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June 20, 2007

Dr. Steve Phurrough
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Baltimore, Maryland 21244

Re: Formal Coverage Reconsideration Request for CAG-00190N

Dear Dr. Phurrough:

This letter is a formal request for a National Coverage Determination (NCD) to reconsider the non-coverage of Autologous Blood-derived Products when used for the treatment of chronic non-healing wounds (CAG-00190N). Autologous platelet-rich plasma (PRP) is currently the prevalent blood product used for treating chronic non-healing wounds, open cutaneous wounds, soft tissue, and bone. This letter sets out the body of clinical evidence to support our conclusion that the data support use of autologous platelet-rich plasma (PRP) gel to improve healing in open cutaneous wounds including chronic wounds, acute surgical incisions and dehiscence wounds.

The evidence will show that PRP gel significantly improves time to healing and wound closure; so much so that resumption of normal activity and return to work are greatly enhanced. The supporting published evidence and data are based on six randomized controlled trials, four non-randomized controlled trials, and eight additional case series. In addition, there is a significant library of unpublished data that, while weighted less by CMS, serves to support the findings in the aforementioned trials. PRP gel meets the qualifications for coverage in the Medicare benefit category of physician service or incident to a physician service as defined under Section 1861 (s)(1) and (s)(2)(A) of the Social Security Act when performed under supervision of a physician.

Cytomedix believes that this new body of evidence warrants CMS' re-evaluation of the coverage of PRP gel for the following open cutaneous wounds, including chronic wounds:

1. Wounds caused by an acute surgical incision or dehiscence.
2. Full-thickness chronic wounds (such as, Wagner grade II or higher[1], University of Texas Classification System Grade 2 or higher[2], or National Pressure Ulcer

[1] Wagner RW. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle 1982;2:64-122.
[2] Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. J Foot Ankle Surg. 1996; 35:528-531.

Advisory Panel Stage III and IV[3]) that have failed an adequate course of standard wound therapy.

The definition of cutaneous is "of, relating to, or affecting the skin."[4] An open, cutaneous wound is an open area or a breach in the integrity of the largest body of tissue in the body; the skin. Open cutaneous wounds include acute surgical wounds, wound dehiscence, and wounds caused by trauma or injury to the intact skin.

Chronic wounds/ulcers are a subset of open cutaneous wounds/ulcers. The Centers for Medicare and Medicaid Services (CMS) has defined a chronic wound in previous Decision Memoranda as "...an open cutaneous wound which has been in existence for longer than one month."[4] The F ood and Drug Administration (FDA) has provided the following definition of a chronic wound in a 2006 industry guidance: "a chronic cutaneous ulcer is defined as a wound that has failed to proceed through an orderly and timely series of events to produce a durable structural, functional, and cosmetic closure."[5]

The FDA guidance document, *Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment*, states that; "three of the major categories of chronic cutaneous ulcers are diabetic ulcers, venous stasis ulcers, and pressure ulcers[5]. In addition, the FDA guidance states that "because wounds differ in their pathophysiology, it is difficult to generalize results obtained from a trial conducted in subjects with one wound type to patients with another wound type. Therefore, separate clinical trials should be considered for each type of wound indication sought. *However, if a scientific rationale and clinical data support clinical activity of a product in more than one wound type, it may be possible for studies performed in one wound type to support another in establishing substantial evidence of efficacy and safety."*[5]

The Wound Healing Society *Guidelines for Diabetic, Venous, Pressure, and Arterial Insufficiency Ulcers* document that a chronic wound should be converted into an acute wound prior to treatment. The Guidelines state: "wound bed preparation is defined as the management of the wound to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures. The aim of wound bed preparation is to convert the molecular and cellular environment of a chronic wound to that of an acute

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[3] 2007 National Pressure Ulcer Advisory Panel Pressure Ulcer Staging System. www.npuap.org. Accessed June 2007

[4] Merriam-Webster Medical Dictionary online. Accessed June 2007.

