October 4, 2011

Louis B. Jacques, MD
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Mail Stop S3-02-01
7500 Security Boulevard
Baltimore, Maryland 21244-1850

RE: Request for Reconsideration of Medicare
National Coverage Determinations Manual, § 270.3,
Autologous Blood Derived Products for Chronic Non-Healing Wounds

Dear Dr. Jacques:

This is a formal request to reopen and revise Section 270.3 of the Medicare National Coverage Determinations Manual, which addresses Autologous Blood-Derived Products for Chronic Non-Healing Wounds. Autologous Platelet-Rich Plasma (PRP) is the prevalent blood-derived therapeutic product used for treating chronic non-healing wounds. This letter, and the accompanying attachments and published articles, set out the body of clinical evidence to support the conclusion that the use of autologous PRP Gel for chronic, non-healing wounds including pressure ulcers, diabetic foot ulcers, and venous ulcers compared to usual wound care, significantly and reliably improves the rate of complete healing, speed and progress to healing, and quality of life in the Medicare population.

There is ample clinical evidence to support this conclusion. In a recently published systematic review of journal articles published in the past 10 years, many citations were identified and 21 randomized controlled trials and comparative studies were eligible for the systematic review.[1] *See* ***Attachment C***. Seventy five percent (75%) of the eligible articles are new since CMS's last reconsideration in 2008. A significant part of the attached case series observational data comes from a wound care registry of 285 wounds treated with autologous PRP Gel (AutoloGel™, Cytomedix, Inc). Within the registry, 45% of the wounds treated were from Medicare beneficiaries, and, upon comparison, their outcome performance was equivalent to the non-Medicare subset. [2] In addition, a recently published article documenting lack of wound healing

[1] Carter, MJ, Fylling, CP, Parnell, LKS. (2011) Use of Platelet Rich Plasma Gel on Wound Healing: A Systematic Review and Meta-Analysis. *www.eplasty.com*, *Open Access Journal of the Journal of Plastic Surgery.* September 15, 2011.

[2] de Leon J, Driver VR, Fylling CP, Carter MJ, Anderson C, Wilson J, et al. (2011) The clinical relevance of treating chronic wounds with an enhanced near-physiological concentration of platelet rich plasma (PRP) gel. *Advances in Skin and Wound Care, 24(8), 357-368.*

during a run-in period of care demonstrated that the application of autologous PRP Gel (AutoloGel™, Cytomedix, Inc) rapidly converted wounds with a non-healing trajectory to a rapidly healing trajectory.[3] This study provides valuable clinical insight since each patient's wound acted as its own control thus demonstrating the positive impact of PRP Gel to improve healing.
(I'm not sure this remains appropriate.)

Introduction

Autologous blood products, and in particular PRP, have been used widely for the treatment of chronic non-healing wounds. The benefits of autologous blood products have been the subject of research published in peer-reviewed medical journals since 1985.

In this submission, we request that CMS update its current National Coverage Determination to authorize Medicare coverage for the use of autologous PRP Gel to treat pressure ulcers, venous ulcers, and diabetic foot ulcers when conventional treatments have been tried for at least 30 days and failed to reduce the wound size or induce an adequate wound healing trajectory.

The information and data discussed in this request amply demonstrate that PRP Gel offers improved results for individuals with chronic wounds when compared with conventional treatments. The advantages of PRP Gel treatment include improved healing, faster healing time, reduced infection and pain, improved net health outcome, and reduced overall cost. This combination of increased effectiveness and efficiency establishes the need to update the current NCD to allow for the use of PRP Gel in clinically appropriate settings.

This request focuses on the use of PRP Gel for the treatment of chronic, non-healing wounds, describes the progress in this field since 2008, and is a specific request for Medicare coverage. It includes:

- Attachment A: The Science of Platelet Rich Plasma (PRP)
- Attachment B: A Standardized Formulation of PRP-Gel Provides Reproducible Efficacy
- Attachment C: Systematic Review of the Platelet Rich Plasma (PRP) Literature
- Attachment D: AutoloGel Platelet Rich Plasma (PRP) Case Series Observational Studies Outcomes – 2001 – 2011
- Attachment E: Platelet Rich Plasma (PRP) Net Health Benefit
- Attachment F: The AutoloGel™ Body of Evidence

