Paper No. 1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

Millenium Biologix, LLC,
Patent Owner

Patent No. RE41,251
Issued: April 20, 2010
Filed: January 30, 2008
Inventors: Sydney M. Pugh, Timothy J. N. Smith,
Michael Sayer, and Sarah D. Langstaff

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

Inter Partes Review No. 2013-00582

PETITION FOR INTER PARTES REVIEW

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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 it is not barred or estopped from requesting *inter partes* review of U.S. Patent No. RE41,251 ("the '251 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 '251 patent; or (ii) has been served a complaint alleging infringement of the '251 patent more than a year prior to the present date. Also, the '251 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 '251 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 '251 patent is the subject of litigation in the Northern District of Illinois (Civil Action no. 1:13-cv-03084), which names as defendants Baxter, ApaTech, Inc., and ApaTech Limited. In addition, the '251 patent is the subject of IPR2013-00583, which was concurrently filed with this petition.

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

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4. Service on Petitioner

Service on Petitioner 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.

D. 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, 6, and 8-13 of the ’251 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, 6 and 8-13 are anticipated under § 102(a) by WO 97/09286 (Ex. 1017).

(2) Claim 8 would have been obvious under § 103 based on WO 097/09286 (Ex. 1017) in view of EP0267624 (Ex. 1024).

(3) Claims 1, and 8-13 are anticipated under § 102(b) by WO 94/26872 (Ex. 1015).

(4) Claim 8 would have been obvious under § 103 based on WO 094/26872 (Ex. 1015) in view of in view of EP0267624 (Ex. 1024).

(5) Claims 1, and 8-13 are anticipated under § 102(b) by Qiu 1993 (Ex. 1016).

(6) Claim 8 would have been obvious under § 103 based on Qiu 1993 (Ex. 1016) in view of in view of EP0267624 (Ex. 1024).

(7) Claims 1 and 8-13 are anticipated under § 102(b) by Ruys 1993a (Ex. 1011).

(8) Claim 6 would have been obvious under § 103 based on Ruys 1993a (Ex. 1011) in view of Bioceramics 1993 (Ex. 1021).

(9) Claim 6 would have been obvious under § 103 based on Ruys 1993a (Ex. 1011) in view of White 1986 (Ex. 1022).

(10) Claim 8 would have been obvious under § 103 based on Ruys 1993a

(Ex. 1011) in view of EP0267624 (Ex. 1024).

(11) Claims 1 and 8-13 are anticipated under § 102(b) by Ruys 1993b (Ex. 1014).

(12) Claim 6 would have been obvious under § 103 based on Ruys 1993b (Ex. 1014) in view of Bioceramics 1993 (Ex. 1021).

(13) Claim 6 would have been obvious under § 103 based on Ruys 1993b (Ex. 1014) in view of White 1986 (Ex. 1022).

(14) Claim 8 would have been obvious under § 103 based on Ruys 1993b (Ex. 1014) in view of EP0267624 (Ex. 1024).

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 '251 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. 1:26-31. In fact, the '251 patent equates the term Skelite™ with "Si-TCP" (*id*. at col. 10:32-33), 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. 17:48-52; Ex. 1003 at ¶¶ 168.

The '251 patent discloses two methods for producing Si-TCP (silicon substituted-TCP): one involves the use of quartz as the source of silicon to make a

thin-film (Example 3); the other involves the use of an organo-silicate as the source of silicon (Example 5). Ex. 1003 at ¶¶ 169. Both processes start with the 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 un-substituted HA and Si-TCP. *See* Ex. 1001 at Examples 1-3, 5; Ex. 1003 at ¶¶ 219-238.

A. Prosecution History and Effective Filing Date of the '251 Patent

1. Prosecution of the '251 Reissue Patent

The '251 patent is a reissue of U.S. Patent No. 6,323,146 ('146 patent), which originally issued from Application No. 09/044,749 ('749 application), filed on March 19, 1998. Ex. 1003 at ¶ 239. The '146 patent originally claimed benefit or priority to three applications: (i) U.S. Application No. 09/029,872 ('872 application), filed June 29, 1998, which is the national phase of PCT/CA96/00585, filed on August 30, 1996 and published as WO 97/09286; (ii) U.S. Application No. 08/576,238, filed December 21, 1995; and (iii) Provisional Application No. 60/003,157, filed September 1, 1995. *Id.* at ¶¶ 239-240. Each application is designated a C-I-P of the preceding application. *Id.*

The '251 patent was reissued from Application No. 12/022,946, filed January 30, 2008. *Id.* at ¶¶ 239-241. Patent Owner stated it 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 ¶ 239 (citing Ex. 1002 at 7). PCT/CA98/00046 was filed January 29, 1998. *Id.* at ¶ 242. Patent Owner did not request amendment of the claims with its reissue application. *Id.* at ¶¶ 239-242; Ex. 1002 at 7.

The Examiner rejected the claims in the reissue (*i.e.*, the original claims of the '146 patent) as being anticipated by Ruys 1993b (Ex. 1014), which the Examiner found taught "an isolated bioresorbable biomaterial compound" wherein "silicon substituted for a portion of the phosphorous atoms in the compound." Ex. 1003 at ¶¶ 243-244 (citing Ex. 1002 at 138). Patent Owner did not dispute the Examiner's characterization of Ruys 1993b. *Id.* at ¶ 245. 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.* at ¶ 246 (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.* at ¶ 246.

2. Prosecution of the Original '146 Patent

During examination of the '749 application that resulted in the '146 patent, Patent Owner pursued claims directed 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 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* that were being claimed. 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 applications were prior art*. Instead, Patent Owner amended the claim to include the word "isolated" and argued that neither publication *taught* an "isolated bioresorbable biomaterial compound." *Id.* at 198-

200 (concerning WO 94/26872) and at 202 (WO 97/09286). At the same time, Patent Owner argued that experimental data characterizing a *mixture* of un-substituted HA and Si-TCP supported its claims to an "isolated …compound." *See id.* at 305; *see also* Ex. 1001 at col. 10:66-67; Ex. 1003 at ¶¶ 317-318. In other words, Patent Owner argued that a *multi-phasic mixture* of Si-TCP and HA supported claims to an "isolated … compound." Yet there is no "isolation" step found in the '251 patent that differs from what is found in both WO 94/26872 and WO 97/09286, and certainly no step that results in separating the Si-TCP from a mixture that includes HA. Ex. 1003 at ¶¶ 305-307. Thus, while the '251 patent purports to have characterized Si-TCP within the mixtures made by the methods in WO 94/26872 and WO 97/09286, it provides no procedure for "isolating" the Si-TCP found in these prior art materials. *Id.* at ¶ 307.

3. Effective Filing Date of the Claims

The effective filing date of claims 1, 6 and 8-13 of the '251 patent is not earlier than January 29, 1998, the filing date of PCT/CA98/00046. *Id.* at ¶¶ 338-339. Applications filed prior to January 29, 1998 to which the '251 patent claims benefit or priority do not provide an adequate written description corresponding to the full scope of the subject matter encompassed by claims 1, 6 and 8-13 under 35 U.S.C. § 112, first paragraph. *Id.* at ¶¶ 337-352.

Claim 1 specifies the "isolated … compound" is "substituted" with Si^{4+}. Ex. 1001 at col. 33:42-46. None of the applications filed prior to January 29, 1998 establish that the inventors had possession of the concept of "substitution." Ex. 1003 at ¶¶ 337-352. Instead, the earlier filed applications describe the effect of adding silicon as being "stabilization." *Id.* In fact, Patent Owner *expressly admitted* during examination of the '749 application that its pre-January 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 ¶¶ 347-348. As explained above, 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 '251 patent claims benefit. *See supra*, at § III.A.1.

Patent Owner's admission that WO 97/09286 does not "describe or teach the concept of 'substitution' of silicon" demonstrates the '872 application does not contain a written description of the invention in the manner required by 35 U.S.C. § 112, first paragraph. Ex. 1003 at ¶ 348 (citing Ex. 1009 at 202). Consequently, because the written description of the '872 application does not establish possession of claims 1, 6 and 8-13, these claims are not entitled to the benefit of

the ’872 application under § 120. The earliest effective filing date of the ’251 patent claims, thus, is not earlier than January 29, 1998. *Id.* at ¶¶ 337-352.

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 advanced education, 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. “An isolated …compound”

The broadest reasonable construction of the term “isolated … compound” encompasses a multi-phasic mixture having as a component substituted-TCP, wherein the mixture is separated from the starting materials used in its preparation. Ex. 1003 at ¶¶ 286, 321-322. This definition includes, for example, a compound that is a multi-phasic mixture containing the allegedly novel component of the

invention, Si-TCP. *Id.* at ¶¶ 285-288.[1] This conclusion is compelled by the disclosure of the '251 patent, and is reinforced by statements made by the Patent Owner during examination of the '146 and '251 patents. *See id.* at ¶¶ 267-322.

The claim language itself dictates that the term "compound" must include multi-phasic materials. Specifically, claim 1 requires that the "isolated bioresorbable biomaterial compound" exhibit a "microporous structure." Ex. 1001 at col. 33:46. The only "substituted" Ca-P material described in the patent that is shown to exhibit such a structure is multi-phasic material that includes both Si-TCP and HA. Ex. 1003 at ¶ 210; *see also* Ex. 1001 at col. 8:69 ("the present invention is a synthetic sintered microporous *polycrystalline* structure…the structure comprising a stabilized calcium phosphate compound….") (emphasis added).

