due to an accident. *Id.* at ¶ 569. The results of the study in Heise 1990 "demonstrate that porous hydroxyapatite ceramic granules may be used as a sole substitute without adding autologous cancellous bone" in certain bone implant applications. *Id.*; *see also id.* at ¶ 83 (citing Ex. 1089 (Uchida 1990) at 2-3 (use of calcium hydroxyapatite ceramics for the treatment of bone tumours and bone defects after the resection of tumours)).

The '495 patent describes a TCP implant which maximizes bone regeneration. *Id.* at ¶¶ 571-572. According to the '495 patent, the disclosed TCP material provides a "biodegradable pharmaceutical composition" which is "readily implantable in a bone cavity to promote formation throughout the cavity of new bone to replace that lost through trauma, disease, resective surgery, and birth defects." *Id.* at ¶ 572 (citing Ex. 1102 at col. 2:3-11). Multi-phasic and composite Ca-P material had also been studied extensively in surgical applications. *See, e.g.*, *id.* at ¶ 680 (citing Ex. 1049 at 9 (biphasic HA and TCP implanted in rat femurs);

Ex. 1029 at 9 (HA and TCP mixtures implanted in rabbit bone); Ex. 1090 at 2-3 (biphasic HA and TCP implanted in dogs)); *see also id.* at ¶¶ 147-148.

Consistent with the literature, the '303 patent discusses numerous clinical and surgical uses for the disclosed HA and TCP materials. *Id.* at ¶¶ 557, 681. Among those described are "to augment bone and fill bony defects, for example, periodontal bony pockets, tooth extraction sockets, and jaw cysts." *Id.* Other applications include "bridging of large tumor cavities after removal of tumor," "the bridging of segmental defects in delayed union or non-union of fractures" and "surgical reattachment of avulsed bone fragments." *Id.*

*In vivo* results in animals reported in the '303 patent showed that, at eleven weeks, "there was good bone formation accompanied by receding fibrous tissue . . . Osteoblasts were actively forming bone while MNGs were resorbing the ceramic." *Id.* at ¶ 558 (citing Ex. 1026 at col. 4:7-11). Further, at six and nine months, "bone maturation and marrow cell formation was progressive at the expense of the disappearing ceramic resorbed by giant cells." *Id.* (citing Ex. 1026 at col. 4:22-26). The '303 patent concludes that the implants were "osteoinductive." *Id.* at ¶ 559 (citing Ex. 1026 at col. 4:28-30).

Given the extensively reported properties of Ca-P materials such as TCP and HA, *see generally* Ex. 1003 at §§ II.E.1 and II.E.5, and the guidance provided in the '303 patent—which discloses implantation of Ca-P material at the site of

skeletal surgery in place of bone—the person of ordinary skill in the art would have been motivated to use the biomaterial compounds described WO 97/09286 in methods that involved "substituting natural bone at sites of skeletal surgery in human and animal hosts" where the methods further involved "implanting said biomaterial compound at the site of skeletal surgery." Ex. 1003 at ¶ 684. The person of ordinary skill in the art would have had a reasonable expectation of success given the extensive literature of Ca-P materials describing the clinical and surgical uses of these compounds, which included the very use claimed. *Id.*

As discussed above in § IV.A.1, the remainder of claim 1 does nothing more than describe inherent functional properties and capabilities of a previously disclosed compound. In any event, the literature reported that Ca-P implant material exhibited these properties. Ex. 1003 at ¶¶ 76-79, 90-91, 686; *see generally id.* at §§ II.E.1 and II.E.5. Claim 1 therefore would have been obvious based on WO 97/09286 in view of the '303 patent. *Id.* at ¶ 687; *see also generally id.* at §§ IV.B.1.a, IV.B.2.b, IV.A.7, and IV.A.16.

#### 3. Claim 2 Would Have Been Obvious Based on WO 97/09286 In View of the '303 Patent

Claim 2 is directed to a "method of repairing large segmental skeletal gaps and non-union fractures arising from trauma or surgery in human and animal hosts" the method involving "implanting said biomaterial compound at the site of the segmental skeletal gap or non-union fracture." Ex. 1003 at ¶ 54. The same

biomaterial compound is specified in both claims 1 and 2. *Id.* at ¶ 588. The recitation of functional properties and capabilities that inherently result from the implantation of the biomaterial compound cannot impart a patentable distinction. *Id.* at ¶ 665. WO 97/09286 in view of the '303 patent would have rendered claim 2 unpatentable for the same reasons these references would have rendered claim 1 unpatentable.

The '303 patent describes implanting a multi-phasic Ca-P ceramic using standard surgical techniques for uses such as "the bridging of segmental defects in delayed union or non-union of fractures." *See supra,* at § IV.A.2; Ex. 1003 at ¶¶ 557, 681. Given the known properties of Ca-P materials, *see generally* Ex. 1003 at §§ II.E.1 and II.E.5, and the guidance provided in the '303 patent—which teaches or suggests use of Ca-P implant material to repair large segmental skeletal gaps and non-union fractures arising from trauma or surgery—the person of ordinary skill in the art would have been motivated to use the biomaterial compounds described WO 97/09286 in methods that involved "implanting said biomaterial compound at the site of the segmental skeletal gap or non-union fracture." *Id.* at ¶ 685. That person also would have had a reasonable expectation of success given the extensive literature describing the clinical and surgical uses of Ca-P compounds, which included the very use claimed. *Id.* Claim 2 thus would have been obvious based on WO 97/09286 in view of the '303 patent. *Id.* at ¶ 687; *see*

*also generally id.* at §§ IV.A.7, IV.A.16, IV.B.1.a, and IV.B.2.b.

#### 4. Claim 4 Would Have Been Obvious Based on WO 97/09286 In View of Bioceramics 1993 and Ohgushi 1990

Claim 4 of the '992 patent describes a "method for providing tissue engineering scaffolds for bone replacement." *Id.* at ¶ 693. The '992 patent defines tissue engineering as "to remove bone cells from the patient's skeleton using an established bone marrow aspiration technique, and then carefully introduce the collected cells (cell seeding) into the open cell structure of the Skelite™ scaffold in a sterile biotechnology facility. The cells and scaffold are then incubated so that the cells have an opportunity to multiply and begin to fill the scaffold with new mineralized matrix. After several weeks, the biological implant is ready for implantation back into the patient." *Id.* (citing Ex. 1001 at col. 22:51-59).

The method claimed in claim 4 involves the steps of: (1) forming the claimed biomaterial compound as a macroporous structure comprising an open cell construction with interconnected voids; and (2) combining mature and/or precursor bone cells with said macroporous structure, and allowing the cells to infiltrate the structure in order to develop new mineralized matrix throughout the structure. *Id.* at ¶ 694. This claim would have been obvious to a person of ordinary skill in the art based on WO 97/09286 in view of Bioceramics 1993 and Oghushi 1990. *Id.* at ¶ 695.