---

[3] Carter, M., Fylling, C., Li, W., De Leon, J., Driver, V., Serena, T., et al. (2011). A statistical analysis of a wound outcomes registry using run-in data: clinical impact of platelet rich plasma gel on healing trajectory. *Int Wound J.* doi: 10.1111/j.1742-481X.2011.00868.x

I. Regulatory Background

1. FDA Clearance

As a preliminary procedural matter, this request to update Section 270.3 to cover Autologous PRP Gel is limited to certain clinical indications that have been reviewed and cleared for use by the Food and Drug Administration. In September 2007, the FDA granted Section 510 (k) clearance for the AutoloGel™ System; in its notice, the FDA approved the following indications for use:

> 510(k) Number: BK060007
> Device Name: Autologel™ System
> Indications For Use:
> The AutoloGel™ System is intended to be used at point-of-care for the safe and rapid preparation of platelet-rich plasma (PRP) gel from a small sample of a patient's own blood. Under the supervision of a healthcare professional, the PRP gel produced by the AutoloGel™ System is suitable for exuding wounds, such as leg ulcers, *pressure ulcers, and diabetic ulcers* and for the management of mechanically or surgically-debrided wounds.
> (emphasis added).

2. Previous CMS Consideration of Autologous Blood Derived Products for Chronic Wounds

CMS's previous consideration of Section 270.3 occurred during 2007 and early 2008 with the final decision memo issued in March 2008. At that time, CMS determined that PRP would remain a non-covered item under Medicare. Its decision was based on the finding that the evidence available at that time was suggestive but not adequate to conclude that autologous PRP is reasonable and necessary for the treatment of chronic non-healing, cutaneous wounds, or for the treatment of acute surgical wounds when the autologous PRP is applied directly to the closed incision, or for dehiscent wounds.[4]

II. Epidemiology of Chronic Wounds

In a review of chronic wounds conducted in 2009, the Agency for Healthcare Research and Quality cited research noting that more than 2.8 million patients in the United States suffer from chronic wounds. The prevalence of chronic ulcers has been estimated to be 120 per 100,000 patients between the ages of 45 and 64 years, which increases to more than 800 per 100,000 patients over age 75.[5] Additional data compiled by the Medicare Evidence Development and

[4] The 2008 DecisionMemo is available at: http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=208&ver=15&NcaName=Autologous+Blood+Derived+Products+for+Chronic+Non-Healing+Wounds&bc=BEAAAAAAIAAA&

[5] Agency for Healthcare Research and Quality, Technology Assessment: Negative Pressure Wound Therapy Devices (2009); available at: http://www.ahrq.gov/clinic/ta/negpresswtd/npwtd02.htm

Coverage Advisory Committee estimated that the cost of treating those wounds is approximately $30 billion per year. Between 15-20% of the Medicare-eligible population suffers from chronic wounds. Within this larger category, approximately 2.5 million patients are treated annually for pressure ulcers, at an annual cost of approximately $12 billion. 10% to 35% of the U.S. population has some type of venous disease, and lower extremity ulcers are reported in 1% to 22% of individuals over age 60.[5] In addition, approximately 15% of all diabetics suffer foot ulcers, which requires the amputation of a foot or limb in about 56,000 cases annually. Among patients over age 65, the majority never ambulate after surgery, and their overall survival rate after five years is less than 30%; for individuals who also have renal failure, that rate drops to less than 14%.[6] This data demonstrates that effective wound therapies are greatly needed.

III. Platelet Rich Plasma (PRP) Gel: A Therapy to Address the Chronic Wound Problem

Platelet rich plasma (PRP) gel is an autologous blood product containing proteins that regulate tissue growth for wound healing. When the PRP is activated, the platelets release cytokines, growth factors, and chemokines to act on the cell receptors to facilitate cellular growth and migration and the fibrinogen in the plasma converts to a fibrin matrix scaffold on which the cells can adhere. This biological system is integral to normal wound healing.

To help understand this complex biological system, ***Attachment A*** provides a detailed description of the scientific mechanism of wound healing and the role of these PRP proteins in facilitating wound healing. ***Attachment B*** describes the importance of specific formulations and standardization of PRP Gel to achieve consistent wound healing outcomes.