[5] Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), June 2006.

healing wound."[6] For these reasons, Cytomedix has included studies regarding different wound etiologies including acute surgical incisions, dehisced surgical wounds, open cutaneous wounds, and chronic wounds in the evidence we present to CMS. As noted in these Guidelines, the scientific community supports that the mechanism of healing of the open cutaneous and soft tissue are predominantly the same as long as standard wound care is utilized to reduce the factors that could affect wound healing, including, but not limited to, wound bioburden, infection, ischemia, edema, hyperglycemia, and pressure.

History of PRP Coverage Consideration

In 1992, the Centers for Medicare and Medicaid Services (CMS) issued a national non-coverage determination for autologous, platelet-derived wound healing formulas intended to treat patients with chronic, nonhealing wounds due to insufficient published evidence of efficacy. In 2003 the agency reconsidered its earlier national non-coverage determination and decided to issue an additional non-coverage decision due to the absence of clinical data on the use of PRP gel to treat chronic wounds.

On February 28, 2007, Cytomedix presented new evidence to the Coverage and Analysis Group, Office of Clinical Science and Quality on the use of PRP gel to treat open cutaneous wounds, including chronic wounds, acute surgical incisions and dehiscence wounds. CMS agreed that it would be appropriate for Cytomedix to submit a formal request for reconsideration of the non-coverage of Autologous Blood-derived Products when used for the treatment of chronic non-healing wounds (CAG-00190N).

Background of Platelet Rich Plasma (PRP) Gel

PRP gel is produced through a process of harvesting blood donated by the patient, and centrifuging to separate the platelet rich plasma from the whole blood. The PRP derived from the process is activated to release the multiple growth factors and other releasates from the platelets and to convert the fibrinogen to a fibrin matrix scaffold from the plasma. The resulting PRP gel is applied to the tissue by a trained health care professional. The gel assists the natural healing process by maintaining a moist wound environment, providing a matrix on which new tissue can grow, and enabling platelet releasates, including growth factors, to contact the wound tissues and initiate the tissue-healing process.

The autologous PRP-based gel can be applied to patients in multiple healthcare settings, such as hospitals, outpatient clinics, physicians' offices, long-term care, long-term acute care, and home care under the supervision of a licensed physician or health care practitioner under a physician's supervision. Additionally, since the patient's own blood

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[6] Barbul A et al. Wound Healing Society Guidelines: Guidelines for the treatment of venous ulcers, pressure ulcers, diabetic ulcers, and arterial insufficiency ulcers. Wound Rep Reg (2006) 14:6; 645–711

is used as the source of the platelets and their growth factors, the risk of infection or immunological reaction that would be present if donor blood products were used is eliminated. Furthermore, the blood is processed at the point-of-care, immediately upon collection from the patient with the resulting gel applied shortly thereafter. Therefore, issues of gel shelf-life, storage or transportation are minimized. The patient's blood-derived gel does not enter into commerce or channels of distribution.

The body of evidence supporting use of PRP gel to treat open cutaneous wounds, in addition to that of damaged soft tissue and bone more broadly, has significantly improved from that presented in CY 2003 to CMS. Cytomedix conducted a randomized controlled trial (RCT) for its PRP gel (AutoloGel) in wound care and to date is the only provider of this technology in the United States that has completed a prospective clinical trial and spent significant resources in this critically important area. The other organizations using Cytomedix's patented technology chose to focus not on chronic wound care, which was in its nascent stages of research worldwide, but instead on other clinical applications in the treatment of soft tissue and bone such as bariatric, cardiovascular, maxillofacial, plastic, and orthopedic surgical settings. That is why there is extensive published evidence in these fields. These other organizations and technologies include:

Company	System
COBE Cardiovascular Inc.	Angel Whole Blood Separation System
Haemonetics Inc.	Cell Saver®
Biomet Orthopedics Inc.	Gravitational Platelet Separation (GPS) System
Medtronic Inc.	Magellan™ Autologous Platelet Separator
Harvest Technologies Corp.	SmartPReP®

Background on Platelet Gel Systems and Patents

Cytomedix holds several major patents covering the use of PRP gel to treat damaged tissue, such as that of open cutaneous wounds and soft tissue and bone in bariatric, cardiovascular, maxillofacial, orthopedic and other surgical settings.