As discussed, WO 97/09286 discloses the biomaterial compound of the

claims. *See id.* at § IV.B.1.a. WO 97/09286 further states that the Ca-P materials disclosed in the reference may be used in "tissue engineering" applications. *Id.* at ¶¶ 474, 606. The person of ordinary skill in the art would have considered WO 97/09286 in conjunction with Bioceramics 1993 and Oghushi 1990 as each reference relates to the development and use of Ca-P materials useful as bone implants. *Id.* at ¶ 696.

Before 1998, interconnected macropores, including pores further comprising an open cell structure, were considered "ideal" for bone implant applications in order to promote vascularization and cell ingrowth. *Id.* at ¶¶ 154-157 (citing Ex. 1021 at 110); *see generally id.* at ¶¶ 141-166, 697. Lin 1991 states that "[m]ost currently investigated porous implants are fabricated to have macropores in the range of 100-400 μm, so as to allow for bone ingrowth…" Ex. 1003 at ¶ 529 (citing Ex. 1023 at 1). Forming the biomaterial compound of claim 1 into a macroporous structure comprising an open cell construction with interconnected voids therefore would have been an obvious design choice. *Id.* at ¶ 697.

Bioceramics 1993 (Ex. 1021) teaches that "[p]orosity and interconnectivity are key determinants of amount and type of ingrowth" in Ca-P bone implant material. Ex. 1003 at ¶ 698; Ex. 1021 at 116-117. Fig. 2 of Bioceramics 1993 (Ex. 1021) shows an "idealized" structure for cortical bone regeneration. Ex. 1003 at ¶¶ 154, 698; Ex. 1021 at 109. This "idealized" structure is shown to exhibit

interconnected porosity. *Id.*; Fig. 4 shows another "idealized" structure for cancellous bone regeneration. Ex. 1003 at ¶¶ 155, 698; Ex. 1021 at 111. This structure exhibits an open cell configuration with interconnected macropores. *Id.*

A person of ordinary skill in the art also would have been motivated by Bioceramics 1993 (Ex. 1021) to take the compounds described in WO 97/09286 and prepare them to have a structure comprising an open cell construction with interconnected voids. Ex. 1003 at ¶ 699. Methods of making a biomaterial compound having a macroporous structure pursuant to claim 4 were well known. *Id.* at ¶¶ 147-164, 699.

Combining the resulting Ca-P macroporous structure with mature or precursor bone cells and allowing the cells to infiltrate the structure to develop new mineralized bone matrix would also have been obvious. *Id.* at ¶ 700. By the mid-1990s, the literature was replete with studies that combined porous Ca-P with bone cells in order to enhance implantation outcomes. *Id.* (citing Ex. 1127 at 1, Ex. 1124 at 1, Ex. 1125 at 1, Ex. 1129 at 1); *see also id.* at ¶ 165. Ohgushi 1990, for example, pretreated HA and TCP ceramics similar in shape to Intepore 200 porous HA, which was known to exhibit an open cell construction with interconnected voids (*see generally id.* at § IV.A.12; Ex. 1022 (White 1986)), with bone marrow cell suspensions. Ex. 1003 at ¶ 701. Ohgushi found that "all implants with marrow cells showed bone formation in the pore regions" and noted that the bone

formation was "active and progressive." *Id*. (citing Ex. 1073 at 3-4). Ohgushi also reported that "some pore areas showed regeneration of bone marrow." *Id*. (citing Ex. 1073 at 4); *see generally id*. at § IV.A.19.

Given these results, it would have been obvious to pretreat Ca-P material comprising an open cell structure with interconnected voids with precursor and mature bone cells in a manner that would allow the cells to infiltrate the structure in order to develop new mineralized matrix throughout the structure. *Id.* at ¶ 702. Methods of combining Ca-P material in bone marrow culture medium for extended periods "to allow cells to adhere to the surface of ceramics and to infiltrate the pore structure" were also known. *See, e.g., id.* (citing Ex. 1127 at 2); *see also id.* at ¶ 165. Longer periods of incubation would have been obvious in order to further facilitate growth within the material. Ex. 1003 at ¶ 703. WO 97/09286 in view of Bioceramics 1993 in further view of Ohgushi 1990 therefore would have rendered claim 4 obvious. *See generally id.* at § IV.B.3.

#### 5. Claim 9 Is Anticipated by WO 97/09286

WO 97/09286 anticipates claim 9 under 35 U.S.C. § 102(b) because it teaches that the disclosed compounds can be formed as "thin films, coatings, powders and bulk ceramic pieces." Ex. 1003 at ¶ 467 (citing Ex. 1017 at 6).

#### 6. Claims 9 and 18 Would Have Been Obvious Based on WO 97/09286 In View of the '303 Patent

If WO 97/09286 does not anticipate the methods described in claim 1, those

methods would have been obvious based on WO 97/09286 in view of the '303 patent. *See supra*, at § IV.A.2. Claim 2 would also have been obvious in view of these references. *See supra*, at § IV.A.3. WO 97/09286 states that the disclosed compounds can be formed as "thin films, coatings, powders and bulk ceramic pieces." Ex. 1003 at ¶ 708 (citing Ex. 1017 at 6). These references therefore would have also rendered obvious claim 9 and 18. *Id.*

#### 7. Claim 36 Would Have Been Obvious Based on WO 97/09286 In View of Bioceramics 1993 and Oghushi 1990

The biomaterial compound of claim 4 is the same as the compound of claims 1 and 2 and is disclosed in WO 97/09286, *id.* at ¶¶ 588, 601, which further discloses that the compounds may be formed as "thin films, coatings, powders and bulk ceramic pieces." *Id.* at ¶ 716 (citing Ex. 1017 at 6). The combination of these references therefore also would have rendered obvious claim 36. *Id.* at ¶¶ 714-717.

#### 8. Claim 11 Is Anticipated by WO 97/09286

WO 97/09286 anticipates claim 11 for the same reasons set forth in § IV.A.1 above, as the compounds described in WO 97/09286 will necessarily include Si-TCP, which contains silicon. *See generally* Ex. 1003 at §§ IV.B.1.a, IV.B.2.a.