IV. Professional Standards for Reviewing Evidence of Chronic Wound Healing

The evaluation of PRP for use in treatment of chronic non-healing wounds must be grounded in accepted professional guidelines. The individual guidelines published by the Wound Healing Society for Pressure, Diabetic, Venous, and Arterial Insufficiency Ulcers, respectively, *each* state that a chronic wound should be converted into an acute wound in order to achieve definitive treatment. Consistent with the clinical overview above, these Guidelines state that: "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 healing wound."[7] Therefore, it is important to understand the role of growth factors and signal

[6] *See* Medicare Evidence Development and Coverage Advisory Committee Meeting Minutes (March 29, 2005; available at: https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?&year=2005&MEDCACId=28&)

[7] JoAnne Whitney, et al., Guidelines for the Treatment of Pressure Ulcers, Wound Repair and Regeneration 14: 663-669, 670 (2006); David L. Steed, et al., Guidelines for the Treatment of Diabetic Ulcers, Wound Repair and Regeneration 14: 680–692, 685 (2006); Martin C. Robson, et al., Guidelines for the Treatment of Venous Ulcers, Wound Repair and Regeneration 14: 649–

molecules in the overall healing process regardless of the underlying wound pathophysiology. Platelets provide the growth factors and signal molecules present in the earliest stages of healing, helping to establish the molecular and cellular environment of an acute healing wound. As a result, bringing platelets to the wound site is essential to healing, and platelet dose and gel formulation are crucial considerations in the healing process.

A standard for evaluation of scientific data in this context has been summarized by the Food and Drug Administration in its guidance document, *Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment.* That guidance instructs 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."*[8]

A recent Agency for Healthcare Research and Quality (AHRQ) assessment of comparative effectiveness methodological research (CER) stated:

> "Data from RCTs [randomized controlled trials] may be insufficient to address a review question about benefit for a number of reasons. RCTs may be inappropriate due to patient values or preferences; the intervention may be hazardous; or randomization may decrease benefit if the intervention effect depends in part on subjects' active participation based on their beliefs and preferences. RCTs may be unnecessary in interventions with obvious benefit, such as the treatment of susceptible organisms with penicillin or where the alternative to treatment of a new and otherwise fatal disease is a high likelihood of death. RCTs may be difficult to implement due to entrenched clinical practice or to active consumer pressure for access to a treatment, problems with recruitment when a drug is already marketed, the need for long-term follow up to detect either benefits or harms, or difficulty randomizing feasible intervention units. In situations where RCT data are impractical, infeasible, or incomplete, observational studies may provide valid and useful data to help address CER questions."[9]

662, 653 (2006); Harriet W. Hopf, et al., Guidelines for the Treatment of Arterial Insufficiency Ulcers, Wound Repair and Regeneration 14: 693–710, 701 (2006)

[8] FDA *Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment* at 2 (2006) (emphasis added). The full document is available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071324.pdf

[9] Norris S, Atkins D, Bruening W, et al. Selecting observational studies for comparing medical interventions. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews [posted June 14, 2010]. Rockville, MD. Available at: http://www.ncbi.nlm.nih.gov/books/NBK47093/

Other reasons why RCTs may be insufficient to answer questions of benefits and harms in wound care relate to exclusion of minorities, vulnerable populations, generalization to "real-world" wound care populations, inappropriate endpoints, and inadequate follow-up time.[10,11,12,13,14,15] In other words, during the last few years, there has been an increasing recognition that an appropriate level of evidence to properly address treatments or interventions would have to include least one well-conducted RCT and one high-level observational study with subjects drawn from representative populations. Such studies typically include cohort, case-control, or comparative designs.

Turning again to AHRQ standards, the sufficient strength of evidence for coverage is described as follows:

> "At least 1 study with greatest design suitability and good execution; or at least 3 studies having moderate or better design suitability, fair or better execution, and consistent results."[16]

Within this definition, the term "greatest" in the context of design suitability means concurrent comparison groups and sufficient measures for other factors affecting outcome; the term "moderate" means non-concurrent comparison or no comparison groups and insufficient measures for other factors affecting outcomes.