The primary patent covers "the process for treating a wound [or damaged tissue]… which comprises applying over the wound [or damaged tissue] an effective amount of a treating composition containing the materials released by platelets during the platelet release reaction and facilitating healing of the wound [or damaged tissue]."[7] Thus, an y company or health care provider that is activating a platelet to heal damaged tissue, no matter how the activation occurs, should have a license from Cytomedix.

[7] U.S. Patent No. 5,165,938 (the "Knighton Patent")

To date, the following companies have secured licensing agreements with Cytomedix to have access to this patent:

DePuy Spine, Inc. (Johnson & Johnson)
Biomet Biologics, Inc.
Medtronic, Inc.
Cobe Cardiovascular, Inc.
Harvest Technologies, Inc.
SafeBlood Technologies, Inc.
Perfusion Partners and Associates, Inc.
Cellmedix, Inc.

While each of these companies activates platelets and uses the platelet releasate contents for tissue repair, the techniques used to process the blood into PRP gel varies. The centrifuges, their characteristics, (i.e. spin time, amount of blood used in machine, processing technique, and kits for processing) are all different. These companies have access to the Cytomedix patent(s), but do not specifically use Cytomedix's AutoloGel centrifuge or wound care kit for processing PRP gel. However all of these techniques have the same resulting end-product, an autologous platelet-rich plasma (PRP) gel which is used to improve healing rates for bone and soft tissue.

Platelet contents can be accessed by different methods. The major technique used is activating the platelet to cause the alpha granules to release their contents, thus providing a platelet releasate containing multiple growth factors and any other alpha granule contents. Most platelet gel companies in the U.S. rely upon bovine thrombin as the platelet activator. Similar European processes use human thrombin (which has not been approved in the U.S. yet) and other agents such as Batroxiban (snake venom) can also activate platelets.

Another method for accessing the platelet contents is by a freeze-thaw method to produce a lysate. The definition of a lysate is an end-product of lysis, which is a process of disintegration or dissolution (as of cells). To our knowledge, it has not been proven that this process maintains the integrity of the alpha granule contents or activity of the multiple growth factors. Therefore, the evidence documented by this request for reconsideration and the literature review pertains only to PRP gel processes involving activation of platelets and not for published literature on the freeze-thaw (lysate) method described above.

The Impact of Wounds On the Lives of Medicare Beneficiaries

Chronic and other open cutaneous wounds have significant impact on the lives of many patients, including Medicare beneficiaries. Chronic and complex wounds can lead to complications that are psychosocial, economic and debilitating in nature. Wounds can lead to extended disability, continued pain and discomfort, and can inhibit daily function

causing problems at work and at home. Some wounds require constant care, inhibiting social interaction. Still others take an economic toll in that return to work is slow, or the beneficiary cannot return to work, causing economic consequences for the family.

Open cutaneous wounds also place a tremendous cost on the health care system. Loss of work can lead to higher insurance claims, social security disability claims and, in Medicare, to issues related to balance billing, out-of-pocket expenses for non-covered items like PRP gel for open cutaneous wounds, stays in extended care facilities, such as long term acute care facilities, and other unexpected costs. AdvaMed, the premier trade association for medical technologies and devices, estimates that the management and treatment of complex open cutaneous wounds cost upwards of $20 billion a year.[8]

Venous Leg Ulcers

There are 2.5 million cases of venous ulcers in the United States.[9] Treatment costs for venous leg ulcers, the most frequently occurring type of chronic wound, costs $2-3 billion per year; $1 billion in outpatient care alone.[10] They also lead to two million lost workdays a year.[11] New medical technologies, like PRP gel, significantly improve patients' lives through reduced time to healing and wound closure.