#### 9. Claims 11 and 20 Would Have Been Obvious Based on WO 97/09286 In View of the '303 Patent

If WO 97/09286 does not anticipate the method described in claim 1, the method would have been obvious based on WO 97/09286 in view of the '303 patent. *See generally id.* at §§ IV.B.1.a and IV.B.2.b. Claim 2 would also have

been obvious based on WO 97/09286 in view of the '303 patent. *Id.* The compounds in each of these claims is disclosed in WO 97/09286 and will necessarily include Si-TCP, which contains silicon. *See generally id.* at § IV.B.1.a. These references would have rendered obvious claims 11 and 20. *Id.*

### 10. Claim 38 Would Have Been Obvious Based on WO 97/09286 In View of Bioceramics and Oghushi 1990

Like the compound of claims 1 and 2, the biomaterial compound of claim 4 is disclosed in WO 97/09286, and will necessarily include Si-TCP, which contains silicon. *Id.* at §§ IV.B.1.a and IV.B.3. The combination of these references therefore also would have rendered obvious claim 38. *Id.*

### 11. Claims 16 and 25 Would Have Been Obvious Based on WO 97/09286 In View of the '303 Patent

Claims 16 and 25 require that the biomaterial compound described in the methods of claims 1 and 2, respectively, be provided as "a composition additionally comprising at least one calcium phosphate material selected from the group consisting of calcium hydroxyapatite, α-TCP, β-TCP, [etc.]." *Id.* at ¶¶ 718-719. Combining the biomaterial compound of claims 1 and 2 in the methods described with an additional Ca-P component would have been an obvious design choice given that Ca-P materials having more than one Ca-P component (*e.g.*, both TCP and HA) were well known, and routinely used in clinical applications. *Id.* at ¶ 722; *see also id.* at ¶¶ 76-78, 89, 93, 147-148, 550-562.

HA and TCP were known to exhibit different rates of bioresorbability. *See* Ex. 1003 at ¶¶ 92, 723. Under similar conditions, the resorbability of HA was, in general, lower than that of TCP. *Id.* In order to engineer the resorption rate of Ca-P implant materials to suit different purposes, it would have been obvious to make Ca-P materials having multiple Ca-P components. *Id.* at ¶ 723.

For example, the '303 patent, which a person of ordinary skill in the art would have considered in conjunction with WO 97/09286, *see id.* at ¶¶ 725-726, identifies the benefits of a TCP/HA combination: TCP provides "a soluble phase … which initiates the giant cell response, is resorbed and may initiate osteoblast differentiation, and that it provides local calcium phosphate to form calcified woven bone. The remaining hydroxyapatite appears to provide an appositional interface and scaffold for the new bone formation." *Id.* at ¶ 724 (citing Ex. 1026 at col. 4:33-39). According to the '303 patent, the two components may be prepared separately and combined in an admixture. *Id.* at ¶ 725. Adding the components separately would be an easy to way to control the amount of each component in the final composition. *Id.* at ¶ 726. Given the wide use of composite Ca-P material in bone implant applications, and the specific teachings in the '303 patent (including the positive results reported therein, *see generally id.* at § IV.A.16), the person of ordinary skill in the art would have found the subject matter of claims 16 and 25 obvious based on WO 97/09286 in view of the '303 patent. *Id.* at ¶¶ 725-726; *see*

*generally id.* at §§ IV.D and IV.D.1. The combination of these references not only would have rendered obvious the methods claimed in claims 1 and 2, but also the compositions claimed in claims 16 and 25.

### 12. Claim 43 Would Have Been Obvious Based on WO 97/09286 In View of Bioceramics 1993 and Ohgushi 1990 In Further View of the '303 Patent

The biomaterial compound of claim 4is the same biomaterial compound of claims 1 and 2. Ex. 1003 at ¶ 588. For the same reason that it would have been obvious to combine the compound of claims 1 and 2 with another Ca-P component in view of the '303 patent, it would also have been obvious to combine the compound of claim 4 with another Ca-P component in further view of the '303 patent. *Id.* at ¶ 745. The person of ordinary skill in the art would have considered WO 97/09286 in view of Bioceramics 1993 and Ohgushi 1990 in further view of the 303 patent because each reference relates to the study and development of Ca-P bone implant material. Ex. 1003 at ¶ 745. The combination of WO 97/09286, Bioceramics 1993, Ohgushi 1990 and the '303 patent would therefore have rendered obvious claim 43. *Id.*; *see generally id.* at § IV.E.

### 13. Claims 17 and 26 Would Have Been Obvious Based on WO 97/09286 In View of the '303 Patent In Further View of Chaki 1994

Claims 17 and 26 require that the composition of claims 16 and 25, respectively, comprise "an additive to increase the mechanical toughness and

strength of" the biomaterial compound. *Id.* at ¶ 746. This claim would have been obvious based on WO 97/09286 in view of the '303 patent and Chaki 1994. *Id.*

Efforts to increase the mechanical strength and toughness of Ca-P materials were well known. Bioceramics 1993 for, example, notes that the "flexural strength and fracture toughness" of HA makes it an "unsuitable material for load-bearing situations." *Id.* at ¶ 747 (citing Ex. 1021 at 86). The '303 patent also recognizes that Ca-P composites may be useful with "augmentation with metal or polymer instrumentation in stress-bearing locations…." *Id.* (citing Ex. 1026 at col. 2:45-3:9). The reference notes that the disclosed materials do "not have initial structural strength suitable for use as a stress-bearing material." *Id.* (citing Ex. 1026 at col. 2:60-64). EP0353476 states that "sintered calcium phosphate…is not necessarily satisfactory in practice because it is neither mechanically strong nor tough." *Id.* at ¶ 748 (citing Ex. 1132 at 2). EP0353476 thus provides methods for improving the mechanical strength and toughness of Ca-P materials such as TCP (Example 11) and HA (Example 1) using reinforcing "whiskers" that are dispersed within the Ca-P composite. *Id.*

Chaki 1994 is a printed publication and is prior art under 35 § U.S.C. 102(b) to the claims. *Id.* at ¶ 581. A summary of the publication is provided in Ex. 1003 at § IV.A.20. The person of ordinary skill in the art would have considered Chaki in conjunction with WO 97/09286 and the '303 patent because each reference

relates to the development and use of Ca-P material suitable for use as bone implants. *Id.* at ¶ 749.

Chaki 1994 further recognizes the need to increase strength of Ca-P implant material. *Id.* at ¶ 748. Chaki 1994 observes that "HA implants often develop cracks" and that the "brittleness of HA is a serious obstacle to its use as load-bearing implants." *Id*. at ¶ 582 (citing Ex. 1130 at 1). Chaki 1994 reports that many efforts had been made to increase to mechanical strength and "fracture toughness" of HA by mixing HA with other materials, such polyethylene, poly(L-lactide), other ceramics such as $Al_2O_3$, and metal. *Id.* (citing Ex. 1130 at 1-2). Chaki 1994 proposes that silver particles can reinforce HA and found that the silver "increased the flexural strength" and observed that silver "provided a considerable reinforcement to HA." *Id*. at ¶¶ 583-84 (citing Ex. 1130 at 8-9); *see generally id*. at § IV.A.20.

