5 – Literature Overview

Butler, Jennie C

From: Lisa Simpson [lsimpson@rtix.com]
Sent: Wednesday, August 16, 2006 5:53 PM
To: Hanna, Myrna
Cc: Butler, Jennie C
Subject: RTI Bone Heterograft Reclassification Petition

Dear Myrna,

I wanted to let you know that none of the information submitted in the "Reclassification Petition, Bone Heterograft", dated August 10th 2006 is considered to be confidential by RTI. As such, I am giving FDA permission to distribute the information as necessary in support of the reclassification efforts.

Thank you,
Lisa

Lisa Simpson
Regulatory Affairs, Director
Regeneration Technologies, Inc.
P.O. Box 2650
11621 Research Circle
Alachua, FL 32616-2650
USA

Phone: 386-418-8888 ext. 4326
Fax: 386-418-3607

This e-mail and any attachments may contain confidential and privileged information. If you are not the intended recipient, please notify the sender immediately by return e-mail, delete this e-mail and destroy any copies. Any dissemination or use of this information by a person other than the intended recipient is unauthorized and may be illegal.

Rationale for Bovine Cortical Ring Xenograft –A Literature Overview

Purpose:

The purpose of this document is to demonstrate the similarities between human and bovine cortical bone as reported in the literature, and to use this information as a basis for a rationale to not conduct *in vivo* testing for the bovine xenograft spinal spacer. This literature review will demonstrate that the available published information supports the safety and effectiveness of bovine bone for use in this indication.

Background:

The biomechanical and biological properties of human allograft bone are well characterized[1-5]. Bovine bone is similarly well characterized.[1-5] A prolific literature exists relating to the comparison of their properties.[1, 6-8, 11]

We proffer a rationale that the scientifically recognized similarities between bovine xenograft bone and human allograft bone support the use of a bovine bone cortical ring spacer in spinal surgeries. Additionally, RTI believes that this rationale obviates the need to perform *in vivo* studies since both human and bovine bone are so well characterized in the scientific literature, and should be considered analogous in spinal applications.

Literature Summary:

In order to gain an overview of relevant publications, recently published pertinent review articles and other compendia were surveyed.

A computerized search of the National Library of Medicine database (PubMed) and the ISI Web of Science: Science Citation Index of the literature published from 1990 through 2005 was performed. A search utilizing keywords such as "bovine bone, human bone, characterization" yielded approximately 100 articles. Included in the citations were over twenty review articles and edited compendia. Several of the most relevant articles, review articles, and edited books discussing bovine and human bone comparisons were chosen for this summary.

In the literature, comparison is often made between human bone and that of other species.[6] Following are several representative tabular presentations of the properties of human and bovine bone.

An example of one of several tables comparing human and bovine bone biomechanical characteristics is reproduced here. It is noteworthy that variations of this well accepted tabulation occur in several seminal references.[4,8]

(The tables included in this document have been scanned or otherwise reproduced from their original sources as cited.)

Rationale for Bovine Cortical Ring Xenograft –A Literature Overview

TABLE 1

Human vs. Bovine biomechanical values

An overview (or representative average) of cortical bone properties for human and bovine is presented by Martin *et al.* in Skeletal Tissue Mechanics (1998)[7]:

Property	Human Value	Bovine Value
Elastic Modulus Transverse	17.4 GPa	20 GPa
Elastic Modulus Longitudinal	9.6 GPa	11.7 GPa
Shear Modulus	3.5 GPa	4.1 GPa
Tensile Yield Stress Longitudinal	115 GPa	141 MPa
Tensile Ultimate Stress Longitudinal	133 MPa	156 MPa
Tensile Ultimate Stress Transverse	51 MPa	50 MPa
Comp Yield Stress Longitudinal	182 MPa	196 MPa
Comp Yield Stress Transverse	121 MPa	150 MPa
Comp Ultimate Stress Longitudinal	195 MPa	237 MPa
Comp Ultimate Stress Transverse	133 MPa	178 MPa
Tensile Ultimate Strain	2.9 – 3.2%	.67 - .72%
Compressive Ultimate. Strain	2.2 – 4.6%	2.5 – 5.2%

Importantly, while their biomechanical properties are similar, the table above demonstrates that the compressive and tensile strength of bovine bone consistently exceeds the human values.