Pressure Ulcers

Pressure ulcers are a major health problem with 2 million treated per year.[9] They are associated with high rates of morbidity and mortality, and, if not healed, present a higher risk of infection. These complications affected Christopher Reeves in his fight to maintain normalcy after his debilitating spinal cord injury. His death was directly attributed to infection of a non-healing pressure ulcer. Pressure ulcers force longer hospital stays, greater rehabilitation time, and considerable use of additional medical resources. Quite remarkably the average hospital length of stay for a patient with a pressure ulcer is five times greater than those without.[12]

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[8] Frykberg RG, Armstrong DG, Giurni J, et. al. Diabetic foot disorders: a clinical practice guideline. American College of Foot and Ankle Surgeons. *J Foot Ankle Surg* 2000:39(5 Suppl):S1-60 in AdvaMed, Advanced Wound Management: Healing and Restoring Lives, June 2006

[9] AdvaMed, Advanced Wound Management: Healing and Restoring Lives, June 2006

[10] McGuckin M, Kerstein MD, Venous leg ulcers and the family physician. Advanced in Wound Care 1998:344-346 in AdvaMed, Advanced Wound Management: Healing and Restoring Lives, June 2006

[11] Onegnas K, Phillips T, Leg ulcer management. Emerg. Med 1999;25:45-53 in AdvaMed, Advanced Wound Management: Healing and Restoring Lives, June 2006.

[12] Allman RM et. al. Pressure ulcers among hospitalized patients. *Ann Intern Med* 1986;105:337-342 in AdvaMed, Advanced Wound Management: Healing and Restoring Lives, June 2006

Diabetic Foot Ulcers

Diabetic foot ulcers are one of the most common complications in people with diabetes with 1.5 million treated per year.[9] The prevalence of diabetic foot ulcers is fairly high in Medicare beneficiaries – three times greater than the general population, only magnifying the wasted dollars spent on treatments of patients who are older and experience longer time to healing and poor wound closure; ultimately costing the system more in treatment and amputation. Each amputation can cost between $20,000 and $60,000 per case, with the total potential cost of the procedure topping $100,000.[13] More than 60% of non-traumatic lower limb amputations in the United States occur among people with diabetes.[14] The Veterans Administration (VA) Health Care System experienced 60,324 amputation discharges due to lower extremity diseases, such as diabetic ulcers, in patients mostly in the higher age brackets between 1989 and 1998.[15] In the Cytomedix prospective, randomized, controlled diabetic foot ulcer study[16] (Reference #R-1),* wounds treated with AutoloGel healed in an average of 6 weeks. Promise such as this could significantly improve the quality of life for diabetic patients.

Cost Effectiveness of PRP Gel for the Treatment of Diabetic Foot Ulcers

In a pharmacoeconomic draft report produced by B&D Consulting for Cytomedix, the authors found a significant cost benefit to using Cytomedix's AutoloGel (PRP gel) over standard of care in diabetic foot ulcers; also markedly improving quality of life years. The finalized report will be forwarded to CMS in the near future.

Summary of Clinical Evidence

Eighteen studies are being presented as clinical evidence demonstrating the efficacy of using PRP gel to treat open cutaneous and chronic wounds. Highlights of key articles demonstrating the impact of PRP gel on the tissue treated include:

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[13] Reiber GE, et. al. Lower extremity foot ulcers and amputations in diabetes. In: Diabetes in America, 2nd ed.(NIH publ. no. 95–1468), edited by M.I. Harris, C. Cowie, and M.P. Stern, U.S. Government Printing Office, Washington, DC, 1995. H.R. 3203 - Diabetic Foot Complication and Lower Extremity Amputation Reduction Act of 2003. Submitted
to the House of Representatives , Sept 30, 2003.

[14] Centers for Disease Control, *National Diabetes Fact Sheet*, 2005.

[15] Mayfield JA, Reiber GE, Maynard C, Czerniecki JM, Caps MT, Sangeorzan BJ. Trends in lower limb amputation in the Veterans Health Administration, 1989-1998. J. Rehabil Res Dev 2000 Jan-Feb; 37(1):23-30.