Given that it was known that increasing the mechanical strength and toughness of Ca-P implant materials was desirable in certain applications, the person of ordinary skill in the art would have been motivated to introduce additives to compositions containing the biomaterial compound of claim 1. *Id.* at ¶ 750. The person of ordinary skill in the art would have had a reasonable expectation of success given the many methods disclosed in the art for using additives to increase the strength and toughness of Ca-P materials, such as those disclosed in Chaki

1994. *See id.* at ¶¶ 747-751; *see generally id.* at § IV.F. WO 97/09286 in view of the '303 patent in further view of Chaki 1994 therefore would have rendered obvious claims 17 and 26. *See generally* Ex. 1003 at § IV.F.

#### 14. Claim 44 Would Have Been Obvious Based on WO 97/09286 In View of Bioceramics 1993 and Ohgushi 1990 In Further View of the '303 Patent In Further View of Chaki 1994

As discussed *supra*, in § IV.A.12, the combination of WO 97/09286, Bioceramics 1993, Ohgushi 1990, and the '303 patent would have rendered obvious claim 43. Introducing additives to compositions comprising the biomaterial compound of claim 4 (*i.e.*, claim 43) would have been obvious in further view of Chaki 1994 for the same reasons that introducing an additive to compositions comprising the biomaterial compound of claims 1 and 2 would have been obvious in view of Chaki 1994. *See supra*, at § IV.A.13. The combination of WO 97/09286 in view of Bioceramics 1993 and Oghushi 1990 in further view of the '303 patent and Chaki 1994 therefore would have rendered obvious claim 44. *Id.*; *see also generally* Ex. 1003 at § IV.F.

### B. Claims 1, 2, 4, 9, 11, 16-18, 20, 25-26, 36, 38, and 43-44 Are Unpatentable Over Ruys 1993a

Ruys 1993a (Ex. 1011) is a printed publication that is prior art under 35 § U.S.C. 102(b) to the claims. Ex. 1003 at ¶ 353. A summary of the publication is provided in Ex. 1003 at § IV.A.2. Ruys 1993a reports "silicon doping" of HA. *Id.*

at ¶ 358. Ruys 1993a states that "[i]f silicon is a bone mineralising agent, it may be possible to enhance the bioactivity of HAP (and other biomaterials) by means of silicon doping." *Id.* (quoting Ex. 1011 (Ruys 1993a) at 1).

#### 1. Claim 1 Would Have Been Obvious Based on Ruys 1993a In View of the '303 Patent

Ruys 1993a (Ex. 1011) describes a process for producing multi-phasic Ca-P material that is strikingly similar to the methods disclosed in the '992 patent. Ex. 1003 at ¶¶ 219-228, 359-361, 369, Appendix D. Both use a sol-gel process to make stoichiometric HA (*i.e.*, HA having a Ca to P ratio of 1.67 consistent with the chemical formula of HA which includes 10 calcium atoms for every 6 phosphorous atoms) using calcium nitrate and ammonium dihydrogen phosphate. *Id.* at ¶ 369. An organo-silicate (tetraethylorthosilicate (TEOS) or tetrapropylorthosilicate (TPOS) in the '992 patent; ethyl silicate (equivalent to TEOS) in Ruys 1993a) is then added to the HA and the resulting precipitate is dried and sintered at temperatures of around 1000º C for one hour. *Id.* at ¶¶ 369, Appendix D.

The methods disclosed in Ruys 1993a are equivalent to the methods disclosed in the '992 patent and therefore necessarily resulted in products having the same physical, chemical, and biological properties, including "biomaterial" properties. *Id.* at ¶¶ 369, 610.

Ruys 1993a suggests that the process created a silicon "substituted"-HA. *Id.* at ¶ 613; Ex. 1011 at 4. However, subsequent work by the inventors of the '992

patent has demonstrated that the methods used in Ruys 1993a actually result in the formation of multi-phasic Ca-P mixtures containing HA and *Si-TCP*. Ex. 1003 at ¶¶ 369-370, 612-613 (citing Ex. 1119 ("Sayer 2003") at 1). The multi-phasic Ca-P mixtures that result from the Ruys 1993a (Ex. 1011) process therefore necessarily included silicon-substituted TCP (Si-TCP) as one component. *Id.* at ¶¶ 369-370, 612-613. According to the '992 patent, silicon has an ionic radius of 0.40 Å. Ex. 1001 at col. 32:15-45; Ex. 1003 at ¶ 615. Thus, Ca-P materials made by the processed disclosed in Ruys 1993a are inherently the same "biomaterial compounds" that are claimed in claims 1, 2, and 4 (the independent claims of the '992 patent). Ex. 1003 at ¶¶ 614-615; *see also generally id.* at § IV.B.1.b.

As discussed, during prosecution of the application resulting in the '146 patent (to which the '992 claims benefit), the Examiner rejected the claims in view of Ruys 1993b, a reference that discloses methods that are equivalent to Ruys 1993a. Ex. 1003 at ¶¶ 268-272, 616. According to the Examiner, Ruys 1993b teaches "an isolated bioresorbable biomaterial compound" wherein "silicon substituted for a portion of the phosphorous atoms in the compound." *Id.* at ¶ 269 (citing Ex. 1007 at 138). Patent Owner did not dispute the Examiner's characterization and instead amended the claims to add the limitation "wherein said compound has a microporous structure." *Id.* at ¶ 270 (citing Ex. 1007 at 158). The claims of the '992 patent do not include the "microporous structure"

limitation. *Id.* at ¶ 272. Therefore, the "biomaterial compound" of the claims is not distinguishable over Ruys 1993a or Ruys 1993b (discussed in § IV.C, below) based on this structural feature. *See* Ex. 1003 at ¶¶ 272, 616.

Using the biomaterial compound disclosed in Ruys 1993a in bone implant applications involving the substitution of bone at surgical sites would have been obvious. *See generally* Ex. 1003 at § IV.B.2.b. Indeed, Ruys 1993 suggests that the Ca-P material made by the methods described in the publication may be "suitable for clinical trials." *Id.* at ¶ 617.

As discussed above at § IV.A.2, the use of Ca-P materials in bone implant applications was well known. *See, e.g.,* Ex. 1003 at § IV.B.2.b (citing Ex. 1021 at 120-122, Ex. 1027 at 2-9, Ex. 1089 at 2, Ex. 1102 at col. 2:3-11); *see also* Ex. 1003 at §§ II.E.1 and II.E.5. A person of ordinary skill would have considered Ruys 1993a in conjunction with the '303 patent, as each is directed to the development and use of Ca-P materials suitable for use as bone implants. *Id.* at ¶ 673. The '303 patent is discussed in detail above, at § IV.A.2, and a summary of the publication is found at Ex. 1003 at § IV.A.16.