[1] While the ordinary meaning of this phrase may also include single phase substituted-TCP, as described above, the patent did not provide methods for separating the phases of multi-phase mixtures created by the methods of the invention such as bi-phasic HA/Si-TCP. *E.g.*, Ex. 1003 at ¶¶ 305-307. 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.

Indeed, the ’251 patent uses the term “compound” to refer to what are, in fact, mixtures of two or more distinct, solid and stable Ca-P phases. Ex. 1003 at ¶ 270. Specifically, the ’251 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 ¶¶ 197-218, 276-288. That multiple Ca-P phases often co-exist within a polycrystalline lattice structure in this manner was well known before January of 1998. *Id.* at ¶ 275.

The use of the term “compound” to refer to materials that contain multiple, distinct Ca-P phases occurs throughout the ’251 patent. *Id.* at ¶¶ 197-218, 276-288. The title of the ’251 patent indicates that the “compounds” of the invention 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 ’251 specification indicates the field of the invention is “a synthetic biomaterial *compound* based on stabilized *calcium phosphate phases*.” Ex. 1001 at col. 1:26-27 (emphasis added).

The ’251 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 ’251 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. 17:15-17

(emphasis added). Both figures, however, describe experimental results from testing of samples of a ***multi-phasic*** mixture of Si-TCP and HA. Ex. 1003 at ¶¶ 214-218. Specifically, Figure 11(b) presents an x-ray crystallographic analysis of a sample of "Si-mHA," which the '251 patent indicates is Si-TCP and HA. Ex. 1001 at col. 17:15-17, 9:10-18, 10:66-67, FIG. 11(b); Ex. 1003 at ¶¶ 214-218. 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 ¶¶ 214-218.

The '251 patent also equates the "compound" of the invention with a commercial product termed "Skelite™." *See, e.g.*, Ex. 1001 at col. 1:27:31 ("This compound which in the alternative may be referred to as Skelite™."); *id*. at col. 10:58-60 ("[t]hese studies . . . led to the characterization of the new compound, an additive stabilized calcium phosphate compound, Skelite™."); *see also* Ex. 1003 at ¶¶ 190-196. The commercially marketed Skelite™ product is a multi-phasic mixture containing ~ 67% Si-TCP and ~ 33% HA. Ex. 1003 at ¶¶ 190-196. The '251 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 ¶ 193.

The way that the '251 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 '251 patent. *Id.* at ¶¶ 190-238, 267-291.

The inclusion of the term "isolated" in claims directed to these "compounds" does not compel a different conclusion. *Id.* at ¶¶ 298-299. The '251 patent nowhere uses the term "isolated" to describe Ca-P compounds. *Id.* at ¶¶ 305-307. Instead, the only instances of the term "isolated" are: (i) in reference to "isolated" *osteoclast cell*s, Ex. 1001 at col. 3:44; 4:5, and (ii) the *claims* in the issued patent, which were amended to include the term "isolated" long after the actual filing date. Ex. 1003 at ¶¶ 310-311; Ex. 1009 at 269-74. In the absence of any definitional or exemplary use in the specification of the term, the term "isolated" must be read with its ordinary meaning. Ex. 1003 at ¶¶ 292-322.

A common ordinary meaning of the term "isolated" is that the material is separated from the environment in which it is found. *See, e.g.*, Ex. 1005 (Webster's) at 4 ("Isolate – 1. a.(1) To set apart from others: cause to be detached from others and alone"); Ex. 1003 at ¶ 293. In the context of the '251 specification, the term "isolated" means that the material has been separated from the environment in which it was produced. Ex. 1003 at ¶¶ 295-297. A synthetic compound thus would be isolated when it is separated from the reaction

environment in which it was created (*e.g.*, to remove reagents and residual solvents used to perform the synthesis). *Id.*

The methods shown in the'251 patent for producing the claimed "compounds" is consistent with this meaning of "isolation." *Id.* at ¶¶ 219-238, 295-297. All of the processes described in the '251 patent result in multi-phasic preparations containing both substituted-TCP and HA phases. *Id.*; *see also id.* at ¶¶ 197-218. These processes show use of a final step of "sintering" the starting materials at high temperature. *Id.* at ¶¶ 219-238, 307. This sintering step functions to, *inter alia*, burn off residual starting materials thus leaving behind the desired multi-phasic material. *Id.* at ¶ 307.

The term "isolated" as used in conjunction with the term "compound" thus, in light of the specification, means simply that the multi-phasic compound has been separated from other starting materials used to synthetically or otherwise prepare that multi-phasic compound. *Id.* at ¶¶ 267-322. The broadest reasonable construction of an "isolated … compound" pursuant to the claims, therefore, encompasses a multi-phasic mixture containing a substituted-TCP phase, which has been separated from other starting materials used to synthetically or otherwise prepare that multi-phasic compound. *Id.* at ¶¶ 321-322.

2. "bioresorbable biomaterial"

A person of ordinary skill in the art would understand the term "bioresorbable" to mean the material or compound is capable of being degraded in the body via either the action of cells (*i.e.*, cell-mediated resportion) or chemical dissolution. *Id.* at ¶ 323. In terms of bone implant material, cell-mediated resorption would involve the activity of osteoclasts. *Id.* Chemical dissolution would involve dissolution of calcium and phosphate into the surrounding media based on the solubility of the material. *Id.*

The specification of the '251 patent suggests that the inventors had a specific definition in mind for the term "biomaterial." *Id.* at ¶ 324. Specifically, at column 10, 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 at col. 10:9-15; Ex. 1003 at ¶¶ 183, 324. The broadest reasonable construction of the term "biomaterial" should employ this definition of the term in the specification. Ex. 1003 at ¶¶ 323-324.

3. "comprising calcium, oxygen and phosphorous wherein a portion of at least one of said elements is substituted with an element Si^{4+}"

As discussed above, *see supra*, at § III.C.1, the broadest reasonable

construction of the term "isolated … compound" necessarily encompasses multi-phasic Ca-P compounds containing at least a substituted-TCP phase, where the multi-phasic compound has been separated from other starting materials used to synthetically or otherwise prepare that multi-phasic compound. *See* Ex. 1003 at ¶¶ 267-322. 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 ¶¶ 190-218, 325.

The subsequent phrase in claim 1 specifies that the "isolated compound" contains "calcium, oxygen and phosphorous" that has been "substituted with an element Si^{4+}." *Id.* at ¶ 326. 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 ¶ 327. 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.*, calcium, oxygen or phosphorous) has been replaced with the element silicon (Si^{4+}). *Id.*[2]

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2 While the ordinary meaning of "comprising" would arguably encompass any silicon substituted Ca-P compound that contains calcium, oxygen and phosphorous, such a construction would encompass compounds not described in the '251 patent. *See* Ex. 1003 at ¶¶ 190-218. The '251 patent disclosure and

(Footnote continued)

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 calcium, or some of oxygen, or some of phosphorous in TCP) are required to undergo "substitution." *Id.* at ¶ 328.

The requirement in the claims for a "substitution" step means the claims are product-by-process claims. *Id.* at ¶ 329. 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

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prosecution history are replete with statements identifying the "novel compound" as containing a particular, new substituted-TCP phase termed "Si-TCP." *Id.*; *see* also ¶¶ 267-291. Whether the claims are construed to encompass silicon substituted Ca-P materials other than silicon substituted-TCP, however, is irrelevant to the invalidity of the claims based on the art cited herein.

compounds have been produced. *See Amgen Inc. v. F. Hoffman-La Roche Ltd*., 580 F.3d 1340, 1370 (Fed. Cir. 2009).

4. "microporous structure" and "macroporous structure comprising…."

The '251 patent claims use the terms "macroporous" and "microporous" structures. Ex. 1001 at col. 33:42-63; Ex. 1003 at ¶¶ 53-60, 331. The '251 patent defines what a "macroporous structure" is. For example, it states that a "macroporous structure comprises an open cell construction with interconnected voids having a pore size of approximately 50 to 1000 micron." Ex. 1001 at col. 23:35-37; Ex. 1003 at ¶ 332. Claim 6 employs this definition of macroporous structure, specifying a macroporous structure "comprising an open cell construction with interconnected voids having a pore size of approximately 50 to 1000 microns." Ex. 1001 at col. 33:61-63. Petitioner proposes the Board adopt this as the broadest reasonable construction. *See* Ex. 1003 at ¶ 332.

By contrast, other than a statement "that varying the preparation conditions of the materials made results in a range of microporous structures of particles of size range 0.1 to 2.0μm," Ex. 1001 at col. 13:64-67, there is no definition of a "microporous structure" in the '251 patent. Ex. 1003 at ¶ 333. A person of ordinary skill would have considered the broadest reasonable construction of the term "microporous structure" to be a structure having pores sizes of about a micron, or less. *Id.* Also, where microporous structures co-exist with

macroporous structures in a bone implant material, the person of ordinary skill would have understood the broadest reasonable construction of "a microporous structure" to mean pores having diameters smaller than the diameters of the macropores found on the same material. *Id*.

5. "wherein said compound has a nanoporous structure"

There is no definition of the term "nanoporous" in the '251 patent. In the context of bone implant material, a person of ordinary skill would understand the broadest reasonable construction of the term "nanoporous structure" to mean pores less than about 0.1 micron in diameter. *Id.* at ¶ 334.