[16] Driver VR, Hanft J, Fylling C, Beriou JM. A Prospective Randomized Controlled Trial of Autologous PRP Gel for the Treatment of Diabetic Ulcers. Ost Wd Mgmt Jun 2006; 52(6):68-87.

* Reference # - refers to a reference listed in the Evidence Table of the Evidence Overview tab and the supporting published article in the Scientific Articles section

- healing 81.3% of the most common sized diabetic foot ulcers compared to 42.1% treated with saline gel
- diabetic foot ulcers had 71.9% area reduction in 5 weeks compared to 9.2% control wounds
- dehisced sternal wound healing in 3.5 versus 6.0 weeks
- reduced hospital stays for cardiac surgery patients of 31.5 vs 52.5 days
- a study of 2,259 cardiac surgery patients demonstrating reduced deep and sternal wound infections (superficial wound infections with PRP 0.3%, no PRP 1.8%, historical control 1.5% and deep wound infections with PRP 0.0%, no PRP 1.5%, historical control 1.7%).

Summaries of these studies are below. Details and the complete articles are included in the Binder.

The review includes six randomized control trials (three of open cutaneous wounds and three of soft and bone tissues), four non randomized control trials (three of open cutaneous wounds and one of soft / bone tissue), and eight additional studies (case series). To gather this evidence, a literature search of articles from 2003 – 2007 was conducted using the terms platelet rich plasma, platelet gel, and platelet releasate. The following inclusions and exclusions were used to filter the most pertinent evidence articles:

Inclusions

- Platelet rich plasma (PRP) gel articles published in peer reviewed journals from 2003 – 2007
- Human studies
- Studies published in English
- The PRP gel system must activate a platelet to release the platelet contents (platelet releasate); not a lysate system.

Exclusions

- Animal studies due to difficulty extrapolating the outcomes to the human.
- In vitro studies due to difficulty extrapolating the outcomes to the human.
- Studies using the platelet lysate process because the literature does not confirm that the platelet contents maintain their viability using this technique.
- Individual case reports because of limited applicability and potential bias.
- Dental, plastic surgery, and bariatric surgery literature due to lack of Medicare coverage in these areas.

Following are summary tables of the studies that met these criteria. A detailed Evidence Summary is in the Evidence Overview section and the complete published articles are provided in the Scientific Articles section of the binder.

While conducting the literature review, it was discovered that there is a large body of evidence supporting the use of PRP gel to treat multiple types of tissue. Tissue is defined as "an aggregate of cells usually of a particular kind together with their intercellular substance that form one of the structural materials of a plant or an animal and that in

animals include connective tissue, epithelium, muscle tissue, and nerve tissue."[4] All of the PRP gel studies were conducted on soft and bone tissue. In Figure 1 below, the broadest tissue category is soft tissue and bone. Each lower level depicted is a subset of this overall category. Thus, the research findings in each of the higher categories support the research in the lower level categories. The open cutaneous tissue, chronic wounds, and diabetic ulcer research are primary support for this reconsideration request. Soft tissue studies and the soft tissue and bone research can be considered corroborative research because the mechanism of healing is the same for each these tissues.