Given the known properties of Ca-P materials such as TCP and HA, *see* Ex. 1003 at ¶¶ 76-79, 90-91, 686; *see also generally id.* at §§ II.E.1 and II.E.5, and the guidance provided in the '303 patent—which discloses implantation of Ca-P material at the site of skeletal surgery in place of bone—the person of ordinary

skill in the art would have been motivated to use the biomaterial compounds described Ruys 1993a in methods that involved "substituting natural bone at sites of skeletal surgery in human and animal hosts" where the methods further involved "implanting said biomaterial compound at the site of skeletal surgery." *Id.* at ¶ 684. The person of ordinary skill in the art would have had a reasonable expectation of success given the extensive literature describing the clinical and surgical uses of Ca-P compounds, which included the very use claimed. *Id.*

Finally, as discussed above in § IV.A.1, the remainder of claim 1 does nothing more than describe inherent functional properties and capabilities of a previously disclosed compound. *See* Ex. 1003 at ¶¶ 76-79, 90-91, 686; *see generally id.* at §§ II.E.1 and II.E.5. Claim 1 is therefore obvious based on Ruys 1993a in view of the '303 patent. Ex. 1003 at ¶ 687; *see also generally id.* at §§ IV.B.1.b and IV.B.2.b.

### 2. Claim 2 Would Have Been Obvious Based on Ruys 1993a In View of the '303 Patent

As explained above, *supra*, at § IV.A.3, the '303 patent describes implanting Ca-P ceramic into a living animal using standard surgical techniques for uses such as "the bridging of segmental defects in delayed union or non-union of fractures." Ex. 1003 at ¶¶ 681-683. The biomaterial compound of claim 1 is the same as the biomaterial compound of claim 2. *Id.* at ¶ 588. The recitation of functional properties and capabilities that inherently result from the implantation of the

biomaterial compound cannot impart a patentable distinction. *Id.* at ¶¶ 76-79, 90-91, 686; *see generally id.* at §§ II.E.1 and II.E.5. For the same reasons that Ruys 1993a in view of the '303 patent would have rendered claim 1 obvious, the combination of these references also would have rendered claim 2 obvious. *See id.* at ¶ 687; *see also generally id.* at §§ IV.B.1.b and IV.B.2.b.

### 3. Claim 4 Would Have Been Obvious Based on Ruys 1993a In View of Bioceramics 1993 and Ohgushi 1990

Ruys 1993a discloses the biomaterial compound of claim 4. *See supra*, at § IV.B.1. As discussed above at § IV.A.4, forming Ca-P compounds, such as those disclosed in Ruys 1993a, as an open cell structure with interconnected voids would have been an obvious design choice in order to facilitate bone ingrowth and vascularization within the implant material. Ex. 1003 at ¶ 697. Bioceramics 1993 teaches that such macrostructural features are "ideal." *Id.* Ohgushi discloses the benefits of combining Ca-P material exhibiting an open cell configuration with interconnected voids with bone marrow in order to further promote bone growth within the implant material. *Id.* at ¶ 701. The person of ordinary skill in the art would have considered these references together as each relates to the development and use of Ca-P bone implant material. *Id.* at ¶ 696. The combination of Ruys 1993a, Bioceramics 1993, and Ohgushi 1990 therefore would have rendered claim 4 obvious. *Id.* at ¶ 702; *see also generally id.* at §§ IV.B.1.c and IV.B.3.

#### 4. Claims 9 and 18 Would Have Been Obvious Based on Ruys 1993a In View of the '303 Patent

Ruys 1993a discloses that the material was made as a powder (*i.e.*, a dried colloidal mixture) that was then tabletted. *Id.* at ¶ 709 (citing Ex. 1011 at 3). Claims 9 and 18 therefore would have been rendered obvious by Ruys 1993a in view of the '303 Patent. *Id.*

#### 5. Claim 36 Would Have Been Obvious Based on Ruys 1993a In View of Bioceramics 1993 and Oghushi 1990

Ruys 1993a discloses that the material was made as a powder (*i.e.*, a dried colloidal mixture) that was then tabletted. *Id.* at ¶ 709 (citing Ex. 1011 at 3). Claim 36 therefore would have been rendered obvious by Ruys 1993a in view of Bioceramics 1993 and Oghushi 1990. *Id.* at ¶ 714-717.

#### 6. Claims 11 and 20 Would Have Been Obvious Based on Ruys 1993a In View the '303 Patent

Ruys 1993a in view of the '303 Patent would have rendered claims 11 and 20 obvious because the compound in Ruys 1993a necessarily includes Si-TCP, wherein silicon has "substituted" for phosphorous in the TCP structure. *See id.* at ¶ 613; *see also generally id.* at §§ IV.B.1.b and IV.B.2.b.

#### 7. Claim 38 Would Have Been Obvious Based on Ruys 1993a In View of Bioceramics 1993 and Oghushi 1990

Ruys 1993a in view of Bioceramics 1993 and Oghushi 1990 would have rendered claim 36 obvious because the compound in Ruys 1993a necessarily includes Si-TCP, wherein silicon has "substituted" for phosphorous in the TCP

structure. *See id.* at ¶ 613; *see also generally id.* at §§ IV.B.1.b and IV.B.3.

#### 8. Claims 16 and 25 Would Have Been Obvious Based on Ruys 1993a In View of the '303 Patent

As discussed above at § IV.A.11, combining the biomaterial compound of claims 1 and 2 with an additional Ca-P component would have been an obvious design choice given that Ca-P materials having more than one Ca-P component (*e.g.*, both TCP and HA) were well known and routinely used in clinical applications. Ex. 1003 at ¶¶ 76-78, 89, 93, 147-148, 550-562, 722. The '303 patent, which the person of ordinary skill in the art would have considered in conjunction with Ruys 1993a for the reasons explained above at § IV.B.1, identifies the benefits of, for example, a TCP/HA combination. Ex. 1003 at ¶ 724. Given the wide use of composite Ca-P material in bone implant applications, and the specific teachings in the '303 patent (including the positive results reported therein, *see id.* at § IV.A.16), the person of ordinary skill in the art would have found the subject matter of claims 16 and 25 obvious in view of Ruys 1993a and the '303 patent. *Id.* at ¶ 730; *see generally id.* at §§ IV.D and IV.D.2.

#### 9. Claim 43 Would Have Been Obvious Based on Ruys 1993a In View Bioceramics 1993 and Oghushi 1990 In Further View of the '303 Patent

The biomaterial compound of claim 4 is disclosed in Ruys 1993a and is the same biomaterial compound of claims 1 and 2. Ex. 1003 at ¶ 588. For the same reason that it would have been obvious to combine the biomaterial compound of

claims 1 and 2 with another Ca-P component in view of the ’303 patent, it would also have been obvious to combine the biomaterial compound of claim 4 with another Ca-P component. *Id.* at ¶ 745. The person of ordinary skill in the art would have considered Ruys 1993a, Bioceramics 1993, Oghushi 1990 and the ’303 patent together as each relates to the study and use of Ca-P bone implant materials. *Id.* at ¶ 744. The combination of Ruys 1993a, Bioceramics 1993, Ohgushi 1990 and the ’303 patent would therefore have rendered obvious claim 43. *See generally id.* at § IV.E.