Similar trends are documented in other compendial tables.

Rationale for Bovine Cortical Ring Xenograft –A Literature Overview

Table 2

This table extracted from An[3] is a typical comparison of the properties of human and bovine cortical bone (table scanned from original cited reference)

Mechanical Properties of Human and Bovine Cortical Bones Tested by Compression, Tensile, and Torsional Testing (all at the tissue level)

Species	Bone	Specimen Dimensions	Strength (MPa)	Elastic Modulus (GPa)	Reference
Compression Test					
Human	Femur	2 × 2 × 6 mm dumbbell	167–215[a]	14.7–19.7[a]	Reilly 1974[15]
		2 × 2 × 6 mm dumbbell	179–209[a]	15.4–18.6[a]	Burstein 1976[16]
		3 mm diam. cylindrical dumbbell	205–206[a]	—	Cezayirlioglu 1985[17]
	Tibia	2 × 2 × 6 mm dumbbell	183–213[a]	24.5–34.3[a]	Burstein 1976[16]
		3 mm diam. cylindrical dumbbell	192–213[a]	—	Cezayirlioglu 1985[17]
Bovine	Femur	3.8 × 2.3 × 76 mm dumbbell	133	24.1–27.6[a]	McElhaney 1964[18]
		2 × 2 × 6 mm dumbbell	240–295[a]	21.9–31.4[a]	Reilly 1974[15]
	Tibia	4 × 5 mm rectangular	165	23.8 ± 2.2	Simkin 1973[19]
		2 × 2 × 6 mm dumbbell	228 ± 31	20.9 ± 3.26	Reilly 1974[15]
		3 mm diam. cylindrical dumbbell	217 ± 27	—	Cezayirlioglu 1985[17]
Means ± SD (n^b)			200 ± 36 (10)	23.0 ± 4.8 (7)	
Tensile Test					
Human	Femur	3.8 × 2.3 × 76 mm dumbbell	66–107[a]	10.9–20.6[a]	Evans 1951[20]
		2 × 2 × 6 mm dumbbell	107–140[a]	11.4–19.7[a]	Reilly 1974[15]
		2 × 2 × 6 mm dumbbell	120–140[a]	15.6–17.7[a]	Burstein 1976[16]
		3 mm diam. cylindrical dumbbell	133–136[a]	—	Cezayirlioglu 1985[17]
	Tibia	2 × 2 × 6 mm dumbbell	145–170[a]	18.9–29.2[a]	Burstein 1976[16]
		1.7 × 1.8 × 25 mm beam	162 ± 15	19.7 ± 2.4	Vincetelli 1985[21]
		3 mm diam. cylindrical dumbbell	154–158[a]	—	Cezayirlioglu 1985[17]
Bovine	Femur	3.8 × 2.3 × 76 mm dumbbell	92	20.5	McElhaney 1964[18]
		2 × 2 × 6 mm dumbbell	129–182[a]	23.1–30.4[a]	Reilly 1974[15]
		3 mm diam. cylindrical dumbbell	162 ± 14[a]	—	Cezayirlioglu 1985[17]
	Tibia	4 × 5 × 30 mm dumbbell	136	7.1 ± 1.1	Simkin 1973[19]
		2 × 2 × 6 mm dumbbell	152 ± 17	21.6 ± 5.3	Reilly 1974[15]
		2 × 2 × 6 mm dumbbell	188 ± 9	28.2 ± 6.4	Burstein 1975[22]
Means ± SD (n^b)			141 ± 28 (13)	19.6 ± 6.2 (10)	
Torsional Test					
Human	Femur	?	53	—	Hazama 1964[23]
		?	54 ± 0.6	3.2	Yamada 1970[24]
		2 × 2 × 6 mm dumbbell	—	3.1–3.7[a]	Reilly 1974[15]
		3 × 3 × 6 mm dumbbell	65–71[a]	—	Reilly 1975[25]
		3 mm diam. cylindrical dumbbell	68–71[a]	—	Cezayirlioglu 1985[17]
	Tibia	3 mm diam. cylindrical dumbbell	66–71[a]	—	Cezayirlioglu 1985[17]
Bovine	Femur	3 × 3 × 6 mm dumbbell	62–67[a]	—	Reilly 1975[25]
		3 mm diam. cylindrical dumbbell	76 ± 6	—	Cezayirlioglu 1985[17]
Means ± SD (n^b)		65 ± 9 (7)	3.3 ± 0.1 (2)		

[a] Range of average values from different subjects.