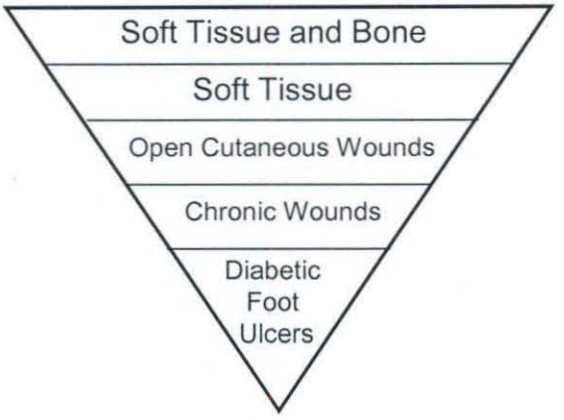

Figure 1: Hierarchy of Tissues

Table 1: PRP Gel Published Evidence by Tissue Type

Number of Studies Favorable to PRP/Total Number of Studies

Type of Tissue Studied	Randomized Controlled Trials	Non-randomized Controlled Trials	Additional Studies	Grand Total
Primary Research				
Chronic Wounds	2/2	1/1		
Open Cutaneous Wounds	1/1	2/2		
Corroborative Research				
Soft Tissue		1/1	1/1	
Soft Tissue & Bone	3/3		4/7	
Total	6/6	4/4	5/8	15/18

Table 2: Summary of PRP Gel Published Evidence

Codes for Article Number
R = Randomized Controlled Trial C = Non-randomized Controlled Trial A = Additional Studies

Article Number	Author	Category	Tissue Type Studied	No. Wounds in Study	Favorable to PRP	Outcomes
Randomized Controlled Trials						
Primary Research						
R-1	Driver	Chronic wounds	Diabetic foot ulcers	40	Yes	In the most common size of diabetic foot ulcers (≤ 7.0 cm^2 in area and ≤ 2 cm^3 in volume - 96% of all diabetic foot ulcers in 9 prospective trials were in this size range). PRP gel healed 13/16 (81.3%) of the wounds versus saline gel control at 8/19 (42.1%) ($p = 0.036$). Almost twice as many wounds were healed in 6 weeks in the PRP group versus saline gel.
R-2	Saldalamachia	Chronic wounds	Diabetic foot ulcers	14	Yes	At the 5 week endpoint of evaluation, the area reduction rate was 71.9% for study group vs. 9.2% for control . ($p = 0.039$)
R-3	Englert	Open cutaneous	Sternal and leg incisions	30	Yes	Overall the experimental APG group reported less chest pain, leg pain, and bruising than control during all measurement times.
Corroborative Research						
R-4	Steigmann	Soft tissue & bone	Sinus augmentation	20	Yes	Increased bone growth
R-5	Kassolis	Soft tissue & bone	Sinus augmentation	10	Yes	Increased bone growth
R-6	Savarino	Soft tissue & bone	Tibial osteotomy	10	Yes	Accelerated healing with newly formed bone

Article Number	Author	Category	Tissue Type Studied	No. Wounds in Study	Favorable to PRP	Outcomes
Non-Randomized Controlled Trials						
Primary Research						
C-1	Mazzucco	Chronic wounds	Dehisced sternal wounds & full thickness necrotic venous, arteriopathic, & pressure ulcers	53	Yes	In dehisced sternal wounds, the healing rate with PRP was 3.5 vs. 6.0 weeks ($p = 0.0002$). The hospital stays were-PRP-31.5 vs. Control-52.5 day ($p < 0.0001$). Necrotic skin ulcers needing reconstruction surgery had decreased wound preparation time to surgery, PRP 15.0 vs. Control 35.5 weeks ($p < 0.0001$).
C-2	Trowbridge	Open cutaneous	Sternal incisions & harvest sites	2,259	Yes	This controlled trial evaluated the superficial and deep infections rates in the sternal area in patients (> 19 yrs) treated with PRP during cardiac surgery from Oct 2002 to Jun 2005. The outcomes were compared to historical control (HC) treated with PRP and those surgeries without PRP. Superficial wound infections-PG-0.3%, NoPG- 1.8%, HC-1.5% ($p<0.05$). Deep sternal wound infections-PG-0.0%, NoPG- 1.5%, HC- 1.7% ($p<0.029$). The reduction in infection rate was caused by the improved healing of the sternal incision.
C-3	Hom	Open cutaneous	Full thickness punch wounds-normal tissue	80	Yes	Over a 42-day period, APG-treated sites had increased wound closure compared to control. ($p<0.02$). APG wound closure velocity was significantly higher than for the controls. ($p=0.001$). APG wounds showed increased endothelial cell proliferation compared with controls. $P<0.04$.
Corroborative Research						
C-4	Everts	Soft tissue	Total knee arthroplasty	165	Yes	Reduced incidence of allogeneic blood transfusions, patient discharged earlier, reduced wound leakage, & reduced wound healing disturbances