When evidence-based medicine (EBM) is used to justify treatments or interventions in medicine, the level of evidence is the foundation for the development of clinical practice guidelines. As a result, there are two key concepts to understand: the *strength of the evidence*, which refers to the

---

[10] Horn SD, Gassaway J. Practice-based evidence study design for comparative effectiveness research. Med Care 2007;45:S50-7.

[11] A EWMA patient outcome group document. Outcomes in controlled and comparative studies on non-healing wounds; recommendations to improve the quality of evidence in wound management. Journal Wound Care 2010;19239-268.

[12] Bagshaw SM, Bellomo R. The need to reform our assessment of evidence from clinical trials: A commentary. Philosophy Ethics Humanities Med 2008;3:23.

[13] Moffatt, CJ, Doherty DC, Smithdale R et al. Clinical Predictors of Leg Ulcer Healing. British J Derm. 2010;162:51-58

[14] Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. New Engl J Med 2000;342:1887-92.

[15] Carter MJ, Fife CE, Walker D, Thomson B. Estimating the applicability of wound care randomized controlled trials to general wound-care populations by estimating the percentage of individuals excluded from a typical wound-care population in such trials. Adv Skin Wound Care. 2009;22:316-24.

[16] Hickam DH, Severance S, Feldstein A, et al. The Effect of Health Care Working Conditions on Patient Safety. Evidence Report/Technology Assessment Number 74. (Prepared by Oregon Health & Science University under Contract No. 290-97-0018.) AHRQ Publication No. 03-E Rockville, MD: Agency for Healthcare Research and Quality. April 2003.

quality, quantity, and consistency of the evidence in any body of studies[17] and *strength of the recommendations*, which describes the importance of a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefit or harm.[18] Study ratings typically follow a I, II, III format in which level I is higher than II; whereas, most recommendation schemes follow an A, B, C evidence-level format in which A is higher than B or where recommendations are provided in terms of strong/weak.[19]

The data presented here follow a systematic review approach, which uses a specific methodological approach to appraise the evidence and represents the highest level of a review of the evidence. In fact, several international organizations consider the systematic review to be class I evidence, including the Oxford Center for Evidence-based Medicine (OCEBM), SIGN, the National Health and Medical Research Council (Australia) when the review only includes RCTs, and NICE, when the systematic review includes meta-analysis. [17, 20]

---

[17] West S, King V, Carey TS, et al. Systems to rate the strength of scientific evidence. Evidence Report/Technology Assessment No. 47 (Prepared by the Research Triangle Institute–University of North Carolina Evidence-based Practice Center under Contract No. 290-97-0011). AHRQ Publication No. 02-E016. Rockville, MD: Agency for Healthcare Research and Quality. April 2002.

[18] Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. *Ann Intern Med*. 2003;139:493-8

[19] Carter MJ. Evidence-based medicine: an overview of key concepts. Ostomy Wound Manage 2010;56:68-85.

[20] Cytomedix respectfully submits that a systematic review differs from the methodology used in the 2008 reconsideration of Section 270.3 of the Medicare National Coverage Determinations Manual. At that time, CMS repeatedly used the phrase "insufficient evidence." Although describing general methodological review principles in its review and subsequent decision not to cover autologous platelet-rich plasma products (PRP) (*see* ***Appendix A***), CMS did not use a systematic review approach, and the Decision Memorandum did not describe the level of evidence specifically required for coverage, stating that "each coverage determination has its own unique methodological aspects." This is a critical omission. The review conducted by CMS in regard to PRP coverage cannot be regarded as a systematic review because it described no specific systematic review methodology, including bias and quality assessment. Rather, it should be considered to be a critical review, because it critically analyzed studies without rating the studies and assessing them a level of evidence. Critical reviews contain more bias than systematic reviews, in part because studies are not rated overall in a systematic fashion; instead, studies are critiqued according to investigators' opinions or beliefs, in part because of publication bias, (Yoshii , 2009) and lack of assessment of this important parameter. Furthermore, although CMS agreed to assess all studies submitted by Cytomedix as part of its assessment of PRP coverage, it did not do so, thus amplifying the publication bias issue. Several organizations have also provided definitions of evidence levels for supporting a treatment or intervention, based upon an evaluation of the benefits and harms, the most commonly used of which are GRADE, SIGN, and the OCEBM. Again, CMS used no systematic process for arriving at the conclusion that there was a "lack of evidence."

