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January 18, 2008

Steve Phurrough, MD, MPA
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Mail Stop C1-09-06
7500 Security Blvd.
Baltimore, MD 21244-1850

Re: Proposed Decision Memorandum for Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190R2)

Dear Dr. Phurrough:

Cytomedix, Inc. appreciates this opportunity to submit comments on the Proposed Decision Memorandum for Autologous Blood-Derived Products (ABDPs) for Chronic Non-Healing Wounds (CAG-00190R2) of December 20, 2007(the "PDM"). Cytomedix manufactures the AutoloGel™ System, which produces autologous platelet-rich plasma (PRP) gel, a type of ABDP, that contains multiple growth factors from the platelets and a fibrin matrix scaffold from the plasma. The Food and Drug Administration (FDA) cleared the AutoloGel™ System under Section 510(k) and determined that when used under the supervision of a healthcare professional, the PRP gel produced by the 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."[1] Citing insufficient evidence, the Centers for Medicare & Medicaid Services (CMS) in the PDM proposes no changes to the current national coverage determination (NCD) for Blood-Derived Products for Chronic Non-Healing Wounds,[2] which denies coverage for any ABDP. Cytomedix respectfully disagrees with CMS's proposed decision to retain the status quo.

As we explained in our request for reconsideration, the body of evidence demonstrating the benefit of the application of autologous PRP has grown significantly in recent years, and now provides sufficient evidence to support coverage of this therapy. In addition, since CMS released the PDM, we have learned of an additional prospective, randomized, controlled, and blinded clinical trial that was presented at the International Symposium on the Diabetic Foot[3] and will be

[1] AutoloGel™ System, 510(k) No. BK060007. Please note that the summary of the FDA clearance in the proposed decision memorandum omits "diabetic ulcers" from the list of wounds for which the PRP gel produced by the system is suitable.

[2] National Coverage Determination Manual, Pub. 100-3, § 270.3.

[3] Friese G. et al., The Use of Autologous Platelet Concentrate Activated by Autologous Thrombin (APC+) is Effective and Safe in the Treatment of Chronic Diabetic Foot Ulcers – A Randomized Clinical Trial, presented at Fifth International Symposium on the Diabetic Foot, May 9-12, 2007. The poster for this study presented at the

submitted for publication that provides additional support for coverage of this therapy. In light of this new evidence and based on a complete review of all of the available data (including some information not discussed in the PDM), we ask that, when finalizing the decision, CMS revise the current NCD applicable to ABDPs as follows:

1. CMS should affirmatively cover the treatment of chronic diabetic foot ulcers using autologous PRP produced by an FDA-cleared device for the production of PRP.[4]
2. CMS should revise the NCD to leave Medicare contractors with the discretion to cover the treatment of other chronic, non-healing wounds using autologous PRP produced by an FDA-cleared device for the production of PRP; or, in the alternative, authorize coverage for these uses when part of a registry under the agency's coverage with evidence development policy.

The bases for our request are discussed in detail below.

I. CMS Should Cover Autologous PRP for Chronic Diabetic Foot Ulcers

While Cytomedix submitted an NCD reconsideration request that discussed a number of different uses of autologous PRP, we now ask CMS to focus solely on uses of autologous PRP for chronic, non-healing wounds. Further, we recommend that CMS divide its analysis of the data for chronic, non-healing wounds into two groups: chronic diabetic foot ulcers and other chronic, non-healing wounds. While a significant body of evidence is now available on the benefits of treatment with autologous PRP in chronic wounds, the evidence on chronic diabetic foot ulcers is particularly strong and should be considered separately from the data for all other chronic, non-healing wounds. We believe that, when viewed in light of the unique methodological aspects discussed below, the additional sources of data we discuss below combined with the studies cited in the PDM provide sufficient evidence to support a positive national coverage decision for chronic diabetic foot ulcers and to allow coverage of other chronic, non-healing wounds at contractor discretion.

A. CMS's Evaluation of the Clinical Literature Must Recognize the "Unique Methodological Aspects" of this Coverage Determination

In the PDM, CMS summarizes seven studies it found through a PubMed search of the literature on the use of PRP in chronic non-healing wounds, including diabetic foot ulcers. CMS concludes that this evidence is "suggestive," but "significantly limited in quality and therefore inadequate"[5] to conclude that "the use of autologous PRP for chronic, non-healing wounds,

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referenced symposium is attached and we understand that CMS may have received additional information from the study.