6. "wherein said compound is resorbed by the cellular activity of osteoclasts and promotes the generation of new mineralized bone matrix by the activity of osteoblasts"

As explained above, *supra* at § III.C.2, resorption may be cell-mediated and may involve the activity of osteoclasts or it may involve chemical dissolution. Ex. 1003 at ¶¶ 323, 335. However, the use of the term "resorbed" in claim 10 would be understood in its broadest reasonable construction to be referring only to *cellular* resorption mediated by osteoclasts. *Id.* at ¶ 335. The other terms in claim 10 make this clear (*i.e.*, "... resorbed <u>*by the cellular activity of osteoclasts*</u>…"). Ex. 1001 at col. 34:7-10. This language also indicates the compound promotes generation of new bone matrix by the activity of osteoblasts. *Id.*

7. "wherein said compound is progressively replaced with natural bone in vivo"

Claim 11 specifies that the compound is to be replaced with natural bone *in vivo* "progressively." *Id.* at ¶¶ 175, 336. 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. *Id.* at ¶ 336..

IV. Precise Reasons for Relief Requested

A. Claims 1, 6, and 8-13 Are Unpatentable Over WO 97/09286.

As explained in § III.A.3., claims 1, 6, and 8-13 are not entitled to an effective filing date prior to January 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 at § III.H. Because WO 97/09286 was published on March 13, 1997, it is prior art to claims 1, 6 and 8-13 of the '251 patent. 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 '251 patent for producing the "isolated … compounds" of the claims. Ex. 1003 at ¶¶ 464-471. WO 97/09286 describes two general methods for producing the desired compounds: one involves the use of quartz as the source of silicon to make a thin-

film; the other involves the use of an organo-silicate as the silicon donor. *Id.* at ¶¶ 464-471, 480-481. Both processes are essentially identical to the exemplified methods described in the ’251 patent for making mixtures containing Si-TCP and HA and necessarily result in exactly the same compositions. *Id.*; *see also id.* at Appendix C.

For example, both WO 97/09286 and the ’251 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, 465; *see also* Appendix C. In the method for making the thin-film, both WO 97/09286 and the ’251 patent employ a quartz substrate coated with HA which is sintered at high temperature. *Id.* at Appendix C. In the other method, involving use an organo-silicate, both WO 97/09286 and the ’251 patent describe use of a solution of tetrapropylorthosilicate (TPOS), which is added to the HA solution before sintering. *Id.*

As the Office recognized during the original examination of the ’146 patent, the processes described in WO 97/09286 for making “stabilized” compounds and those described in the ’251 patent for making “substituted” compounds are *identical*. As the Examiner stated with respect to WO 97/09286:

> 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*. When the prior art and appellicant both

> describe processes which are indistinguishable, then *the products may also be assumed to be inherently indistinguishable*." Ex. 1009 at 264-65) (emphasis added).

Ex. 1003 at ¶¶ 602-603. Indeed, at sintering temperatures of around 1000º C, the thin-film process disclosed in WO 97/09286 and the '251 patent each resulted in material containing approximately 33% HA and 67% TCP. *Id.* at ¶ 593. Further, the '251 patent and WO 97/09286 use the *exact same figures* to describe the makeup, activity and morphology of the "products" that result from the thin-film processes disclosed in each document. *Id.* at ¶ 594 (citing Ex. 1017 at FIGS. 6 and 9; Ex. 1001 at FIGS. 20 and 22). Given that the methods disclosed in WO 97/09286 are the same as those described in the '251 patent for making multi-phasic materials that include Si-TCP, those methods necessarily will produce multi-phasic material that includes at least Si-TCP. *Id.* at ¶¶ 594-595. Therefore, the "stabilized compositions" described in WO 97/09286 are inherently the same "isolated … compounds" referenced in the '251 patent, and encompassed by claims 1, 6, 8 and 10-13. *Id.* at ¶¶ 593-598.

Because the material made in WO 97/09286 is necessarily the same as that made in the '251 patent, the properties would also necessarily be the same. WO 97/09286 explains that the materials made by the processes disclosed in that publication are bioresorbable and exhibited characteristics of bioactivity. *Id.* WO 97/09286 states that the "artificial bioactive composition of 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*." *Id.* at ¶¶ 590, 478 (citing Ex. 1017 at 12, 29) (emphasis added).

The materials described in WO 97/09286 also exhibited a microporous structure, which is illustrated, *inter alia*, in Figures 10 and 11. *Id.* at ¶ 591 (citing Ex. 1017 at 11) (thin film showed "surface microporous structure.").

Later publications by the inventors confirm that the multi-phasic 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 ¶¶ 440-448, 487, 599-600. These publications also confirm the materials made in WO 97/09286 exhibited a microporous structure. *Id.* WO 97/09286 therefore expressly or inherently discloses every element of claim 1, and anticipates this claim under 35 U.S.C. § 102(a). *See generally* Ex. 1003 at §§ IV.A.7. and IV.B.1.

During prosecution of the application that resulted in the '146 patent, Patent Owner conceded that the multi-phasic Ca-P mixtures disclosed in WO 97/09286 were the same as the multi-phasic mixtures disclosed in the '251 patent, but argued that the claimed invention was distinguishable over WO 97/09286 because the inventors had "isolated therefrom" the compound that was the alleged invention. Ex. 1003 at ¶ 313 (citing Ex. 1009 at 202).

The ’251 patent, however, does not disclose any “isolation” steps other than those that are disclosed in the WO 97/09286 publication. Ex. 1003 at ¶¶ 207, 469-470. Specifically, the processes that are described in WO 97/09286 for making the “stabilized compositions” and those shown in the ’251 patent for making the “substituted compound” end with a sintering step. *Id.* at ¶ 604. The sintering steps in these processes, used to form the material, would also have resulted in the removal of residual reactants, and would thereby yield the same “isolated … compound.” *Id.* WO 97/09286 therefore anticipates claim 1. *See generally* Ex. 1003 at §§ IV.A.7. and IV.B.1.

2. WO 97/09286 Anticipates Claim 6

Claim 6 depends on claim 1, and specifies the isolated compounds of claim 1 have “a macroporous structure comprising an open cell construction with interconnected voids having a pore size of approximately 50 to 1000 microns.” Ex. 1001 at col. 33:59-63. As explained above (§ IV.A.1.), WO 97/09286 discloses the “isolated…compound” of claim 1. *See also* Ex. 1003 at §§ IV.A.7. and IV.B.1.

WO 97/09286 states that a particular use of the material made by the processes described in the publication includes subsequent formation of the material into a “bulk ceramic” that “can have a macroporosity within the structure in order to provide an artificial three dimensional bone tissue similar to that found

in vivo." Ex. 1017 at 6; Ex. 1003 at ¶ 489. It also states that a particular aspect, "is the fabrication of ceramic pieces with a fine globular surface microporosity and internal microporosity which leads to bioactivity, and a larger *macrostructure of pores of dimensions 50-1000 µm or more*, within the internal structure." Ex. 1017 at 6 (emphasis added); Ex. 1003 at ¶ 490. WO 97/09286 also explains that the macropores are "suited" for "ingrowth of bone matrix" and allowing cells to "access the interior" of the implant. Ex. 1017 at 25; Ex. 1003 at ¶ 491.

Interconnected voids in an open cell structure were known to facilitate bone ingrowth and to be necessary for providing access to the interior regions of implant material. Ex. 1003 at ¶¶ 144-166. A person of ordinary skill in the art would have understood that the macropores described in WO 97/09286 comprised an open cell construction with interconnected voids. *Id.* at ¶ 680. WO 97/09286 thus anticipates claim 6. *See generally* Ex. 1003 at §§ IV.A.7 and IV.C.1.

3. WO 97/09286 Anticipates Claim 8

Claim 8 of the '251 patent is dependent on claim 1 and specifies the compound "has a nanoporous structure." Ex. 1001 at col. 34:1-2. As explained above (§ IV.A.1.), WO 97/09286 discloses the "isolated…compound" of claim 1. *See also* Ex. 1003 at §§ IV.A.7. and IV.D.7.

A person of ordinary skill in the art would understand that any chemical method of making a Ca-P material that resulted in micropores would inherently

result in pores having a range of sizes. Ex. 1003 at ¶ 727. Later published work by the inventors confirms that the thin-film materials, which exhibited a microporous morphology, also exhibited a nanoporous structure. *Id.* at ¶ 730 (citing Ex. 1057 at 6 (noting that "an individual particle indicates the presence of nanoporosity with the body of the particle.")). This later published work also indicates that pores were found in particle grains 5-10 nm in size, thus satisfying the "nanoporosity" requirement specified in claim 8. *Id.* at ¶ 730; Ex. 1057 at 6. WO 97/09286, thus, anticipates claim 8. Ex. 1003 at § IV.A.7. and IV.D.7.

4. Claim 8 Would Have Been Obvious Over WO 97/09286 In View of EP0267624

Patent Owner may contend that the WO 97/09286 does not describe a compound having a "nanoporous" structure pursuant to claim 8. Such a contention would conflict with the inherent physical properties of the compounds that result from the methods described in WO 97/09286 (Ex. 1017). *See supra*, at §§IV.A.3.