As a result, Cytomedix proposes that an adequate level of evidence according to the AHRQ definitions can be met with the current literature to support coverage of standardized autologous platelet-rich plasma gel for use in treating diabetic foot ulcers and pressure ulcers.

V. Clinical Evidence That Demonstrates the Effectiveness of PRP

As noted in the introduction, the body of clinical evidence since the time of the FDA's clearance of the AutoloGel™ System and CMS's 2008 reconsideration has grown substantially. This additional evidence is not simply additive to the evidence previously reviewed; it targets specific queries set out by CMS in its manuals and in other published guidance documents. That evidence, which is presented in detail, is summarized below.

Attachment C: Systematic Review of the Platelet Rich Plasma (PRP) Literature

An exhaustive review was conducted on the PRP literature published in the last 10 years. Only RCTs and comparative effectiveness studies were included in the review. Twenty one studies met the inclusion criteria. The wounds included in the systematic review include:

a) Chronic wounds
b) Acute wounds with PRP added to a surgical site prior to primary closure
c) Acute wounds with PRP added to a surgical site followed by secondary closure

The review includes:

a) Descriptions of the studies, types of wounds, and interventions used.
b) Detailed outcomes in each study.
c) Quality review of the studies: The score sheet documenting the SIGN grade based on the total score of external validity and internal validity (bias and confounding)
d) Quality assessment and summary of findings for studies comparing use of platelet-rich plasma treatments against standard care for chronic wounds (GRADE).
e) Quality assessment and summary of findings for studies comparing use of platelet-rich plasma treatments against standard care for acute wounds (GRADE).
f) Meta-analysis of PRP's impact on complete healing, reduction of infection, and reduction of pain.

This systematic review establishes that that PRP Gel results in improved wound healing, faster wound healing, reduced infection, and reduced pain.

Attachment D: AutoloGel Platelet Rich Plasma (PRP) Case Series Observational Studies Outcomes – 2001 – 2011

Because the AHRQ recommendations described above state that large observational studies are beneficial for comparative effectiveness research, the outcomes in 9 case series (observational studies) are documented. Data from 323 wounds are included in the analyses. In particular, the

largest wound registry (n = 285 wounds) documented the use of autologous PRP-Gel (AutoloGel™) and demonstrated that wounds in Medicare beneficiaries had the same healing progress as those wounds in non-Medicare beneficiaries, as shown in the following table.

	N	% wounds with volume reduction	Mean volume reduction % (cm^2)	Number of weeks to outcome	Number of treatments to outcome
Medicare	111[21]	89.9%	64.6%	2.2	2.8
Non-Medicare	135	91%	62.9%	2.3	2.8
		p = 0.75			

Similar results were identified in the Frykberg 65-wound registry.[22]

These observational studies document that PRP results in wound healing, faster wound healing progress compared to previous wound duration without healing, re-animation of stalled wounds into a positive wound-healing trajectory, reduction and closure of undermining and sinus tracts/tunneling in wounds, and growth of granulation tissue to prepare a wound for grafting. These types of outcomes were seen in Medicare patients, wounds of multiple etiologies, and wounds in patients with complex co-morbidities.

Attachment E: Platelet Rich Plasma (PRP) Net Health Benefit

Among CMS' concerns was whether or not a therapy contributes to the patient's quality of life or their net health benefit. The importance of a healed wound or progress toward healing is documented from the literature. The multiple net health benefit features described in the systematic review and observational studies are tabulated. In addition, a qualitative research survey was conducted with health professionals that had used autologous PRP-Gel (AutoloGel™) to treat patients' chronic wounds. Using AutoloGel™ to treat chronic wounds improved the net health outcome of the patients that were treated. The patients self-described their distinct positive changes in multiple areas of their lives due to the wound healing progress with AutoloGel™.

Cost effectiveness and improvement in a patient's quality of life are important net health benefits. AutoloGel™ was documented as being the most cost effective therapy for wound care over a 5 year period compared to standard of care and other advanced wound therapies as well as providing the best quality of life.[23] PRP Gel studies have also documented minimal adverse events from the use of PRP Gel. A recent safety study of 110 patients treated with multiple applications of AutoloGel™ has demonstrated no adverse events during the entire treatment

[21] 24% were under age 65, but eligible due to disability.