[b] Number of data sets from the literature.

Rationale for Bovine Cortical Ring Xenograft –A Literature Overview

TABLE 3

Liebschner[6] further tabulates biomechanical properties of cortical bone from various sources including human and bovine (table scanned from original cited reference)

1704 M.A.K. Liebschner / Biomaterials 25 (2004) 1697–1714

Table 3
Mechanical properties of cortical bone tissue—Young's modulus (E), strength (S), ultimate strain (ε_f), and mineral content (mineral weight/wet bone weight) of various bones

Species	Bone	Test	Mineral content	E (GPa)	Strength (MPa)	ε_f	References
Human	Femur	Tension	0.496	16.7	166	0.029	Currey, 1998 [113]
	Femur	Tension		11.4–19.7	107–140		Reilly, 1974 [42]
	Femur	Tension		3.9–11.9	90.6–116		Ascenzi, 1968 [114]
	Tibia	Tension		18.9–29.2	145–170		Burstein, 1976 [115]
	Tibia	Tension		19.7±2.4	162±15		Vincetelli, 1985 [116]
	Femur	Compression		14.7–19.7	167–215		Reilly, 1974 [42]
	Femur	Compression		4.9–9.5	90–167		Ascenzi, 1968 [114]
	Tibia	Compression		24.5–34.3	183–213		Burstein, 1976 [115]
	Femur	Torsion		54±0.6	3.2		Yamada, 1970 [117]
	Femur	Torsion		65–71	3.1–3.7		Reilly, 1974 [42]
	Femur	Torsion		5.0±0.2	7.41±3.2		Jepsen, 1997 [25]
	Tibia	Torsion		66–71			Cezayirlioglu, 1985 [118]
	Femur	Bending		9.82–15.7	103–238		Keller, 1990 [119]
	Tibia	Bending		6.75±1.00	150–180		Choi, 1990 [29]
Bovine	Femur	Tension		24.1–27.6	133		McElhaney, 1964 [120]
	Femur	Tension		21.9–31.4	240–295		Reilly, 1974 [42]
	Femur	Tension	0.562	26.1	148	0.004	Currey, 1998 [113]
	Femur	Tension		24.5±5.1	172±22		Burstein, 1972 [121]
	Femur	Tension		5.4–16.9	112–120		Ascenzi, 1967 [122]
	Tibia	Tension			217±27		Cezayirlioglu, 1985 [118]
	Tibia	Tension		21.9–31.4	240–295		Reilly, 1974 [42]
	Tibia	Tension	0.499	19.7	146	0.018	Currey, 1998 [113]
	Tibia	Tension		23.8±2.21			Simkin, 1973 [123]
	Femur	Compression		20.5	92		McElhaney, 1964 [120]
	Femur	Compression		23.1–30.4	129–182		Reilly, 1974 [42]
	Tibia	Compression		21.6±5.3	152±17		Reilly, 1974 [42]
	Tibia	Compression		28.2±6.4	188±9		Burstein, 1975 [124]
	Tibia	Compression		7.10±1.05			Simkin, 1973 [123]
	Femur	Torsion			62–67		Reilly, 1975 [36]
	Femur	Torsion			76±6		Cezayirlioglu, 1985 [118]
Cattle	Femur	Tension		19.4±0.7	228±5		Currey, 1998 [113]
	Tibia	Bending		21.0±1.9	230±18		Martin, 1993 [125]
Horse	Femur	Bending		17.1–19.9	204–247		Schryver, 1978 [126]
	Femur	Tension	0.541	21.2±1.9	152	0.008	Currey, 1998 [113]
	Radius	Bending		16.2–20.2	217–249		Schryver, 1978 [126]
Sheep	Metatarsus	Tension, Bending		18.96±2.2			Currey, 1988 [127]
Donkey	Radius	Tension, Bending		17.6±2.0			Currey, 1988 [127]
Rabbit	Humerus	Bending		13.6±0.7	165±5		An, 1996 [128]
	Femur	Bending		13.6±0.4	137±6		An, 1996 [128]
	Femur	Bending		10.7±2.5	88±20		Ayers, 1996 [129]
	Tibia	Bending		21.3±0.7	195±6		An, 1996 [128]
	Tibia	Bending		23.3±7.0	192±47		Ayers, 1996 [129]
	Humerus	Bending		13.3±0.6	167±5		An, 1996 [128]
Rat	Femur	Bending		6.9±0.3	180±6		Jorgensen, 1991 [130]
	Femur	Bending		8.0±0.4	134±4		Barengolts, 1993 [131]
	Femur	Bending		4.9±4	153±45		Ejersted, 1993 [132]
Mouse	Femur	Bending		8.8–11.4	104–173		Simske, 1992 [133]
	Femur	Bending		5.3±1.8	40±13		Ayers, 1996 [129]
	Femur	Bending, anterior		11.4±3.1	197±36		Jepsen, 1997 [25]
	Femur	Bending, posterior		7.9±3.1	187±36		Jepsen, 1997 [25]
	Tibia	Bending		8.9±0.2	78±12		Ayers, 1996 [129]