#### 10. Claims 17 and 26 Would Have Been Obvious Based on Ruys 1993a In View of the ’303 Patent In Further View of Chaki 1994

As discussed above at § IV.A.13, the addition of additives to increase the mechanical strength and toughness of Ca-P materials was well known. Ex. 1003 at ¶ 747. The person of ordinary skill would have considered Chaki 1994 in conjunction with Ruys 1993a and the ’303 patent as each reference relates to the development and use of Ca-P material for use as bone implants. *Id.* at ¶ 749.

Chaki 1994 recognizes the need to increase the mechanical strength and toughness of Ca-P implant material. *Id.* at ¶ 748. Chaki 1994 summarizes a number of methods that have been used to reinforce Ca-P implant material, including methods that involved the use of materials, such as polyethylene, poly(L-lactide), ceramics such as $Al_2O_3$, and metal. *Id.* Chaki 1994 also discloses the use

of silver to reinforce HA and found that such addition increased the flexural strength of the composite material. *Id.* at ¶¶ 748-750. Given that it was known that increasing the mechanical strength and toughness of Ca-P implant materials was desirable in certain applications, the person of ordinary skill in the art would have been motivated to introduce additives to compositions containing the biomaterial compound of claims 1 and 2. *Id.* at 750. The person of ordinary skill in the art would have had a reasonable expectation of success given the many methods disclosed in the art for using additives to increase the strength and toughness of Ca-P materials. *Id.* at ¶¶ 747-750. Claims 17 and 26 therefore would have been obvious in view of Ruys 1993a in view of the '303 patent in further view of Chaki 1994. *Id.*; *see generally id.* at § IV.F.

#### 11. Claim 44 Would Have Been Obvious Based on Ruys 1993a In View of Bioceramics 1993 and Oghushi 1990 In Further View of the '303 Patent and Chaki 1994

As discussed *supra*, in §IV.B.9, the combination of Ruys 1993a, Bioceramics 1993, Ohgushi 1990, and the '303 patent would have rendered obvious claim 43. Introducing additives to enhance the mechanical strength and toughness of compositions comprising the biomaterial compound of claim 4 (*i.e.*, claim 43) would have been obvious in further view of Chaki 1994 for the same reasons that introducing an additive to compositions comprising the biomaterial compound of claims 1 and 2 would have been obvious in view of Chaki 1994. *See*

*supra*, at § IV.B.10. The person of ordinary skill in the art would have considered Ruys 1993a, Bioceramics 1993, Oghushi 1990, the '303 patent, and Chaki 1994 together as each relates to the study and use of Ca-P bone implant materials. *Id.* The combination of Ruys 1993a in view of Bioceramics 1993 and Oghushi 1990 in view of the '303 patent in further view of Chaki 1994 therefore would have rendered obvious claim 44. *Id.*; *see generally* Ex. 1003 at § IV.F.

### C. Claims 1, 2, 4, 9, 11, 16-18, 20, 25-26, 36, 38, and 43-44 Are Unpatentable Over Ruys 1993b

Ruys 1993b is a printed publication and is prior art under 35 § U.S.C. 102(b) to the claims. Ex. 1003 at ¶ 383. A summary of the publication is provided in Ex. 1003 at § IV.A.4. Ruys 1993b suggests that "The purpose of the present work was to address the potential benefits and problems involved in the silicon doping of HAp, since HAp has the advantage over bioactive glasses and glass-ceramics of being chemically similar to bone material." *Id.* at ¶ 387 (citing Ex. 1014 at 4).

#### 1. Claim 1 Would Have Been Obvious Based on Ruys 1993b In View of the '303 Patent

Ruys 1993b (Ex.1014) describes a process for producing multi-phasic Ca-P material that is strikingly similar to the methods disclosed in the '992 patent. *Id.* at ¶ 399, Appendix E. Both processes use a sol-gel process to make stoichiometric HA. *Id*. This HA is then used as a starting material for the addition of silicon using an organo-silicate via sintering. *Id*.

In both Ruys 1993b and the patent, HA is made using calcium nitrate and ammonium dihydrogen phosphate. Ex. 1003 at ¶ 620, Appendix E. An organo-silicate (TEOS in Ruys 1993b; TEOS or TPOS in the '992 patent) is then added to the HA and the resulting precipitate is dried and sintered at temperatures of around 1000º C for one hour. *Id.* The methods disclosed in Ruys 1993b are equivalent to the methods disclosed in the '992 patent and therefore necessarily resulted in products having the same physical, chemical, and biological properties. *Id.* at ¶ 621. The materials disclosed would therefore necessarily be bioresorbable, bioactive, and hence useful as a "biomaterial." *Id*. at ¶¶ 621-622.

Ruys 1993b suggests in the paper that the process created a silicon "substituted"-HA. Ex. 1003 at ¶ 623; Ex. 1014 (Ruys 1993b) at 2. However, subsequent work by the inventors of the '992 patent has demonstrated that the methods used in Ruys 1993b actually result in the formation of multi-phasic Ca-P mixtures containing HA and *Si-TCP*. *See* Ex. 1003 at ¶ 623; Ex. 1119 at 1. The multi-phasic Ca-P mixtures that result from the Ruys 1993b (Ex. 1014) process therefore necessarily included silicon substituted-TCP (Si-TCP) as one component. Ex. 1003 at ¶ 626. According to the '992 patent, silicon has an ionic radius of 0.40 Å. Ex. 1001 at col. 32:15-45; Ex. 1003 at ¶ 626. Thus, Ca-P materials made by the processed disclosed in Ruys 1993b are inherently the same "biomaterial compounds" that are claimed by claim 1. Ex. 1003 at ¶ 626.

During examination of the ’872 application, the Ruys 1993b reference was found to describe the same process as in the ’872 application (identical to WO 97/09286), which is also the same process described in the ’992 patent for producing the claimed “biomaterial compounds.” *See id.* at ¶ 624. Specifically, the Board upheld a rejection for anticipation, stating: “It appears that Appellants are doing no more than what Ruys [1993b] discloses. That is, Applicants have doped hydroxyapatite with silicon (stabilizing entity) to produce a product that includes α-TCP.” *Id.* (citing Ex. 1113 at 45).