Nonetheless, if it is determined that WO 97/09286 does not describe compounds that have a "nanoporous structure," such compounds would have been obvious to a person of ordinary skill based on WO 97/09286 in view of EP0267624 (Ex. 1024). Ex. 1003 at § IV.D.2. EP0267624 is prior art to the claims under § 102(b). *Id.* at § IV.A.14. EP0267624 was not considered during prosecution of the application resulting in '251 patent, or during prosecution of any predecessor application to which the '251 patent claims benefit. *Id.* at ¶ 554.

The porosity of Ca-P implant material was well known to be a key factor in determining the success of bone implant material. Ex. 1003 at ¶¶ 142-166. Interconnected macropores, for example, were understood to be beneficial for bone ingrowth and vascularization, particularly in three-dimensional bulk ceramic material, while micropores were understood to be desirable irrespective of the form or shape of the Ca-P material in order to promote resorption by increasing the surface area. *Id.*; *see also id.* at ¶ 761.

EP0267624 (Ex. 1024) describes a porous calcium phosphate based bone prosthesis having open pores with an average size of 0.01 to 2.0 μm, and closed pores with an average size of 0.01-30 μm, as well as methods of making such materials. *Id.* at ¶ 555; Ex. 1024 at 3. Structures with pore sizes below 0.1 μm would be considered by a person of ordinary skill in the art to be a "nanoporous structure." EP0267624 (Ex. 1024) indicates that pores of the sizes described in it have the advantage of preventing encapsulation of bone implant material by fibrous tissue. Ex. 1003 at ¶ 556; Ex. 1024 at 3. It also states that the "fine closed pores in addition to the open pores" permit "the continuity of the work surface of the bone prosthesis." *Id.* EP0267624 further states that an advantage of fine pores is that "the cross-sectional area of the bone prosthesis is increased without increasing the average size of the pores." *Id.*

EP0267624 would have motivated a person of ordinary skill in the art to incorporate a nanoporous structure into any Ca-P material intended for use as a bone implant material, such as the materials described in WO 97/09286, for reasons similar to why microporosity was deemed desirable, namely, to increase the surface area and enhance resorption. Ex. 1003 at ¶ 734. A person of ordinary skill also would have considered the teachings of EP0267624 in conjunction with those in WO 97/09286, as each is directed to the development and use of calcium phosphate materials in bone implant applications. *Id.* A person of ordinary skill also would have a reasonable expectation of being able to successfully develop Ca-P materials having a nanopore structure based on the combined teachings of WO 97/09286 in view EP0267624. *Id.* Consequently, claim 8 would have been considered obvious to a person of ordinary skill based on WO 97/09286 in view of EP0267624. *See generally* Ex. 1003 at § IV.D.2.

5. WO 97/09286 Anticipates Claim 9

Claim 9 specifies that biomaterial of claim 1 "exhibits monoclinic pseudorhombic symmetry and is in the monclinic space group $P2_1/a$." As explained in § IV.A.1, above, the methods described in WO 97/09286 (Ex. 1017) necessarily resulted in the formation of a multi-phasic compound containing Si-TCP and HA. Ex. 1003 at ¶¶ 588-605. Later publications by the inventors show that "Si-TCP has a monoclinic structure with a space group $P2_1/a$." Ex. 1119 at 1;

Ex. 1003 at ¶ 781. The'251 patent also states that Si-TCP exhibits this symmetry and space group. Ex. 1001 at col. 7:44-45. Thus, the particular crystalline structure of Si-TCP is an inherent property of the Si-TCP-containing compounds described in both WO 97/09286 and the '251 patent. Ex. 1003 at ¶¶ 778-781. WO 97/09286 (Ex. 1017) thus anticipates claim 9. *See generally* Ex. 1003 at § IV.E.

6. WO 97/09286 Anticipates Claims 10-12

Claims 10-12 do not specify limitations that define structural or chemical properties of the "isolated … compounds" of claim 1. Instead, these claims specify only functional effects observed when the claimed materials are used. *Id.* at ¶¶ 782-787. Ca-P bone implant material, including both HA and TCP, were reported in the literature to have these properties. *Id.* at ¶¶ 63-98, 558-584. Claims 10-12 thus simply specify functional properties or capabilities inherent to the multi-phasic Ca-P compounds that are described in WO 97/09286. *Id.* at ¶¶ 782-787.

A claim that simply specifies an inherent property of a previously disclosed compound cannot render that compound 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."). Because none of the limitations specified in claims 10-12 impart any structural feature or chemical component not already present in the

"isolated…compound" disclosed in WO 97/09286, those claims are inherently anticipated by WO 97/09286. Ex. 1003 at § IV.F.

7. WO 97/09286 Anticipates Claim 13

Claim 13 specifies that the "isolated…compound" has a "calcium to phosphorous atomic ratio [that] is less than 1.67." Ex. 1001 at col. 34:17-19. As explained in § IV.A.1, above, the methods described in WO 97/09286 (Ex. 1017) will necessarily result in the formation of a multi-phasic compound containing Si-TCP and HA. Ex. 1003 at ¶¶ 588-605. According to the '251 patent, "[i]n the formation of the Si-TCP compound, compositional analysis suggests that the Ca:P ratio decreases from approximately 1.67 (HA) to 1.5 (TCP)." Ex. 1001, at col. 18:28-30; Ex. 1003 at ¶¶ 788-791. The calcium-to-phosphorous atomic ratio specified in claim 13 is an inherent property of the compound when Si-TCP is formed using the methods described in the '251 patent and WO 97/09286. Ex. 1003 at ¶ 791. WO 97/09286, thus, anticipates claim 13. *See generally* Ex. 1003 at § IV.G.

B. Claims 1 and 8-13 Are Unpatentable Over WO 94/26872

WO 94/26872 (Ex. 1015) was published on November 24, 1994, and is prior art under § 102(b) to claims 1, and 8-13. *Id*. at ¶ 427. A summary of WO 94/26872 is provided in Ex. 1003 at § IV.A.5.

1. WO 94/26872 Anticipates Claim 1

WO 94/26872 generally discloses Ca-P based thin films made by sintering HA on a quartz substrate. Ex. 1015 at 1; *see* Ex. 1003 at § IV.A.5. The thin-film coating process described in WO 94/26872 for making "stabilized compositions" is essentially identical to the thin-film coating process described in the '251 patent for making multi-phasic Si-TCP material. Ex. 1003 at ¶¶ 429-438. Both the method in WO 94/26872 and the '251 patent start with the formation of HA using 4.722 grams of calcium nitrate in water and 1.382 grams of ammonium dihydrogen phosphate. *See* Ex. 1003 at ¶¶ 219-224, 432-437, Appendix B. Both the method in WO 94/26872 and the '251 patent also employ a quartz substrate as the silicon donor. *Id.* The quartz is coated with HA and then sintered at high temperature in both references. *Id.* The thin-film coating method described in WO 94/26872, thus, would have necessarily resulted in an isolated compound comprising calcium, oxygen, and phosphorous wherein silicon substitutes for one of the elements, *i.e.*, material containing Si-TCP. Ex. 1003 at ¶¶ 438, 609.

Notably, the specification of the '251 patent admits that the "thin film" methods described in WO 94/26872 produce the compounds of the '251 patent:

> "The Applicants have developed a process to provide a stabilized calcium phosphate synthetic biomaterial compound which is fully biocompatible and has a morphology capable of consistently

> supporting bone cell activity thereon. *This is provided in accordance with that method described in the Applicant's co-pending published PCT application WO 94/26872*…." Ex. 1001 at col. 9:66-col. 10:8 (emphasis added).

Ex. 1003 at ¶ 608. During examination of the '146 patent, the Examiner determined that the processes described in WO 94/26872 are the same as those described in the '251 patent, and will necessarily yield the same compounds. As the Examiner stated:

> "Since *applicants admit the compounds taught in this application are identical to the claimed composition*, when the substituting element is silicon, the taught composition would inherently have the claimed properties." Ex. 1009 at 261-262. (emphasis added)

Ex. 1003 at ¶ 430. Because the materials are the same, the properties would also necessarily be the same. *Id*. at ¶¶ 438, 450. The specification of the '251 patent confirms that the thin-film material disclosed in WO 94/26872 was bioresorbable and exhibited characteristics of bioactivity: "cell-mediated resportion was shown to occur…. Enhanced deposition of mineralized bone matrix also occurs on these ceramics in the presence of osteoblasts." Ex. 1001 at col. 4:8-23; Ex. 1003 at ¶ 449. The '251 patent also confirms that the thin-film process disclosed in WO 94/26872 exhibited a microporous structure: "cross-sectional transmission

electron microscopy indicated a microporous physical structure." Ex. 1001 at col. 4:24-36; Ex. 1003 at ¶ 450.

Later publications by the inventors also confirm that the materials made by the processes disclosed in WO 94/26872 included Si-TCP, were bioresorbable and bioactive, and hence were suitable for use as a "biomaterial." Ex. 1003 at ¶¶ 440-448; Ex. 1057 at 6. The subsequent publications also confirm that the materials exhibited a microporous structure. *Id*. Thus, because WO 94/26872 describes a process that results in a multi-phasic Si-TCP/HA compound that exhibits a microporous structure, and is bioresorbable and biocompatible, it anticipates claim 1. *See generally* Ex. 1003 at §§ IV.A.5 and IV.B.2.

During prosecution of the application that resulted in the '146 patent (which reissued as the '251 patent), Patent Owner argued that the claimed invention was distinguishable over WO 94/26872 (as it did with respect to WO 97/09286) because the inventors had "isolated therefrom" the compound that was the alleged invention. *Id.* at ¶¶ 313-314, 617.