[4] As discussed in Section I(A) below, there are at least three companies, including Cytomedix, that have FDA clearance for their PRP systems. However, it is only the AutoloGel™ system whose FDA clearance includes a specific statement (suitable for certain wounds, such as diabetic ulcers) that applies to the gel that is produced by the system. Our coverage requests focus on FDA-cleared systems for the production of PRP, not just those that apply to the gel.

[5] Proposed Decision Memorandum (PDM), at 12.

compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population."[6] Throughout its review of the evidence, CMS notes its concerns about the relatively small sample sizes, lack of randomization, and lack of blinding in several of the studies under consideration. These concerns are consistent with CMS's "General Methodological Principles of Study Design," including the hierarchy of study designs the agency uses to assess individual studies.[7] As CMS notes, however, "each coverage determination has unique methodological aspects."[8] We believe that this statement is particularly noteworthy for the purposes of this coverage determination. In this case, there are "unique methodological aspects" due to complexities of chronic wound care and research regarding treatments including autologous PRP. These must be considered in evaluating the evidence.

While we understand CMS's preference for large, prospective, double-blind, randomized clinical trials, these trials are extremely difficult to conduct for autologous PRP. First, it is difficult to conduct large scale wound healing studies because patients often have multiple comorbidities and therefore do not meet the inclusion criteria. In the Driver study, 650 patients were prescreened, yielding 129 patients to enter the active screening, after which 72 (11%) met the criteria.[9] Another example is a venous ulcer study using autologous PRP that was withdrawn due to difficulty enrolling patients.[10] In light of the difficulty of enrolling large numbers of patients in point-of-care wound treatment trials, CMS should recognize that smaller cohorts (particularly those that yield statistically significant results) are valuable and are needed to ensure that the patients in the trial have similar conditions. Second, unlike therapies that are manufactured by a company and can be packaged with blinded labels, PRP gel is processed at the point of care and therefore is difficult to blind. Additionally, physicians have indicated an unwillingness to participate in prospectively randomized controlled trials for various reasons, including the difficulty in obtaining patients and their view that patients should receive autologous PRP and not just standard of care treatment, as would be true in the control arm of a study.

Citing the Marx article, CMS also expresses concern that the ability of the available evidence to demonstrate a positive health outcome may be limited by variations in the quality of PRP used in the studies. In fact, however, the Marx article is supportive of our position because we are requesting that coverage extend only to devices cleared by the FDA for production of PRP. The Marx article makes clear that concerns about the quality of PRP are driven by studies in which the PRP was not produced by an FDA-cleared system, which would not fall within the coverage we seek. Specifically, Marx notes that only 2 of the 7 centrifuges studied were FDA-cleared for this purpose and "of all of the devices tested, these 2 FDA-cleared PRP devices produced the greatest platelet concentrations and, most important, release of a therapeutic level

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[6] Id. at 13.
[7] Id. at 13-14.
[8] Id. at 13.
[9] Driver VR et al., A Prospective, Randomized, Controlled Trial of Autologous Platelet-Rich Plasma Gel for the Treatment of Diabetic Foot Ulcers, Ostomy/Wound Management 2006;52(6):68-87.
[10] Clinical Effectiveness of Topical Autologous Platelet Gel for the Treatment of Venous Ulcers, ClinicalTrials.gov identifier NCT00273234.

of bioactive growth factors."[11] The remaining five centrifuges, not the FDA-cleared devices, were the ones found to have inadequate quality. As such, if CMS adopts the proposed coverage request, it need not fear that inadequate devices or poor quality PRP will be covered, since the Marx study cited by CMS found that FDA-cleared devices consistently produce quality autologous PRP.

CMS also identifies "process factors," such as the type of centrifuge used, centrifugation time and RPMs, and method of growth factor release, as potential causes of variations in the quality of PRP.[12] It is true that different processes may be used to process the blood into PRP gel, but these differences do not equate to variations in quality. As noted earlier, a host of companies market different centrifuges and wound care kits that are cleared by the FDA for production of PRP, but the end-product is the same no matter which of these systems is used: autologous multiple growth factors within a fibrin matrix scaffold. Therefore, if CMS is going to establish a coverage decision that applies to all autologous PRP produced using FDA-cleared devices, it is appropriate for CMS to consider evidence generated using all such products.