[22] Frykberg, R. G., Driver, V. R., Carman, D., Lucero, B., Borris-Hale, C., Fylling, C. P., et al. (2010). Chronic wounds treated with a physiologically relevant concentration of platelet-rich plasma gel: a prospective case series. *Ostomy Wound Manage, 56*(6), 36-44.

[23] Dougherty, E. J. (2008). An evidence-based model comparing the cost-effectiveness of platelet-rich plasma gel to alternative therapies for patients with nonhealing diabetic foot ulcers. *Adv Skin Wound Care, 21*(12), 568-575.

time.[24] As a result, there is strong evidence that autologous PRP Gel does improve the net health benefit of the patient.

V. The Body of Evidence Supports Coverage for Platelet Rich Plasma

The large body of published literature on the use of PRP for the treatment of wounds meets the FDA Guidance document recommendation, the Wound Healing Society Guidelines, and the AHRQ standard of evidence.

In addition, the evidence meets the rigorous standard developed by the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC). At its meeting on March 29, 2005, which focused on the usual care of chronic wounds, they described areas that a therapy should meet to be considered for coverage. The following table summarizes how PRP Gel meets these criteria, which are explained in more detail in ***Attachments C, D, E, and F***:

MEDCAC Area	**PRP Gel Impact**
Complete healing	Several studies documented statistically significant healing versus control
Time to healing	Faster rate
Partial healing rate	Faster healing trajectory. Re-animating or "kick-starting" a wound after it has stalled
Recurrence	Less recurrence
Elimination of infection	Infection reduction or elimination
Amputation	Amputations reduced
Reduction of pain	Pain reduced
Resumption of normal activity	Return to life, school, activities of daily living, rehabilitation, family life

Other areas that MEDCAC did not address:

Salvage of exposed tendons	Granulation tissue covered the tendons so they were spared
Reduction of major surgeries	Wound healed or progressed so major surgeries were averted
Preparation for skin grafts	Granulation tissue grew quickly so skin grafts could be performed to definitively close the wound on a timely basis
Reduced need for NPWT	Professionals used PRP Gel instead of NPWT due to more tissue growth in a shorter period of time for less cost
Cost effectiveness	Reduced cost compared to existing wound therapies or standard of care due to healing efficacy

[24] AutoloGel™ Post Marketing Surveillance Study, *Data on file at the Company*

Adverse events	Minimal to none

In addition, the evidence in this request supports the use of PRP in the following targeted populations:

Medicare beneficiaries	While most of the studies included patients that were Medicare beneficiaries, specifically, the de Leon and Frykberg studies documented that Medicare beneficiaries had the same healing progress as non-Medicare beneficiaries.
Providers (facilities/physicians) in community practice rather than tertiary care specialty centers (universities, etc)	The data in the studies were predominantly from community settings: hospitals, outpatient clinics, long-term care, home care, physician's offices.

VI. Summary

Since the 2008 CMS non-coverage decision for blood products for the treatment of chronic wounds, extensive new literature has been published documenting the efficacy of autologous PRP Gel for the treatment of wounds. In addition, AHRQ broadened its evidence criteria to include large observational studies in addition to RCTs and comparative analysis studies. The published PRP literature includes all of the above.

The use of PRP Gel for the treatment of wounds can facilitate healing, improve healing rates, reverse a non-healing trajectory to a healing trajectory, shorten the time to healing, reduce length of stay, reduce excess use of expensive treatment modalities, has minimal to no adverse events, improves the net health benefit to the patient and their family, and is cost effective.

Based on meeting these evidence criteria and having the documented outcomes described, we respectfully request that CMS reverse its non-coverage decision and provide coverage for the use of PRP Gel, especially for the treatment of diabetic, venous, and pressure ulcers. We have attached a proposed revision to Section 270.3 that reflects the research and data presented in this submission. Alternatively, we believe that CMS can cover PRP gel through a National Coverage Determination with data collection as a condition of coverage; this would provide a practical means by which CMS can obtain the necessary data to evaluate the performance of PRP gel and to confirm the outcomes presented in this request.