Rationale for Bovine Cortical Ring Xenograft –A Literature Overview

TABLE 4

Zioupos, *et al.*[9] reference young's modulus and the tensile and mineral properties of human, bovine and other species' bone: (table scanned from cited reference)

Mechanical Properties — Young's Modulus (E) Ultimate Tensile Stress (UTS), Ultimate Tensile Strain (ε_f), and Mineral Content (mineral weight/wet bone weight) of Various Bones[13,14]

Species and Tissue	Mineral Content	E (GPa)	UTS (MPa)	ε_f
Red deer, immature antler	0.385	10	250	0.109
Red deer, mature antler	0.393	7.2	158	0.114
Reindeer, antler	0.411	8.1	95	0.051
Polar bear (3 months), femur	0.441	6.7	85	0.044
Narwhal, tusk cement	0.454	5.3	84	0.060
Narwhal, tusk dentine	0.466	10.3	120	0.037
Sarus crane, tarsometatarsus	0.467	23.1	218	0.018
Walrus, humerus	0.482	14.2	105	0.026
Fallow deer, radius	0.493	25.5	213	0.019
Human adult, femur	0.496	16.7	166	0.029
Bovine, tibia	0.499	19.7	146	0.018
Polar bear (9 months), femur	0.501	11.2	137	0.042
Leopard, femur	0.514	21.5	215	0.034
Brown bear, femur	0.517	16.9	152	0.032
Donkey, radius	0.522	15.3	114	0.020
Sarus crane, tibiotarsus	0.523	23.5	254	0.031
Flamingo, tibiotarsus	0.523	28.2	212	0.013
Roe deer, femur	0.525	18.4	150	0.011
Polar bear (3.5 years), femur	0.529	18.5	154	0.022
King penguin, radius	0.540	22.1	195	0.010
Horse, femur	0.541	24.5	152	0.008
Wallaby, tibia	0.551	25.4	184	0.010
Bovine femur	0.562	26.1	148	0.004
King penguin, ulna	0.577	22.9	193	0.011
Axis deer, femur	0.586	31.6	221	0.019
Fallow deer, tibia	0.589	26.8	131	0.006
Wallaby, femur	0.599	21.8	183	0.009
King penguin, humerus	0.621	22.8	175	0.008
Fin whale, *T. bulla*	0.768	34.1, 31.3[a]	—, 33[a]	0.002, 0.0011[a]
Mesoplodon rostrum	0.960	41[a]	60[a]	0.0015[a]

Note: The mineral content was derived from calcium content measurements assuming that the tissues have the same element stoichiometry. Note that the two most mineralized tissues at the bottom of the list are extremely brittle compared to all the rest.