For analogous reasons, the method described in Ruys 1993b (Ex. 1014) inherently will result in a compound meeting the requirements of the claims. Ex. 1003 at ¶ 625. During prosecution of the application resulting in the ’251 patent (which reissued from a patent to which ’992 claims benefit), the Examiner rejected the claims in view of Ruys 1993b. *Id.* at 268-272. According to the Examiner, Ruys 1993b teaches “an isolated bioresorbable biomaterial compound” wherein “silicon substituted for a portion of the phosphorous atoms in the compound.” *Id.* Patent Owner did not dispute the Examiner’s characterization and instead amended the claims to add the limitation “wherein said compound has a microporous structure.” *Id.* The claims of the ’992 patent do not include this “microporous structure” limitation. *Id.*

Using the biomaterial compound disclosed in Ruys 1993a in bone implant

applications involving the substitution of bone at surgical sites would have been obvious. *See generally* Ex. 1003 at § IV.B.2.b. Indeed, Ruys 1993b states that the materials made by the processes disclosed in the reference may be assessed in "clinical trials." *Id.* at ¶ 627.

As discussed above at § IV.A.2, the use of Ca-P materials in bone implant applications was well known. *See, e.g.,* Ex. 1003 at § IV.B.2.b (citing Ex. 1021 at 120-122, Ex. 1027 at 2-9, Ex. 1089 at 2, Ex. 1102 at col. 2:3-11). A person of ordinary skill would have considered Ruys 1993a in conjunction with the '303 patent, as each is directed to the development and use of Ca-P materials suitable for use as bone implants. *Id.* at ¶ 673. The '303 patent is discussed in detail above, at § IV.A.2 and summary of the publication is found at Ex. 1003 at § IV.A.16.

Given the known properties of Ca-P materials such as TCP and HA, *see id.* at ¶¶ 76-79, 90-91, 686; *see generally id.* at §§ II.E.1 and II.E.5, and the guidance provided in the '303 patent—which discloses implantation of Ca-P material at the site of skeletal surgery in place of bone—the person of ordinary skill in the art would have been motivated to use the biomaterial compounds described Ruys 1993b in methods that involved "substituting natural bone at sites of skeletal surgery in human and animal hosts" where the methods further involved "implanting said biomaterial compound at the site of skeletal surgery." Ex. 1003 at

¶ 684. The person of ordinary skill in the art would have had a reasonable expectation of success given the extensive literature describing the clinical and surgical uses of Ca-P compounds, which included the very use claimed. *Id.*

Finally, as discussed above in § IV.A.1, the remainder of claim 1 does nothing more than describe inherent functional properties and capabilities of a previously disclosed compound. *See* Ex. 1003 at ¶¶ 76-79, 90-91, 686; *see generally id.* at §§ II.E.1 and II.E.5. Claim 1 is therefore obvious based on Ruys 1993b in view of the '303 patent. Ex. 1003 at ¶ 687; *see also generally id.* at §§ IV.B.1.c and IV.B.2.b.

### 2. Claim 2 Would Have Been Obvious Based on Ruys 1993b In View of the '303 Patent

As explained above, *supra*, at § IV.A.3, the '303 patent describes implanting Ca-P ceramic into a living animal using standard surgical techniques for uses such as "the bridging of segmental defects in delayed union or non-union of fractures." Ex. 1003 at ¶¶ 681-683. The biomaterial compound of claim 1 is the same as the biomaterial compound of claim 2. *Id.* at ¶ 588. The recitation of functional properties and capabilities that inherently result from the implantation of the biomaterial compound cannot impart a patentable distinction. *Id.* at ¶¶ 76-79, 90-91, 686; *see generally id.* at §§ II.E.1 and II.E.5. For the same reasons that Ruys 1993b in view of the '303 patent would have rendered claim 1 obvious, the combination of these references also would have rendered claim 2 obvious. *See id.*

at ¶ 687; *see also generally id.* at §§ IV.B.1.c and IV.B.2.b.

#### 3. Claim 4 Would Have Been Obvious Based on Ruys 1993b In View of Bioceramics 1993 and Oghushi 1990

Ruys 1993b discloses the biomaterial compound of claim 4. *See supra*, at § IV.C.1. As discussed above at § IV.A.4, forming Ca-P compounds, such as those disclosed in Ruys 1993b, as an open cell structure with interconnected voids would have been an obvious design choice in order to facilitate bone ingrowth and vascularization within the implant material. Ex. 1003 at ¶ 697. Bioceramics 1993 teaches that such macrostructural features are "ideal." *Id.* Ohgushi discloses the benefits of combining Ca-P material exhibiting an open cell configuration with interconnected voids with bone marrow in order to further promote bone growth within the implant material. *Id.* at ¶ 701. The person of ordinary skill in the art would have considered these references together as each relates to the development and use of Ca-P bone implant material. *Id.* at ¶ 696. The combination of Ruys 1993b, Bioceramics 1993, and Ohgushi 1990 therefore would have rendered claim 4 obvious. *Id.* at ¶ 702; *see also generally id.* at §§ IV.B.1.c and IV.B.3.

#### 4. Claims 9 and 18 Would Have Been Obvious Based on Ruys 1993b In View of the '303 Patent

Ruys 1993b discloses that the implant material was made as a powder (*i.e.*, a crushed filter cake) that was pelletted. *Id.* at ¶ 710 (citing Ex. 1014 at 7). Claims 9 and 18 therefore would have been rendered obvious by Ruys 1993b in view of the

'303 Patent. *Id.*

#### 5. Claim 36 Would Have Been Obvious Based on Ruys 1993b In View of Bioceramics 1993 and Oghushi 1990

Ruys 1993b discloses that the implant material was made as a powder (*i.e.*, a crushed filter cake) that was pelletted. *Id.* at ¶ 710 (citing Ex. 1014 at 7). Claim 36 therefore would have been rendered obvious by Ruys 1993a in view of Bioceramics 1993 and Oghushi 1990. *Id.* at ¶ 714-717.

#### 6. Claims 11 and 20 Would Have Been Obvious Based on Ruys 1993b In View the '303 Patent

Ruys 1993b in view of the '303 Patent, would have rendered claims 11 and 20 obvious because the compound in Ruys 1993a necessarily includes Si-TCP, wherein silicon has "substituted" for phosphorous in the TCP structure. *See id.* at ¶ 626; *see also generally id.* at §§ IV.B.1.c and IV.B.2.b.

#### 7. Claim 38 Would Have Been Obvious Based on Ruys 1993b In View of Bioceramics 1993 and Oghushi 1990

Ruys 1993b in view of Bioceramics 1993 and Oghushi 1990 would have rendered claim 38 obvious because the compound in Ruys 1993a necessarily includes Si-TCP, wherein silicon has "substituted" for phosphorous in the TCP structure. *See id.* at ¶ 626; *see also generally id.* at §§ IV.B.1.c and IV.B.3.