The '251 patent, however, does not disclose any "isolation" steps other than those disclosed in WO 94/26872. *Id.* at ¶ 617. Specifically, the processes that are described in WO 94/26872 for making the "stabilized compositions" and those shown in the '251 patent for making the "substituted compound" both end with the sintering step. *Id.* at ¶¶ 222-223, 437. The sintering steps in these processes would

have resulted in the removal of residual reactants, and would thereby yield the same "isolated … compound." *Id.* at ¶ 617. WO 97/09286 therefore anticipates claim 1. *See generally* at §§ IV.A.5 and IV.B.2.

2. WO 94/26872 Anticipates Claim 8

WO 94/26872 describes materials made by processes that necessarily impart onto those materials nanoporous structures. *Id.* at ¶¶ 729-731. A person of ordinary skill in the art would understand that any chemical method of making a Ca-P material that resulted in micropores would inherently result in pores having a range of sizes. *Id.* at ¶ 725. Later published work by the inventors also confirms that the materials produced by the thin-film methods disclosed in WO 97/09286, which exhibit a microporous morphology, also exhibit a nanoporous structure. *Id.* at ¶ 730; Ex. 1057 at 6 (noting that "an individual particle indicates the presence of nanoporosity with the body of the particle."). This later published work also indicates that pores were found in particle grains 5-10 nm in size, thus satisfying the "nanoporosity" limitation. *Id.* Consequently, WO 94/26872 anticipates claim 8. *See generally* Ex. 1003 at §§ IV.A.5 and IV.D.3.

3. Claim 8 Would Have Been Obvious Over WO 94/26872 In View of EP0267624

Patent Owner may contend that WO 94/26872 does not expressly describe an "isolated ... compound" comprising a nanoporous structure. Such a contention would conflict with the inherent physical properties of a compound prepared

according to the methods described in WO 94/26872. *Id.* at ¶ 725. In particular, the processes used to produce the materials described in WO 94/26872 inherently will result in materials that comprise nanoporous structures. *Id.*

Nonetheless, if it is determined that WO 94/26872 does not describe materials that comprise a nanoporous structure, a person of ordinary skill in the art would have considered production of such materials to have been obvious based on the guidance in WO 94/26872 considered in view of EP0267624. *See generally* Ex. 1003 at §§ IV.A.5 and IV.D.4.

The thin film process described in WO 94/26872 is essentially the same as the thin-film process dscribed in WO 97/09286. *Id.* at ¶ 462. Like WO 97/09286, the resulting mixtures necessarily will include both HA and Si-TCP. *Id.* at ¶¶ 436, 481. Both HA and TCP were reported to be bioresorbable and bioactive, and were both widely used as Ca-P bone implant material. *See generally* Ex. 1003 at §§ II.E. According to WO 94/26872, the material made was resorbable. *Id.* at ¶¶ 438-439, 449. The publication states that "predominantly HA films" typically resulted in low levels of resorption, while predominantly TCP films showed high levels of resorption. Ex. 1015 (WO 94/26872) at 30; Ex. 1003 at ¶ 439. WO 94/26872 also states that the thin films made are "similar to materials implanted in the body." Ex. 1015 at 28; Ex. 1003 at ¶ 439.

Given the reported properties of the material in WO 94/26872, and the recognition in the field that HA and TCP were useful in bone implant applications, the person of ordinary skill in the art would have been motivated to study and use the material made by the processes disclosed in WO 94/26872 in bone implant applications. Ex. 1003 at ¶ 740. The person of ordinary skill in the art would have considered WO 94/26872 in conjunction with EP0267624 as each relates to Ca-P material known to be useful in bone implant applications and the study and development of such materials. *Id.* The person of ordinary skill in the art also would have had a reasonable expectation of success given the the combined teachings of the two references. *Id.* at ¶ 743.

A person of ordinary skill in the art would have recognized from EP0267624 the benefits of producing Ca-P materials having a nanoporous structure (*e.g.*, to reduce the incidence of encapsulation of the implant material and increase its surface area). *Id.* For the same reasons that WO 97/09286 in view of EP0267624 renders claim 8 obvious, *see supra* § IV.A.4., claim 8, would have been obvious to a person of ordinary skill in the art based on WO 94/26872 in view of EP0267624. *See generally* Ex. 1003 at §§ IV.D.4.

4. WO 94/26872 Anticipates Claim 9

The methods described in WO 94/26872 will result in the formation of a multi-phasic mixture containing Si-TCP. *Id.* at ¶¶ 429-438. Later publications by

the inventors show that "Si-TCP has a monoclinic structure with a space group $P2_1/a$." *Id.* at ¶ 781; Ex. 1119 at 1. The specification of the '251 patent also states that Si-TCP exhibits this symmetry and space group. Ex. 1003 at ¶ 781; Ex. 1001 at col. 7:44-45. Thus, the particular crystalline structure of Si-TCP is an inherent property of Si-TCP. *Id.* at ¶ 781. Given that the process described in WO 94/26872 results in Si-TCP, this publication inherently anticipates claim 9. *See generally id*. at §§ IV.E.

5. WO 94/26872 Anticipates Claims 10-12

As explained above (*see* § IV.A.6.), claims 10-12 do not specify limitations that define structural or chemical properties of the "isolated … compounds" of claim 1. Ex. 1003 at ¶¶ 782-787. Instead, these claims specify only functional effects observed when the claimed materials are used. *Id.*; *see also supra* at § IV.A.6. Ca-P bone implant material, including both HA and TCP, were reported in the literature to have these properties. Ex. 1003 at § II.E. Claims 10-12 thus simply specify functional properties or capabilities inherent to the multi-phasic Ca-P compounds that are described in WO 94/26872. *Id.* at ¶ 785. Consequently, claims 10-12 are anticipated by WO 94/26872. *See generally id.* at §§ IV.F.

6. WO 94/26872 Anticipates Claim 13

Claim 13 specifies that "biomaterial compound" has a "calcium to phosphorous atomic ratio [that] is less than 1.67." Ex. 1001 at col. 34:17-19. As

explained in § IV.B.1, the methods described in WO 94/26872 (Ex. 1015) will necessarily result in the formation of a multi-phasic compound containing Si-TCP and HA. Ex. 1003 at ¶¶ 429-438. According to the '251 patent, "[i]n the formation of the Si-TCP compound, compositional analysis suggests that the Ca:P ratio decreases from approximately 1.67 (HA) to 1.5 (TCP)." Ex. 1001 at col. 18:28-30; Ex. 1003 at ¶ 791. The calcium-to-phosphorous atomic ratio specified in claim 13 is an inherent property of the compound when Si-TCP is formed using the methods described in the '251 patent and 94/26872. *Id.* WO 94/26872, thus, anticipates claim 13. *See generally* Ex. 1003 at §§ IV.G.

C. Claims 1 and 8-13 Are Unpatentable Over Qiu 1993.

Qiu 1993 (Ex. 1016) is an article co-authored by J.E. Davies, who is named as an applicant on WO 94/26872. A summary of the publication is provided in Ex. 1003 at § IV.A.6. It is a printed publication and is prior art under 35 § U.S.C. 102(b) to claims 1, 6, and 9-13. *Id.* at ¶ 451. Qiu 1993 was not before the PTO during prosecution of the application resulting in the '251 patent, or any predecessor application to which the '251 patent claims priority. *Id.* at ¶ 452.

1. Qiu 1993 Anticipates Claim 1

Like WO 94/26872, Qiu 1993 discloses methods for making Ca-P based thin films made by sintering HA on quartz. Ex. 1003 at ¶ 453. The methods described in Qiu 1993 are essentially identical to the methods described in WO 94/26872,

except the methods in Qiu 1993 are performed on half the scale as the methods disclosed in WO 94/26872. *Id.* at ¶ 454. The methods described in Qiu 1993 therefore would have necessarily resulted in "isolated" multi-phasic mixtures made of Si-TCP as one component. *Id.* at ¶ 455. In fact, Qiu 1993 reports that the material made exhibited a "surface microporosity" and characteristics of bioactivity. Ex. 1016 at 9 ("The collagen, laid down by the bone cells, was intergrated ith the surface of the cement line matrix."); Ex. 1003 at ¶ 456. For the same reasons that WO 94/26872 anticipates claim 1 under 35 U.S.C. § 102(b), Qiu 1993 also anticipates claim 1. *See generally* Ex. 1003 at §§ IV.A.6. and IV.B.3.

2. Qiu 1993 Anticipates Claim 8

As with WO 94/26872, Qiu 1993 describes materials made by processes that necessarily impart onto those materials nanoporous structures. *Id.* at ¶¶ 744-746. Consequently, Qiu 1993 anticipates claim 8. *See generally* Ex. 1003 at § IV.D.5.

3. Claim 8 Would Have Been Obvious Based on Qiu 1993 In View of EP0267624

As explained in § IV.C.1., the methods disclosed in Qiu 1993 are equivalent to the methods disclosed in WO 94/26872 and would have resulted in the same material, *i.e.*, multi-phasic mixtures made of Si-TCP and HA. Ex. 1003 at §§ IV.A.6 and IV.D.6.