Article Number	Author	Category	Tissue Type Studied	No. Wounds in Study	Favorable to PRP	Outcomes
Additional Studies						
Corroborative Research						
A-1	Maiorana	Soft tissue & bone	Sinus augmentation	10	Yes	Increased bone regeneration and graft stability
A-2	Mendez	Soft tissue & bone	Alveoplasty	14	Yes	Increased alveolar bone regeneration, increased healing, less pain, & less edema
A-3	Pomerantz	Soft tissue & bone	Sinus Surgery	32	Yes	Improved quality of life scores
A-4	Carreon	Soft tissue & bone	Spinal fusion	152	No	Incidence of non-union based on radiographic evidence or surgical exploration was the same in both groups.
A-5	Castro	Soft tissue & bone	Spinal fusion	84	No	The pseudoarthrosis rate of the study group (64%) was not significantly different compared to the control group (45%). Length of hospitalization was equivalent between the study and control group.
A-6	Jenis	Soft tissue & bone	Spinal fusion	37	No	Pain reduction and radiographic changes were the same in both groups
A-7	Franchini	Soft tissue & bone	Fracture bone reconstruction	19	Yes	Increased bone regeneration and osteoinduction
A-8	Gardner	Soft tissue	Total knee arthroplasty	98	Yes	Smaller decrease in post-op hemoglobin, greater range of motion, earlier discharge, less pain medications

Additional Unpublished Chronic Wound Studies

In addition to published studies, Cytomedix also has a significant library of non-published clinical evidence from prospective cohort studies and several case series studies of Cytomedix's PRP gel AutoloGel that are summarized with the accompanying materials for this submission. Wounds (n = 195) studied in these data sets included diabetic foot ulcers, venous ulcers, pressure ulcers, ischemic wounds, surgical dehiscence, collagen vascular disease wounds, insect bites from a brown recluse spider, and trauma wounds. Analyses and results of the clinical data derived from Cytomedix' unpublished studies support the use of PRP gel to treat chronic wounds has a greater rate of wound healing / closure than standard wound therapy and standard wound care. In addition, the healing occurs in a shorter period of time compared with the extended duration of various previous treatments with continued nonhealing. Details about these data sets are in the Evidence Overview; see Appendices D – I.

National Consensus Guidelines for PRP

The professional Guidelines cited in the previous NCD were written prior to the publication of any RCT's related to the use of PRP gel on open cutaneous wounds, including chronic wounds, acute surgical incisions and dehiscence wounds. Clinical trial principal investigators and physician supporters are in discussions with their respective professional societies to educate them about these new data. With this education, PRP gel may be included in future guidelines.

Cytomedix has begun outreach to all the major wound care provider organizations including the American College of Foot and Ankle Surgeons, American Diabetes Association, Wound Healing Society, American Professional Wound Care Society and Wound Ostomy and Continence Nurses Association.

Proposed Coverage Decision

We propose the following language for national coverage of treatment of open cutaneous wounds, including chronic wounds, acute surgical incisions and dehiscence wounds utilizing PRP gel:

> *"CMS was asked to reconsider its national non-coverage determination for Autologous Blood-derived Products when used for the treatment of chronic non-healing wounds. After thorough review, CMS has determined that the results from the use of Platelet Rich Plasma (PRP) gel for the treatment of open cutaneous wounds, including chronic wounds, acute surgical incisions and dehiscence wounds, are sufficient to establish Medicare coverage effective date certain, 2007*
>
> *The wounds eligible for coverage include the following open cutaneous wounds:*
> 1. *Wounds caused by an acute surgical incision or dehiscence.*