#### 8. Claims 16 and 25 Would Have Been Obvious Based on Ruys 1993b In View of the '303 Patent

As discussed above at § IV.A.11, combining the biomaterial compound of claims 1 and 2 with an additional Ca-P component would have been an obvious

design choice given that Ca-P materials having more than one Ca-P component (*e.g.*, both TCP and HA) were well known, and routinely used in clinical applications. Ex. 1003 at ¶¶ 76-78, 89, 93, 147-148, 550-562, 722. The '303 patent, which the person of ordinary skill in the art would have considered in conjunction with Ruys 1993b for the reasons explained above at § IV.B.1, identifies the benefits of, for example, a TCP/HA combination. Ex. 1003 at 724. According to the '303 patent, the two components may be prepared separately and combined in an admixture. *Id.* Adding the components separately would be an easy to way to control the amount of each component in the final composition. *Id.* at ¶ 732. Given the wide use of composite Ca-P material in bone implant applications, and the specific teachings in the '303 patent (including the positive results reported therein, *see id.* at § IV.A.16), the person of ordinary skill in the art would have found the subject matter of claims 16 and 25 obvious in view of Ruys 1993b and the '303 patent. *Id.* at ¶ 733*; see generally id.* at §§ IV.D and IV.D.3.

#### 9. Claim 43 Would Have Been Obvious Based on Ruys 1993b In View Bioceramics 1993 and Oghushi 1990 In Further View of the '303 Patent

The biomaterial compound of claim 4 is the same biomaterial compound of claims 1 and 2. Ex. 1003 at ¶ 588. The person ordinary skill in the art would have considered Ruys 1993b, Bioceramics 1993, Oghushi 1990 and the '303 patent together as each relates to the development and study of Ca-P bone implant

material. *Id.* at ¶ 744. For the same reasons that combining the compound of claims 1 and 2 with another Ca-P component would have been obvious in the methods described in each of the claims in view of the '303 patent, combining the compound of claim 4 with another Ca-P component would also have been obvious in view of the '303 patent. *See generally id.* at § IV.E.

### 10. Claims 17 and 26 Would Have Been Obvious Based on Ruys 1993b In View of the '303 Patent In Further View of Chaki 1994

As discussed above at § IV.A.13, the addition of additives to increase the mechanical strength and toughness of Ca-P materials was well known. Ex. 1003 at ¶ 747. The person of ordinary skill in the art would have considered Chaki 1994 in conjunction with Ruys 1993b and the '303 patent because each reference relates to the development and use of Ca-P material suitable for use as bone implants. *Id.* at ¶ 749. Chaki 1994 recognizes the need to increase the strength and toughness of Ca-P implant material. *Id.* at ¶ 748. Chaki 1994 summarizes a number of methods that have been used to reinforce Ca-P implant material, including methods that involved the use of materials, such as polyethylene, poly(L-lactide), ceramics such as $Al_2O_3$, and metal. *Id.* Chaki 1994 also discloses the use of silver to reinforce HA and found that such addition increased the flexural strength of the composite material. *Id.* at ¶¶ 748-750. Given that it was known that increasing the mechanical strength and toughness of Ca-P implant materials was desirable in

certain applications, the person of ordinary skill in the art would have been motivated to introduce additives to compositions containing the biomaterial compound of claims 1 and 2. *Id.* at ¶ 750. The person of ordinary skill in the art would have had a reasonable expectation of success given the many methods disclosed in the art for using additives to increase the strength and toughness of Ca-P materials. *Id.* at ¶¶ 747-750. Claims 17 and 26 therefore would have been obvious in view of Ruys 1993b in view of the '303 patent in further view of Chaki 1994. *Id.*; *see generally id.* at § IV.F.

#### 11. Claim 44 Would Have Been Obvious Based on Ruys 1993b In View of Bioceramics 1993 and Oghushi 1990 In Further View of the '303 Patent In Further View of Chaki 1994

As discussed *supra*, in §IV.C.9, the combination of Ruys 1993a, Bioceramics 1993, Ohgushi 1990, and the '303 patent would have rendered obvious claim 43. Introducing additives to compositions comprising the biomaterial compound of claim 4 would have been obvious in further view of Chaki 1994 for the same reasons that introducing an additive to compositions comprising the biomaterial compound of claims 1 and 2 would have been obvious in view of Chaki 1994. *See supra*, at § IV.C.10. The person of ordinary skill in the art would have considered these Ruys 1993b, Bioceramics 1993, Oghushi 1990, the '303 patent, and Chaki 1994 together as each relates to the development and study of Ca-P bone implant material. *Id.* The combination of Ruys 1993b in

view of Bioceramics 1993 and Oghushi 1990 in further view of the ’303 patent in further view of Chaki 1994 therefore would have rendered obvious claim 44. *Id.*; *see generally* Ex. 1003 at § IV.F.

Petitioner reserves the right to identify alternative theories or evidence responsive to the contentions of the Patent Owner to establish claims 1, 2, 4, 9, 11, 16-18, 20, 25-26, 36, 38, and 43-44 are unpatentable over the identified prior art.

## V. CONCLUSION

For the foregoing reasons, the Petitioner respectfully requests that Trial be instituted and that claims 1, 2, 4, 9, 11, 16-18, 20, 25-26, 36, 38, and 43-44 of the ’992 patent be canceled.

Dated: September 24, 2013

Respectfully Submitted,

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# PETITION FOR INTER PARTES REVIEW

# OF U.S. PATENT NO. RE 41,251

## Attachment A:

## Proof of Service of the Petition

## CERTIFICATE OF SERVICE

I hereby certify that on this 24th day of September, 2013, a copy of this PETITION FOR INTER PARTES REVIEW has been served by Federal Express on the following address for patent owner(s):

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# PETITION FOR INTER PARTES REVIEW

# OF U.S. PATENT NO. RE 41,251

## Attachment B:

## List of Evidence and Exhibits Relied Upon in Petition

| Exhibit # | Reference Name |
|---|---|
| 1001 | U.S. Patent No. 6,585,992 (filed Oct. 4, 2001) |
| 1002 | U.S. Patent No. 6,585,992 (filed Oct. 4, 2001) File Wrapper |
| 1003 | Declaration of Dr. Antonios Mikos re '992 Patent with appendices |
| 1004 | Curriculum Vitae of Dr. Antonios Mikos |
| 1005 | WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY 1199 (Merriam-Webster Inc. 1993) |
| 1006 | U.S. Patent No. RE 41,251 (filed Jan. 30, 2008) |
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| 1102 | U.S. Patent No. 5,011,495 (filed Feb. 16, 1990) |
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| 1105 | Japanese Patent No. JPH 06277673A (filed Mar. 30, 1993) (original version and English Translation) |
| 1106 | Japanese Patent No. JP 07008550 (filed Jun. 28, 1993) (original version and English Translation) |
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| 1110 | Excerpt of U.S. Provisional Patent Application No. 60/003,157 (filed Sept. 1, 1995) File Wrapper |
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