Qiu also 1993 reports that the material it made exhibited a "surface microporosity" and characteristics of bioactivity. Ex. 1016 at 9 ("The collagen,

laid down by the bone cells, was intergrated with the surface of the cement line matrix."); Ex. 1003 at ¶ 748. In addition Qiu 1993 suggests that the materia made "may be optimally engineered …for interfacial bonding with bone to implants." *Id.* For the same reasons that WO 94/26872 in view of EP0267624 renders claim 8 obvious, *see* Ex. 1003 at ¶¶ 747-749, claim 8 would have been obvious to a person of ordinary skill in the art based on Qiu 1993 in view of EP0267624. *See generally* Ex. 1003 at §§ IV.A.6 and IV.D.6.

4. Qiu 1993 Anticipates Claim 9

The methods disclosed in Qiu 1993 are equivalent to the methods disclosed in WO 94/26872 and would have resulted in the same material, *i.e*., multi-phasic mixtures made of Si-TCP and HA. *Id.* at § IV.A.6. For the same reasons that WO 94/26872 inherently anticipates claim 9, Qiu 1993 also inherently anticipates claim 9. *Id.* at § IV.E.

5. Qiu 1993 Anticipates Claims 10-12

Claims 10-12 do not specify limitations that define structural or chemical properties of the "isolated … compounds" of claim 1. Ex. 1003 at ¶¶ 782-787. Instead, these claims specify only functional effects observed when the claimed materials are used. *Id.* at ¶ 785. Ca-P bone implant material, including both HA and TCP, were reported in the literature to have these properties. *See generally id.* at § II.E. Claims 10-12 thus simply specify functional properties or capabilities

inherent to the multi-phasic Ca-P compounds that are described in Qiu 1993 (Ex. 1016). *Id.* at ¶ 755. Qiu 1993 thus anticipates claims 10-12. *See generally id.* at §§ IV.F.

6. Qiu 1993 Anticipates Claim 13

The methods disclosed in Qiu 1993 are equivalent to the methods disclosed in WO 94/26872 and would have resulted in the same material, *i.e.*, multi-phasic mixtures made of Si-TCP and HA. *Id.* at ¶¶ 451-459. For the same reasons that WO 94/26872 inherently anticipates claim 13, Qiu 1993 also inherently anticipates claim 13. *Id.* at ¶¶ 788-791.

D. Claims 1, 6 and 8-13 Are Unpatentable Over Ruys 1993a

Ruys 1993a (Ex. 1011) is prior art to claims 1, 6, 8-13 under 35 U.S.C. § 102(b). *Id.* at ¶ 377. A summary of the publication is provided in Ex. 1003 at § IV.A.2. Ruys 1993a reports "silicon doping" of HA. *Id.* at ¶ 379. Given the role of silicon in bone mineralization and the activity of bioglass, 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.* at ¶ 382 (quoting Ex. 1011 (Ruys 1993a) at 1).

1. Ruys 1993a Anticipates Claim 1

Ruys 1993a (Ex. 1011) describes a process for producing multi-phasic Ca-P materials that is strikingly similar to the methods disclosed in the '251 patent. Ex. 1003 at ¶¶ 623-625, 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 ¶¶ 393-394. An organo-silicate (tetraethylorthosilicate (TEOS) or tetrapropylorthosilicate (TPOS) in the '251 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 ¶¶ 225, 383. The methods disclosed in Ruys 1993a are equivalent to the methods disclosed in the '251 patent and therefore necessarily resulted in products having the same physical, chemical, and biological properties. *Id.* at ¶¶ 393-394, 625.

Ruys 1993a suggests that the process created a silicon "substituted"-HA. *Id.* at ¶¶ 384, 628; Ex. 1011 at 4. However, subsequent work by the inventors of the '251 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 ¶¶ 393-394 (citing Ex. 1119 ("Sayer 2003") at 1). In a 2003 publication, the authors report that "firing a stoichiometric calcium hydroxyapatite precipitate with SiO_2 produces Si-TCP, hydroxyapatite, β-TCP and an amorphous component." *Id.* Si-TCP is defined in the publication as "tricalcium phosphate stabilized by the substitution of silicon for phosphorous." *Id.* Sayer 2003 attributes the formation of Si-TCP to the loss of OH from the HA material, which

creates OH "vacancies" within the HA lattice. *Id.* In other words, the firing of stoichiometric HA in the presence of SiO_2 results in HA instability due to the loss of OH. *Id.* This ensuing instability results in the formation of Si-TCP in the evolving crystalline structure. *Id.*

The multi-phasic Ca-P mixtures that result from the Ruys 1993a (Ex. 1011) process therefore necessarily included Si-TCP as one component. *Id.* at ¶ 393. As with the sintering step of materials shown in the '251 patent, the sintering step in Ruys 1993a would have resulted in removal of residual reactants, thereby resulting in an "isolated compound" of HA and Si-TCP phases. *Id.* at ¶¶ 386-387.

Ruys 1993a confirms that the morphology of the material that was produced included pores. *Id.* at ¶¶ 388-391 (citing Ex. 1011at 4 ("Both the density and porosity trends reveal that the addition of very small amounts of silicon (as colloidal SiO_2) reduced the sintering efficiency.")). Because the pores are stated to be caused by incomplete sintering, the person of ordinary skill in the art would understand the pores formed to be micropores. *Id.*

Petitioner observes that during prosecution of the application resulting in the '251 patent, the Examiner rejected the claims in view of Ruys 1993b (Ex. 1014), a reference that discloses methods that are equivalent to Ruys 1993a. *Id.* at ¶ 244-245. 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 of the products produced by the Ruys 1993b process. *Id*. Instead, Patent Owner amended the claims to add the limitation "wherein said compound has a microporous structure." *Id.* Unlike the Ruys 1993b paper (Ex. 1014), which does not expressly state that the multi-phasic materials produced by its process exhibited porosity, Ruys 1993a (Ex. 1011) explains that the material made by its process – the same process also described in Ruys 1993b (Ex. 1014) – did exhibit porosity, which the person of ordinary skill in the art would understand to be micropores. *Id.* at ¶¶ 388-391, 625, 632. Thus, Ruys describes an "isolated" multi-phasic "compound" containing HA and Si-TCP, which is bioresorbable and bioactive, and which exhibits a "microporous structure" pursuant to claim 1. *Id.* at ¶¶ 393-394. Ruys 1993a (Ex. 1011) thus anticipates claim 1 under 35 U.S.C. § 102(b). *See generally* Ex. 1003 at §§ IV.B.4.

2. Claim 6 Would Have Been Obvious Based on Ruys 1993a In View Of Bioceramics 1993

Ruys 1993a (Ex. 1011) discloses the "isolated compound" of claim 1. *See generally* Ex. 1003 at § IV.B.4. Ruys 1993 (Ex. 1011) does not expressly state that the materials prepared by its process exhibit the particular macroporous structure specified in claim 6. This, however, would have been an obvious design choice. Ex. 1003 at ¶ 683.

A person of ordinary skill would have considered Ruys 1993a (Ex. 1011) in conjunction with Bioceramics 1993 (Ex. 1021). *Id.* at ¶ 689. Bioceramics 1993 (Ex. 1021) is prior art under 35 § U.S.C. 102(b) to claims 1, 6, 8-13. *Id.* at ¶ 522. A summary of Bioceramics 1993 is provided in Ex. 1003 at § IV.A.11. This reference was not considered by the PTO during examination of the application resulting in the '251 patent, or any predecessor application to which the '251 patent claims priority. *Id.* at ¶ 523.

Ruys 1993a (Ex. 1011) states that the "[e]nhancement of the bioactivity of HAP is generally achieved by increasing the porosity…." of the material. Ex. 1003 at ¶ 684 (quoting Ex. 1011 at 3). This suggestion in Ruys 1993a is consistent with what was well known in the prior art. Ex. 1003 at § I.E. For example, Bioceramics 1993 (Ex. 1021) explains that interconnected macropores, including macropores further comprising an open cell structure, were considered "ideal" for bone implant applications in order to promote vascularization and cell ingrowth. Ex. 1003 at ¶ 685; Ex. 1021 at 110. Bioceramics 1993 (Ex. 1021) also teaches that "[p]orosity and interconnectivity are key determinants of amount and type of ingrowth" in Ca-P bone implant material. Ex. 1003 at ¶ 686; Ex. 1021 at 116-117. In addition, Bioceramics 1993 explains further that:

> To design an implant for osteoconduction it would seem logical to mimic the architecture of this interstitial or stromal bone. Since

> osteons average 190-230 μm in diameter, and intercommunicate through Volksmann canals, an idealized bone graft substitute would mimic osteon-evacuated cortical bone and have an interconnected porous system of channels of similar dimensions (Fig. 2)." Ex. 1021 at 108.

Ex. 1003 at ¶ 687. Bioceramics 1993 (Ex. 1021) also teaches that "[a]n ideal cancellous bone graft substitute would mimic osteon-evacuated cancellous bone and have a thin lattice interconnected by pores of 500-600 μm." *Id.* at ¶ 528.

Fig. 2 of Bioceramics 1993 (Ex. 1021) shows an "idealized" structure for cortical bone regeneration. Ex. 1003 at ¶¶ 155, 529; Ex. 1021 at 182. This "idealized" structure is shown to exhibit an interconnected porosity. *Id.*; Ex. 1021 at 182. Fig. 4 shows another "idealized" structure for cancellous bone regeneration. Ex. 1003 at ¶ 156, 530; Ex. 1021 at 111. This structure also exhibits an open cell configuration with interconnected macropores. *Id.*; Ex. 1021 at 1011.