These are the unique methodological aspects of the research relevant to this NCD, and CMS should consider them as it evaluates the available evidence for autologous PRP. Thus, in this regard, we respectfully urge CMS to be cognizant of these unique aspects and consider consistency across numerous smaller studies, as exists here and is further discussed below. While we recognize that CMS affords greater weight to data from prospective, randomized, controlled, blinded trials, CMS also should afford due weight to data from other studies, and not simply discount them entirely. Finally, CMS should consider data from studies using any FDA-cleared system for producing autologous PRP in making its final decision.

B. The Evidence Supports Coverage of Autologous PRP for Chronic Diabetic Foot Ulcers

We have identified three prospective, randomized, controlled trials, including one new study and one that was not discussed in the PDM, that demonstrate the efficacy of autologous PRP for healing chronic diabetic foot ulcers. These studies and the evidence from Cytomedix's prospective cohort registry of Indian Health Service (IHS) patients provide sufficient evidence to support a conclusion that the use of autologous PRP for chronic diabetic foot ulcers, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population.

First, the study by Driver et al., discussed in the PDM, includes CMS's desired criteria for clinical research. This multi-center, prospective, randomized, controlled, and blinded study used the most rigorous protocol possible. It examined the primary outcome of interest to CMS: incidence of complete wound healing.[13] While we acknowledge that the study population was reduced from 72 patients to 40 patients as a result of protocol violations, we note that the

[11] Marx RE, Platelet-Rich Plasma: Evidence to Support Its Use, J. Oral Maxillofac. Surg. 2004;62:489-496.
[12] PDM, at 12.
[13] Id. at 4.

exclusion of patients from the final analysis was based on strictly objective criteria and that the per protocol population included patients age 65 or greater. The analysis of the per protocol population found an improvement in complete wound closure within 12 weeks in patients treated with autologous PRP (13/19 patients, or 68.4%) compared to the control group, which received saline gel (9/21, or 42.9%) ($p = 0.125$).[14] At a minimum, this strongly suggests an improved outcome in a prospective, randomized, controlled, and blinded study.

CMS states in the PDM, "a statistically significant result was not found until the authors narrowed down the evidence database and performed a previously unplanned statistical analysis."[15] This is not true; the analysis was planned. As documented in a letter from FDA,[16] stratification of wound size was to be analyzed in the evaluation of the study, and this stratified analysis found that 88% of the wounds were <7 cm^2, the most common wound size. When the data from this group of wounds were analyzed, the difference between the treatment arm and the control arm was even more pronounced. Thirteen of 16 patients who received autologous PRP (81.3%) achieved complete healing in 12 weeks, compared to 8 of 19 patients in the control group (42.1%) ($p=0.036$).[17] These statistically significant results, for a cohort that Cytomedix had planned to analyze from the early stages of the study, demonstrate the ability of autologous PRP, produced by an FDA-cleared device for the production of PRP, to improve the rate of complete wound healing in patients with chronic diabetic foot ulcers.

CMS found that the results of the Driver study can "serve to generate hypotheses for future randomized, controlled trials, but not to conclusively demonstrate the ability of autologous PRP to improve the rate of wound closure in patients with chronic, non-healing wounds."[18] We believe that this study provides greater evidence than this quote suggests, particularly given the agency's statements about the quality of evidence it seeks. CMS is seeking "evidence of sufficient quality" which is most likely found in studies that include the following characteristics: "the selection of a clinically relevant cohort, the consistent use of a single good reference standard, the blinding of readers of the index test, and reference test results."[19] The Driver study meets all these criteria: a clinically relevant cohort of the most common sized diabetic foot ulcers; a blinded study; complete healing as the reference test; and statistically significant healing in the reference test result. The Driver study is a valid, prospective, randomized, controlled, blinded trial that demonstrates the effectiveness of autologous PRP because it achieved a statistically significant improvement in complete wound healing among this clinically relevant cohort. Its use of a redefined patient population in the subset efficacy

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[14] Driver VR et al., A Prospective, Randomized, Controlled Trial of Autologous Platelet-Rich Plasma Gel for the Treatment of Diabetic Foot Ulcers, Ostomy/Wound Management 2006;52(6):68-87.

[15] PDM, at 11.

[16] Letter from B. Golding, Director, Division of Hematology, Office of Blood Research and Review, Center for Biologics Evaluation and Research, FDA to J. Hunter, November 19, 2004, at 2 ("FDA notes that you propose to change the index foot ulcer size from at least 1.0 cm^2 to no more than 20 cm^2 to at least 0.5 cm^2 to no more than 20 cm^2. *This change is acceptable since you plan to stratify your healing results based on wound size.*") (emphasis added). This letter is available upon request.