We welcome the opportunity to meet with you to discuss any of the evidence supporting Medicare coverage for autologous PRP Gel or to answer any questions. For convenience, please contact Cytomedix' counsel, Robert Wanerman, at (202) 861-1885, or rwanerman@ebglaw.com.

Sincerely,

Jean M. de Leon, M.D.
Diplomat of the American Board of PM&R
Medical Director of Wound Care
Baylor Specialty Hospital
Dallas, TX

Vickie R Driver MS DPM FACFAS
Associate Professor of Surgery
Director, Clinical Research Limb Preservation and Wound Healing Director, Research Fellowship and International Scholars Program Boston University Medical Campus and Boston University School of Medicine
Boston, MA

Caroline E. Fife, MD
Medical Director, University of Texas Health Science Center
Memorial Herman Center for Wound Care and Lymphedema Management
Chief Medical Officer, Intellicure, Inc
Houston, TX

Robert G. Frykberg, DPM, MPH
Chief, Podiatry and Residency Director
Phoenix VA Healthcare System
Phoenix, AZ

William W. Li, MD
President, Medical Director, and Co-Founder
The Angiogenesis Foundation
Boston, MA

Martin P. Rosendale
President and Chief Executive Officer
Cytomedix, Inc
Gaithersburg, MD

Thomas E. Serena, MD, FACS, FAPWCA
Founder and Medical Director
Penn North Centers for Advanced Wound Care
Professor, Gannon University
Warren, PA

Request for Reconsideration of Medicare
National Coverage Determinations Manual, § 270.3,
Autologous Blood Derived Products for Chronic Non-Healing Wounds

Signature Page

Jean M. de Leon, M.D.
Diplomat of the American Board of PM&R
Medical Director of Wound Care
Baylor Specialty Hospital
Dallas, TX

Request for Reconsideration of Medicare
National Coverage Determinations Manual, § 270.3,
Autologous Blood Derived Products for Chronic Non-Healing Wounds

Signature Page

Vickie R Driver MS DPM FACFAS
Associate Professor of Surgery
Director, Clinical Research Limb Preservation and Wound Healing Director, Research Fellowship and International Scholars Program Boston University Medical Campus and Boston University School of Medicine
Boston, MA

Request for Reconsideration of Medicare
National Coverage Determinations Manual, § 270.3,
Autologous Blood Derived Products for Chronic Non-Healing Wounds

Signature Page

Caroline E. Fife, MD
Medical Director, University of Texas Health Science Center
Memorial Herman Center for Wound Care and Lymphedema Management
Houston, TX

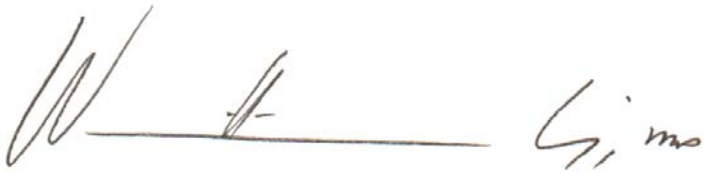
Request for Reconsideration of Medicare
National Coverage Determinations Manual, § 270.3,
Autologous Blood Derived Products for Chronic Non-Healing Wounds

Signature Page

Robert G. Frykberg, DPM, MPH
Chief, Podiatry and Residency Director
Phoenix VA Healthcare System
Phoenix, AZ

Request for Reconsideration of Medicare
National Coverage Determinations Manual, § 270.3,
Autologous Blood Derived Products for Chronic Non-Healing Wounds

Signature Page



William W. Li, MD
President, Medical Director, and Co-Founder
The Angiogenesis Foundation
Cambridge, MA

Request for Reconsideration of Medicare
National Coverage Determinations Manual, § 270.3,
Autologous Blood Derived Products for Chronic Non-Healing Wounds

Signature Page

Martin P. Rosendale
President and Chief Executive Officer
Cytomedix, Inc
Gaithersburg, MD

Request for Reconsideration of Medicare
National Coverage Determinations Manual, § 270.3,
Autologous Blood Derived Products for Chronic Non-Healing Wounds