A person of ordinary skill would have considered the teachings of Ruys 1993a (Ex. 1011) in conjunction with those in Bioceramics 1993 (Ex. 1021) as each reference is directed to the development and use of Ca-P materials in bone implant applications. Ex. 1003 at ¶ 684. A person of ordinary skill in the art also would have been motivated by Bioceramics 1993 (Ex. 1021) to take the compounds described in Ruys 1993a and prepare them to have a structure

comprising an open cell construction with interconnected voids having pore sizes falling in the range of 50 to 1000 microns. *Id*. at ¶¶ 689-690.

Methods of making a biomaterial compound having a macroporous structure pursuant to claim 6 were well known. Ex. 1003 at ¶¶ 147-164, 690. Methods of making Ca-P material exhibiting both microporosity and interconnected macropores were also well-known, and examples of such materials were known to be useful in bone implant applications. *Id.*; Bioceramics 1993 (Ex. 1021) at 86, 116-117, 119. The person of ordinary skill in the art would therefore have had a reasonable expectation of success that the combination of Ruys 1993a in view Bioceramics 1993 would be successful. *Id.* at ¶ 696. Consequently, claim 6 would have been considered obvious based on Ruys 1993a (Ex. 1011) in view of Bioceramics 1993 (Ex. 1021). Ex. 1003 at ¶ 697.

3. Claim 6 Would Have Been Obvious Based on Ruys 1993a In View of White 1986

As discussed in § IV.D.1. above, Ruys 1993a anticipates the subject matter of claim 1. White 1986 (Ex. 1022) is prior art under 35 § U.S.C. 102(b) to claims 1, 6, 8, and 10-12. Ex. 1003 at ¶ 537. A summary of White 1986 (Ex. 1022) is provided in Ex. 1003 at § IV.A.12. White 1986 (Ex. 1022) was not before the PTO during prosecution of the application resulting in the ’251 patent, or any predecessor application to which the ’251 patent claims priority. *Id*. at ¶ 538.

Consistent with the prior art, Ruys 1993a (Ex. 1011) states that the "[e]nhancement of the bioactivity of HAP is generally achieved by increasing the porosity…." *Id.* at ¶ 684 (citing Ex. 1011 at 3). Before 1998, interconnected macropores, including pores further comprising an open cell structure, were considered to be "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 ¶¶ 146-166.

White 1986 (Ex. 1022) also reflects this well known benefit associated with interconnected macropore structures. For example, White 1986 (Ex. 1022) explains that the "degree of interconnectivity and the nominal pore size were *critical* factors that determined the success of the implant" with "maximal interconnectivity…found to facilitate ingrowth." *Id.* at ¶ 688 (citing Ex. 1022 at 4 (emphasis added)). With respect to pore size, White 1986 explains that the:

> range required for the spectrum of porous implantable devices has been found within naturally occurring marine structures. Different species have been identified with pore sizes that range nominally from 10 μm to over 800 μm in diameter." *Id.* at ¶ 688 (citing Ex. 1022 at 5).

In fact, the desirability of an interconnected porous structure in order to promote bone ingrowth and vascularization within Ca-P implant material is discussed throughout the literature. Ex. 1003 at ¶¶ 146-166.

A person of ordinary skill also would have considered the teachings of Ruys 1993a (Ex. 1011) in conjunction with those in White 1986 (Ex. 1022), as each is directed to the development and use of Ca-P materials in bone implant applications. *Id.* at ¶ 689. White 1986 (Ex. 1022) would have provided motivation to a person of ordinary skill in the art to take the compounds disclosed in Ruys 1993a and form the compounds as a macroporous structure comprising an open cell construction with interconnected voids having pore sizes in the range of approximately 50 to 1000 microns. *See* Ex. 1003 at ¶ 689.

Moreover, methods of making a biomaterial compound having the macroporous structure required by claim 6 were well known. *See id.* at ¶ 696. In fact, methods of making Ca-P material exhibiting both microporosity and interconnected macropores were known and examples of such materials were known to be useful in bone implant applications. *Id.*; *see also id.* at ¶¶ 146-166. The person of ordinary skill in the art would therefore have had a reasonable expectation that the combination of Ruys 1993a in view of Bioceramics 1993 would be successful. Consequently, claim 6 would have been considered obvious

to a person of ordinary skill based on Ruys 1993a (Ex. 1011) in view of White 1986 (Ex. 1022). *Id.* at ¶ 690.

4. Ruys 1993a Anticipates Claim 8

The synthetic Ca-P ceramic materials exhibiting a microporous structure described in Ruys 1993a (Ex. 1011) will inherently exhibit a nanoporous structure. *Id.* at ¶¶ 750-751. Consequently, Ruys 1993a anticipates claim 8. *Id.*

5. Claim 8 Would Have Been Obvious Based on Ruys 1993a In View of EP0267624

Patent Owner may contend the methods described in Ruys 1993a (Ex. 1011) do not result in a material possessing a nanoporous structure pursuant to claim 8. Such a contention would conflict with the inherent physical properties of a compound prepared according to the methods described in Ruys 1993a (Ex. 1011). *Id.* Nonetheless, if it is determined that Ruys 1993a (Ex. 1011) does not inherently disclose an "isolated … compound" comprising a nanoporous structure, a person of ordinary skill would have considered production of such an isolated compound with that property to have been obvious to a person of ordinary skill in the art based on the teachings in Ruys 1993a considered in view of EP0267624 (Ex. 1024). *Id.* at ¶¶ 752-755.

The porosity of Ca-P implant material was well known to be a key factor in determining the success of bone implant material. Ex. 1003 at ¶¶ 142-166. Interconnected macropores, for example, were understood to be beneficial for bone

ingrowth and vascularization, particularly in three-dimensional bulk ceramic material, while micropores were understood to be desirable irrespective of the form or shape of the Ca-P material in order to promote resorption by increasing the surface area. *Id.*; *see also id.* at ¶ 761.

EP0267624 (Ex. 1024) describes a porous Ca-P based bone prosthesis having open pores with an average size of 0.01 to 2.0 μm, and closed pores with an average size of 0.01-30 μm, as well as methods of making such materials. Ex. 1003 at ¶ 555; Ex. 1024 at 3. A structure with pore sizes below 0.1 μm would be considered by a person of ordinary skill in the art to be a "nanoporous structure." *Id.* EP0267624 (Ex. 1024) indicates that pores of the sizes described in it have the advantage of preventing encapsulation of bone implant material by fibrous tissue. Ex. 1024 at 3; Ex. 1003 at ¶ 556. EP0267624 further states that an advantage of fine pores is that "the cross-sectional area of the bone prosthesis is increased without increasing the average size of the pores." *Id.*

EP0267624 would have motivated a person of ordinary skill in the art to include a nanoporous structure into any Ca-P material intended for use as a bone implant material, such as the materials described in Ruys 1993a, for the same reasons why micropores were deemed beneficial, *i.e.*, to increase surface area thereby enhancing resorption. *Id.* at ¶ 763. A person of ordinary skill also would have considered the teachings of EP0267624 in conjunction with those in Ruys

1993a, as each is directed to the development and use of Ca-P materials in bone implant applications. *Id.* at ¶ 764. A person of ordinary skill also would have a reasonable expectation of being able to successfully develop Ca-P materials having a nanopore structure based on the combined teachings of Ruys 1993a in view of EP0267624. *Id.* Consequently, claim 8 would have been considered obvious to a person of ordinary skill based on Ruys 1993a in view of EP0267624. *See generally* Ex. 1003 at § IV.D.8.

6. Ruys 1993a Anticipates Claim 9

As explained above in § IV.D.1., the methods described in Ruys 1993a (Ex. 1011) will necessarily result in the formation of a multi-phasic mixture containing Si-TCP and HA. Ex. 1003 at ¶¶ 623-625, 628-632. Later publications by the inventors show that "Si-TCP has a monoclinic structure with a space group $P2_1/a$." Ex. 1003 at ¶ 781; Ex. 1119 at 1. The specification of the '251 patent also states that Si-TCP exhibits this symmetry and space group. Ex. 1003 at ¶ 781; Ex. 1001 at col. 7:44-45. Thus, the particular crystalline structure of Si-TCP is an inherent property of Si-TCP. Ex. 1003 at ¶ 781. Ruys 1993a (Ex. 1011) therefore inherently anticipates claim 9. See generally Ex. 1003 at § IV.E.

7. Ruys 1993a Anticipates Claims 10-12

As explained above (*see* § IV.A.6.), claims 10-12 do not specify limitations that define structural or chemical properties of the "isolated … compounds" of

claim 1. *Id.* at ¶¶ 782-787. Instead, these claims specify only functional effects observed when the claimed materials are used. *Id.* Ca-P bone implant material, including HA and TCP, were reported to have these properties. Ex. 1003 § II-E. Claims 10-12 thus simply specify functional properties or capabilities inherent to the multi-phasic Ca-P compounds that are described in Ruys 1993a (Ex. 1011). *Id.* Ruys 1993a (Ex. 1011) thus anticipates claims 10-12. *See generally* Ex. 1003 at § IV.F.