2. *Full-thickness chronic wounds (such as, Wagner grade II or higher[1], University of Texas Classification System Grade 2 or higher[2], or National Pressure Ulcer Advisory Panel Stage III and IV[3]) that have failed an adequate course of standard wound therapy.*

Criteria for Coverage

- *PRP gel may be used to treat an open cutaneous wound at the time of an acute surgical incision or dehiscence.*
- *PRP gel may be used to treat a chronic wound which is an open cutaneous wound which has failed to proceed through an orderly and timely series of events to produce a durable structural, functional, and cosmetic closure. Specifically, full thickness chronic open cutaneous wounds are covered under this decision memorandum.*
- *The use of PRP gel will be covered as adjunctive therapy for chronic wounds in addition to standard and wound etiology specific wound care.*
    - *Standard wound care in patients with chronic wounds includes: assessment of a patient's vascular status and correction of any vascular problems in the affected limb if possible, optimization of nutritional status, debridement by any means to remove devitalized tissue, maintenance of a clean, moist bed of granulation tissue with appropriate moist dressings, appropriate off-loading, and necessary treatment to resolve any infection that might be present, such as systemic antibiotics and surgical debridement.*
    - *Specific wound care based on type of wound includes frequent repositioning of a patient with pressure ulcers (usually every 2 hours); off-loading of pressure and good glucose control for diabetic ulcers; establishment of adequate circulation for arterial ulcers; and the use of a compression system for patients with venous ulcers.*
- *Wounds must be evaluated at least every 30 days during administration of PRP gel. Continued treatment with PRP gel is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment. Measurable signs of improved healing include a decrease in wound size either in surface area or volume, decrease in amount of exudates or decrease in amount of necrotic tissue.*
- *PRP gel should be discontinued when the wound demonstrates healing with 100% epithelialization.*
- *PRP gel will only be covered when prescribed by a physician and when applied by the physician or a designated health professional who has been trained in the proper procedure.*

Other

All other uses of PRP gel not otherwise specified for the treatment of open cutaneous wounds, including chronic wounds, acute surgical incisions and

dehiscence wounds, remain at the local Medicare Administrative Contractor discretion.

Benefit Category

Physicians' Services
Incident to a physician's professional service
Outpatient Physical Therapy Services
Outpatient hospital services incident to a physician's service
Acute Care Inpatient Service
Long Term Care Hospital Service
Ambulatory Surgery Center Service
Home Health Services"

Coding

This national coverage determination should result in the issuance of appropriate HCPCS and CPT codes to describe the use of PRP gel in Medicare-covered settings of care. By clarifying coverage nationally CMS will maintain consistent practice across settings of care and Medicare contractors, fiscal intermediaries and Medicare Administrative Contractors.

Conclusion

Based on new clinical evidence that has been published since 2003 documenting the use of PRP gel in the treatment of open cutaneous wounds, including chronic wounds, acute surgical incisions and dehiscence wounds, Cytomedix believes there is a sufficiently strong argument for CMS to reverse its non-coverage decision. The evidence indicates a substantial body of positive outcomes from published scientific studies, including a significant number of randomized controlled trials, showcasing the impact of PRP gel on wound closure and time to wound healing. As a result, we conclude that PRP gel is reasonable and necessary for Medicare recipients for the treatment of open cutaneous wounds, including chronic wounds, acute surgical incisions and dehiscence wounds and meets a significant unmet medical need. The standard of care is changing, and current therapies do not evidence the same wound closure and time to healing properties that PRP gel evidences across chronic wound and surgical settings.

We respectfully request that CMS reconsider its current national non-coverage decision of 2003 and provide Medicare beneficiaries access to this important technology and process. We are available to meet with you and your colleagues to discuss PRP gel and its application across clinical settings in more detail, if this would be helpful.

Sincerely,

Kshitij Mohan Ph.D., Chairman and Chief Executive Officer

Cc: Marcel Salive M.D., Director, Division of Medical and Surgical Services
Lori Paserchia M.D., Medical Officer
Beverly Lofton, Principal Analyst
Marc Samuels, Hillco Partners LLC.