Signature Page

Thomas E. Serena, MD, FACS, FAPWCA
Founder and Medical Director
Penn North Centers for Advance Wound Care
Professor, Gannon Unversity
Warren, PA

APPENDIX

Proposed Amendment to Section 270.3

270.3 - Blood-Derived Products for Chronic Non-Healing Wounds - (Various Effective Dates Below)
(Rev. 83, Issued: 05-02-08, Effective: 03-19-08, Implementation: 06-02-08)

A. General

Wound healing is a dynamic, interactive process that involves multiple cells and proteins. There are three progressive stages of normal wound healing, and the typical wound healing duration is about 4 weeks. While cutaneous wounds are a disruption of the normal, anatomic structure and function of the skin, subcutaneous wounds involve tissue below the skin's surface. Wounds are categorized as either acute, in where the normal wound healing stages are not yet completed but it is presumed they will be, resulting in orderly and timely wound repair, or chronic, in where a wound has failed to progress through the normal wound healing stages and repair itself within a sufficient time period.

Platelet-rich plasma (PRP) is produced in an autologous or homologous manner. Autologous PRP is comprised of blood from the patient who will ultimately receive the PRP. Alternatively, homologous PRP is derived from blood from multiple donors.

Blood is donated by the patient and centrifuged to produce an autologous gel for treatment of chronic, non-healing cutaneous wounds that persists for 30 days or longer and fail to properly complete the healing process. Autologous blood derived products for chronic, non-healing wounds includes both: (1) platelet derived growth factor (PDGF) products, and (2) PRP.

The PRP is different from previous products in that it contains whole cells including white cells, red cells, plasma, platelets, fibrinogen, stem cells, macrophages, and fibroblasts.

The PRP is used by physicians in clinical settings in treating chronic, non-healing wounds, open, cutaneous wounds, soft tissue, and bone. Alternatively, PDGF does not contain cells and was previously marketed as a product to be used by patients at home.

B. Nationally Covered Indications

Effective [ ], PRP Gel produced by systems that have received clearance or approval by the Food and Drug Administration for the treatment of pressure ulcers, venous ulcers, or diabetic foot ulcers may be covered for those indications following a period of at least 30 days during which alternative covered treatments have been unsuccessful in reducing wound area or depth.

C. Nationally Non-Covered Indications

1. Effective December 28, 1992, the Centers for Medicare & Medicaid Services (CMS) issued a national non-coverage determination for platelet-derived wound-healing formulas intended to treat patients with chronic, non-healing wounds. This decision was based on a lack of sufficient published data to determine safety and efficacy, and a public health service technology assessment.

2. Effective July 23, 2004, upon reconsideration, the clinical effectiveness of autologous PDGF products continues to not be adequately proven in scientific literature. As the evidence is insufficient to conclude that autologous PDGF in a platelet-poor plasma is reasonable and necessary, it remains non-covered for treatment of chronic, non-healing cutaneous wounds. Also, the clinical evidence does not support a benefit in the application of autologous PRP for the treatment of chronic, non-healing, cutaneous wounds. Therefore, CMS determines it is not reasonable and necessary and is nationally non-covered.

3. Effective April 27, 2006, coverage for treatments utilizing becaplermin, a non-autologous growth factor for chronic, non-healing subcutaneous wounds, remains nationally non-covered under Part B based on section 1861(s)(2)(A) and (B) of the Social Security Act because this product is usually administered by the patient.
4. Effective March 19, 2008, upon reconsideration, the evidence is not adequate to conclude that autologous PRP is reasonable and necessary and remains non-covered for the treatment of chronic non-healing, cutaneous wounds. Additionally, upon reconsideration, the evidence is not adequate to conclude that autologous PRP is reasonable and necessary for the treatment of acute surgical wounds when the autologous PRP is applied directly to the closed incision, or for dehiscent wounds.
5. Effective [ ], upon reconsideration, the evidence is not adequate to conclude that autologous PRP is reasonable and necessary for the treatment of chronic non-healing wounds except as indicated in Subsection (B), above.

D. Other

In accordance with section 310.1 of the National Coverage Determinations Manual, the routine costs in Federally sponsored or approved clinical trials assessing the efficacy of autologous PRP in treating chronic, non-healing cutaneous wounds are covered by Medicare.