8. Ruys 1993a Anticipates Claim 13

Claim 13 specifies that "biomaterial compound" has a "calcium to phosphorous atomic ratio [that] is less than 1.67." As explained in § IV.D.1., above, the methods described in Ruys 1993a (Ex. 1011) will necessarily result in the formation of a multi-phasic compound containing Si-TCP and HA. Ex. 1003 at ¶¶ 393-394, 623-632. According to the '251 patent, "[i]n the formation of the Si-TCP compound, compositional analysis suggests that the Ca:P ratio decreases from approximately 1.67 (HA) to 1.5 (TCP)." *Id.* at ¶ 79; Ex. 1001 at col. 18:28-30. The calcium-to-phosphorous atomic ratio specified in claim 13 is an inherent property of the compound when Si-TCP is formed using the methods described in the '251 patent and Ruys 1993a. Ex. 1003 at ¶ 791. Ex. 1011 thus, anticipates claim 13. *Id.* at ¶ 79.

E. Claims 1, 6 and 8-13 Are Unpatentable Over Ruys 1993b.

Ruys 1993b is prior art under 35 § U.S.C. 102(b) to claims 1, 6, 8-13. *Id.* at ¶ 407. A summary of Ruys 1993b is provided in Ex. 1003 at § IV.A.4. Ruys 1993b observes "[s]ince silicon may enhance the bioactivity of these glass-based materials, the relatively low bioactivity of HAp may be due to the absence of silicon from its structure….The purpose of the present work was to address the potential benefits and problems involved in the silicon doping of HAp…." *Id*. at ¶ 411.

1. Ruys 1993b Anticipates Claim 1

Ruys 1993b (Ex.1014) describes a process for producing multi-phasic Ca-P materials that is strikingly similar to the methods disclosed in the '251 patent. *Id.* at ¶ 634. 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*. at ¶ 635, Appendix E.

In both Ruys 1993b and the patent, HA is made using calcium nitrate and ammonium dihydrogen phosphate. Ex. 1003 at ¶¶ 219-221, 225, 415-417, 422-423, 635. An organo-silicate (TEOS in Ruys 1993b; TEOS or TPOS in the '251 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 '251 patent and therefore

necessarily resulted in products having the same physical, chemical, and biological properties. *Id.* at ¶ 636.

Ruys 1993b suggests in the paper that the process created a silicon "substituted"-HA. Ex. 1003 at ¶ 639; Ex. 1014 (Ruys 1993b) at 2. However, as explained above (§ IV.D.1.), subsequent work by the inventors of the '251 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 ¶¶ 394, 422, 639; Ex. 1119 at 10.

The multi-phasic Ca-P mixtures that result from the Ruys 1993b (Ex. 1014) process therefore necessarily included Si-TCP as one component. Ex. 1003 at ¶ 639. As with the sintering step found in the '251 patent, *id.* at ¶ 307, the sintering step in Ruys 1993b would have resulted in the removal of residual reactants, thereby resulting in an "isolated compound" of HA and Si-TCP phases. Ex. 1003 at ¶ 637.

During examination of the '872 application (the predecessor application of the application resulting in the '146 patent), the Ruys 1993b reference was found to describe the same process as that set forth in the '872 application (identical to WO 97/09286), which is also the same process described in the '251 patent for producing the claimed "isolated … compounds." *See id.* at ¶ 640. Specifically, the Board upheld a rejection for anticipation based on Ruys 1993b (Ex. 1014), 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 claim 1 of the '251 patent. Ex. 1003 at ¶ 642.

Notably, during the reissue resulting in the '251 patent, the Examiner rejected the claims, finding them anticipated by Ruys 1993b. *Id.* at ¶ 243. 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 ¶ 244 (citing Ex. 1002 at 138). Patent Owner did not dispute the Examiner's characterization and instead added the phrase "wherein said compound has a microporous structure" to claim 1. *Id.* at ¶ 245 (citing Ex. 1002 at 158). This amendment should not have rendered the claims patentable because the methods disclosed in Ruys 1993b would have inherently resulted in a compound having a microporous structure. Ex. 1003 at ¶¶ 641-642. Claim 1 is thus anticipated under § 102(b) by Ruys 1993b (Ex. 1014). *See generally id.* at § IV.B.5.

2. Claim 6 Would Have Been Obvious Based on Ruys 1993b In View Of Bioceramics 1993

The methods disclosed in Ruys 1993b are equivalent to the methods disclosed in Ruys 1993a and would have resulted in the same material, *i.e.*, multi-phasic mixtures made of Si-TCP and HA. Ex. 1003 at ¶ 425. Like Ruys 1993a, Ruys 1993b relates to the study and development of Ca-P bone implant material. *Id.* at ¶ 692. For the same reasons that Ruys 1993a in view of Bioceramics 1993 would have rendered claim 6 obvious, Ruys 1993b in view of Bioceramics 1993 would also have rendered claim 6 obvious. *See generally id.* at ¶¶ 692-697.

3. Claim 6 Would Have Been Obvious Based on Ruys 1993b In View Of White 1986

The methods disclosed in Ruys 1993b are equivalent to the methods disclosed in Ruys 1993a and would have resulted in the same material, *i.e.*, multi-phasic mixtures made of Si-TCP and HA. *Id.* at ¶ 425. Like Ruys 1993a, Ruys 1993 relates to the study and development of Ca-P bone implant material. *Id*. at ¶ 692. For the same reasons that Ruys 1993a in view of White 1986 would have rendered claim 6 obvious, Ruys 1993b in view of White 1986 would also have rendered claim 6 obvious. *Id.* at ¶¶ 692-697.

4. Ruys 1993b Anticipates Claim 8

Ruys 1993b (Ex. 1014) inherently discloses synthetic Ca-P materials exhibiting a microporous structure. *Id.* The materials disclosed in Ruys 1993b

(Ex. 1014) would inherently possess a nanoporous structure. *Id.* at ¶¶ 424-426. Consequently, Ruys 1993b (Ex. 1014) anticipates claim 8. *Id.* at ¶¶ 756-757.

5. Claim 8 Would Have Been Obvious Based on Ruys 1993b in View of EP0267624

The methods disclosed in Ruys 1993b are equivalent to the methods disclosed in Ruys 1993a and would have resulted in the same material, *i.e.*, multi-phasic mixtures made of Si-TCP and HA. Ex. 1003 at ¶ 625. Like Ruys 1993a, Ruys 1993 relates to the study and development of Ca-P bone implant material. For the same reasons that Ruys 1993a in view of EP0267624 would have rendered claim 8 obvious, Ruys 1993b in view of EP0267624 would also have rendered claim 8 obvious.

6. Ruys 1993b Anticipates Claim 9

The methods disclosed in Ruys 1993b are equivalent to the methods disclosed in Ruys 1993a and would have resulted in the same material, *i.e.*, multi-phasic mixtures made of Si-TCP and HA. Ex. 1003 at ¶ 425. For the same reasons that Ruys 1993a inherently anticipates claim 9, Ruys 1993b also inherently anticipates claim 9. *Id.* at ¶¶ 778-781.

7. Ruys 1993b Anticipates Claims 10-12

As explained above (*see* § IV.A.6.), claims 10-12 do not specify limitations that define structural or chemical properties of the "isolated … compounds" of claim 1. *Id.* at ¶¶ 782-787. Instead, these claims specify only functional effects

observed when the claimed materials are used. *Id.*; *see also* § IV.A.6. Ca-P bone implant material, including both HA and TCP, were reported in the literature to have these properties. Ex. 1003 at § II.E. Claims 10-12 thus simply specify functional properties or capabilities inherent to the multi-phasic Ca-P compounds that are described in Ruys 1993b (Ex. 1011). *Id.* at ¶¶ 782-787. Ruys 1993b (Ex. 1014) thus anticipates claims 10-12. *See id.*

8. Ruys 1993b Anticipates Claim 13

The methods disclosed in Ruys 1993b are equivalent to the methods disclosed in Ruys 1993a and would have resulted in the same material, *i.e.*, multi-phasic mixtures made of Si-TCP and HA. For the same reasons that Ruys 1993a inherently anticipates claim 13, Ruys 1993b also inherently anticipates claim 13.

V. CONCLUSION

For the foregoing reasons, the Petitioner respectfully requests that Trial be instituted and that claims 1, 6, 8-13 of the ’251 patent be canceled.

Dated: September 16, 2013

Respectfully Submitted,

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PETITION FOR INTER PARTES REVIEW

OF U.S. PATENT NO. RE41,251

Attachment A:

Proof of Service of the Petition

CERTIFICATE OF SERVICE

I hereby certify that on this 16th 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. RE41,251

Attachment B:

List of Evidence and Exhibits Relied Upon in Petition

Exhibit #	Reference Name
1001	U.S. Patent No. RE 41,251 (filed Jan. 30, 2008)
1002	U.S. Patent No. RE 41,251 (filed Jan. 30, 2008) File Wrapper
1003	Declaration of Dr. Antonios Mikos re '251 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. 6,585,992 (filed Oct. 4, 2001)
1007	U.S. Patent No. 6,585,992 (filed Oct. 4, 2001) File Wrapper
1008	U.S. Patent No. 6,323,146 (filed Mar. 19, 1998)
1009	U.S. Patent No. 6,323,146 (filed Mar. 19, 1998) File Wrapper
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1013	K.S. Leshkivich & E.A. Monroe, *Synthetic silicate sulphate apatite: mechanical properties and biocompatibility testing*, 4 J. MATERIALS SCI. 86 (1993)
1014	A.J. Ruys, *Silicon-Doped Hydroxyapatite*, 29 J. AUSTL. CERAMICS SOC. 71 (1993)
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