Rationale for Bovine Cortical Ring Xenograft –A Literature Overview

In addition to the listed tabular summaries, a number of references specifically address comparisons of bovine bone and its biomechanical relationship to human bone.[10, 11]

Currey[10] reviews the mechanical properties of a diverse group of vertebrate bone and lists comparisons human and bovine bone. A salient conclusion is that the two tissues are similar in biomechanical characteristics with bovine being of higher compressive and tensional strength.[19] In a comparative study, Poumarat and Squire[11] present the mechanical properties of human, bovine bone, and a processed bovine bone xenograft. They demonstrate the biomechanical similarities of human and bovine while showing that the bovine constructs (processed and unprocessed xenograft) are stronger with respect to stiffness.[20]

Likewise, several recent publications demonstrate the mechanical properties and biological characterization of human and bovine bone.[12-14]

Currey reviews the properties of stiffness and toughness as a function relation to anatomic purpose for a number of species, and posits that bovine femoral bone, as an example of a limb, is stiff, strong, and good at resisting impact loads[21]. Similarly, Doblare, *et al.*[13] present a review of the biology and mechanics of bone and bone fracture. Their summary outlines a macromechanical fracture toughness comparison between bovine and human bone showing the higher strength of bovine bone.

Other data that relate to the biomechanical nature of bovine bone appear in section 18 of this submission.

A number of references deal specifically with bovine bone and its adaptability to biomedical applications[15-18].Johnson, *et al.* characterize bovine bone after several steps to remove fat and protein materials by various processes. While dealing primarily with cancellous bone, their overarching conclusion is that bovine bone lends itself well to biomedical (xenograft) applications when proper processing techniques are utilized[15-17].
Lofgren, *et al.*[18] describe the use of bovine xenograft in cervical spinal surgery. They compare clinical outcome assessment of autogenous, allogenic and heterologous bone grafts used in single-level cervical Cloward surgeries. Their overall clinical conclusion was that fusion outcomes were ultimately similar for all three grafts, with a slightly better trend for autograft. However, when taking in consideration the postoperative complications for autograft, all grafts were suitable in the procedure[23].

Safety Of Bovine Xenograft In Clinical Applications

A number of studies provide evidence of the long standing safe use of bovine xenograft in surgical procedures.[23,24] Salama reported good results using a mixture of deproteinized calf bone (Kiel bone) and autologous iliac bone marrow for the treatment of pseudarthroses[23].

More recently, Maica, *et al.*[24] describe use of bovine xenograft in cervical spinal surgery. They report a retrospective study of 52 patients over 5 years. The study concludes that the use of the interbody xenograft gives a safe and solid interbody fusion when used with rigid plate fixation.

Rationale for Bovine Cortical Ring Xenograft –A Literature Overview

SUMMARY:

The properties of bovine cortical bone are amply characterized in the scientific literature. The similarities between bovine and human cortical bone with regard to biomechanical properties are likewise well established.

Because of the well documented characterization of bovine cortical bone, we conclude that it is not necessary to perform *in vivo* studies, and that bovine cortical bone is at least as safe and effective as human allografts for use as a cortical ring spacer in non cervical vertebral surgeries.

References:

1. Bonucci, E; "Basic Composition and Structure of Bone", pp. 3-21; in An, Yuehuei H., Draughn, Robert A. eds..; Mechanical Testing of Bone and the Bone-Implant Interface; CRC Press (2000)
2. An, Yuehuei H., Draughn, Robert A.; "Basic Concepts of Mechanical Property Measurement and Bone Biomechanics, pp. 23- 40; in An, Yuehuei H., Draughn, Robert A. eds..; Mechanical Testing of Bone and the Bone-Implant Interface; CRC Press (2000)
3. An, Yeuhuei; "Mechanical Properties of Bone", pp. 41-63; in An, Yuehuei H., Draughn, Robert A. eds..; Mechanical Testing of Bone and the Bone-Implant Interface; CRC Press (2000)
4. An, Yuehuei H., Draughn, Robert A. eds..; Mechanical Testing of Bone and the Bone-Implant Interface; CRC Press (2000)
5. Currey, J. D. (1999). "What determines the bending strength of compact bone?" Journal Of Experimental Biology 202(18): 2495-2503.
6. Liebschner, M. A. (2004). "Biomechanical considerations of animal models used in tissue engineering of bone." Biomaterials 25(9): 1697-714.
7. Martin, R. B., D. B. Burr, *et al.* (1998). Skeletal tissue mechanics. New York, Springer. (ISBN 0-387-98474-7)
8. Cowin, S. C. (2001). Bone mechanics handbook. Boca Raton, FL, CRC Press. (ISBN 0-8493-9117-2)
9. Zioupos, P, *et al.*; "Factors Affecting Mechanical Properties of Bone", in An, Yuehuei H., Draughn, Robert A. eds..; Mechanical Testing of Bone and the Bone-Implant Interface; CRC Press (2000)
10. Currey, J. D. (1998). "Mechanical properties of vertebrate hard tissues." Proc Inst Mech Eng [H] 212(6): 399-411.
11. Poumarat, G. and P. Squire (1993). "Comparison of mechanical properties of human, bovine bone and a new processed bone xenograft." Biomaterials 14(5): 337-40.
12. Currey, J. D. (1999). "The design of mineralised hard tissues for their mechanical functions." J Exp Biol 202(Pt 23): 3285-94.
13. Doblare, M., J. M. Garcia, *et al.* (2004). "Modelling bone tissue fracture and healing: a review." Engineering Fracture Mechanics **71**(13-14): 1809-1840.
14. Ritchie, R. O., J. H. Kinney, *et al.* (2005). "A fracture mechanics and mechanistic approach to the failure of cortical bone." Fatigue & Fracture Of Engineering Materials & Structures **28**(4): 345-371.

Rationale for Bovine Cortical Ring Xenograft –A Literature Overview

15. Johnson, G. S., M. R. Mucalo, *et al.* (2000). "The processing and characterization of animal-derived bone to yield materials with biomedical applications: part 1: modifiable porous implants from bovine condyle cancellous bone and characterization of bone materials as a function of processing." J Mater Sci Mater Med **11**(7): 427-41.
16. Johnson, G. S., M. R. Mucalo, *et al.* (2000). "The processing and characterization of animal-derived bone to yield materials with biomedical applications. Part II: milled bone powders, reprecipitated hydroxyapatite and the potential uses of these materials." J Mater Sci Mater Med **11**(11): 725-41.
17. Anderson, I. A., M. R. Mucalo, *et al.* (2000). "The processing and characterization of animal-derived bone to yield materials with biomedical applications. Part III: material and mechanical properties of fresh and processed bovine cancellous bone." J Mater Sci Mater Med **11**(11): 743-9.
18. Lofgren, H., V. Johannsson, *et al.* (2000). "Rigid fusion after cloward operation for cervical disc disease using autograft, allograft, or xenograft: a randomized study with radiostereometric and clinical follow-up assessment." Spine **25**(15): 1908-16.
19. Currey, J. D. (1998). "Mechanical properties of vertebrate hard tissues." Proc Inst Mech Eng [H] **212**(6): p. 402, Table 1
20. Poumarat, G. and P. Squire (1993). "Comparison of mechanical properties of human, bovine bone and a new processed xenograft." Biomaterials 14(5): p.39, Table 1.
21. Currey, J. D. (1999). "The design of mineralised hard tissues for their mechanical functions." J Exp Biol 202(Pt 23): p. 3287.
22. Doblare, M., J. M. Garcia, *et al.* (2004). "Modelling bone tissue fracture and healing: a review." Engineering Fracture Mechanics **71**(13-14): p. 1819, Table 1
23. Salama, R. (1983). "Xenogeneic bone grafting in humans." Clin Orthop Relat Res(174): 113-21.
24. Malca, S. A., P. H. Roche, *et al.* (1996). "Cervical interbody xenograft with plate fixation: evaluation of fusion after 7 years of use in post-traumatic discoligamentous instability." Spine **21**(6): 685-90.