[17] Id.

[18] PDM, at 11-12.

[19] PDM, at 3.

analysis is based on objective criteria and does not detract from the validity of the study. As such, the statistically significant results of a clinically relevant cohort should be given substantial weight in CMS's analysis, and not be viewed as only a starting point for future studies.

Second, data from a new prospective, randomized, controlled, and blinded trial help to confirm the conclusions reached by the Driver study. A study by Friese et al. compared rates of complete wound healing over a 12-week period in 41 patients with chronic diabetic foot ulcers of size >7 cm^2.[20] The study population included patients age 65 or greater. Twenty patients received autologous PRP and conventional care, and 21 patients received only conventional care. Significantly more patients achieved complete healing (11/20 patients, or 55%) in the test group than in the control group (5/21 patients, or 24%) ($p<0.05$). These data strongly indicate that treatment with autologous PRP can improve the rate of complete healing of chronic diabetic foot ulcers, even in patients with large wounds. While this study has not been published, our understanding is that it will be submitted for publication. The results of the Friese study on wounds greater than 7 cm^2, together with the results of the Driver study on wounds less than 7 cm^2, demonstrate the ability of autologous PRP produced by an FDA-cleared device for the production of PRP to improve the rate of complete wound healing in patients with chronic diabetic foot ulcers, regardless of their size.

Third, published data from another prospective, randomized, controlled, and blinded trial were included in our request letter, but were not discussed in the PDM. The study by Saldalamacchia et al. compared treatment of chronic diabetic foot ulcers with autologous PRP plus standard care to standard care alone over a five week period.[21] In the autologous PRP group, 71% (5/7) of patients achieved complete healing or wound area reduction of 50% or more in five weeks. In the control group, 29% of patients (2/7) in the control group achieved complete healing or wound area reduction of 50% or more in the same time period. The average rate of reduction of wound area was significantly larger in patients who received autologous PRP (71.9% reduction in five weeks) than in the control group (9.2% reduction) ($p=0.039$). Additionally, all of the patients in the autologous PRP group improved, but only one of the patients in the control group improved, while one worsened and the wound area of the others remained unchanged. The authors concluded, "our results from a controlled study, although obtained in a small group of patients, strongly support safety and effectiveness of platelet gel in addition to standard care as a means for accelerating the healing process in diabetic foot ulcerations."[22] Although this study used a different endpoint than the Driver or Friese studies, the results are relevant because they indicate that patients treated with autologous PRP produced by an FDA-cleared device had significantly faster rates of healing than patients who received conventional care.

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[20] Friese G. et al., (poster attached).

[21] Saldalamacchia G et al., A Controlled Study of the Use of Autologous Platelet Gel for the Treatment of Diabetic Foot Ulcers, Nutr. Metab. Cardiovasc. Dis. 2004;14:395-396.

[22] Id. at 396.

Finally, further evidence supporting the use of autologous PRP in the treatment of diabetic foot ulcers can be seen from data from the prospective cohort registry Cytomedix implemented in conjunction with the Oklahoma City Indian Health Services (IHS). This registry collected data prospectively on 35 patients with a total of 46 chronic wounds who were seen for management of various types of wounds, including diabetic foot ulcers, venous ulcers, pressure ulcers, and collagen vascular disease wounds, at five IHS sites between August 1, 2004 and July 31, 2005. All of the patients received AutoloGel™. Eight of the nine (89%) chronic diabetic foot ulcers that were treated during this period completely healed in an average of 11.3 weeks.[23] The number of weeks to healing ranged from 1 to 13,[24] therefore most wounds that healed did so in approximately the 12 week time period examined in Driver and Friese. This rate of healing is similar to the results of the majority wound size group in the Driver study, although the registry patients' wounds ranged in size up to 52 cm.[25] Based on the registry data for patients with diabetic foot ulcers and other chronic wounds, IHS concluded that "the use of the AutoloGel™ System in a comprehensive wound care program is essential for providing improved clinical outcomes and cost effectiveness for the IHS System."[26] We believe that CMS should reach the same conclusion as the IHS and issue a national coverage decision to allow Medicare beneficiaries to receive autologous PRP for chronic diabetic foot ulcers.

The data from these three prospective, randomized, controlled clinical trials and the IHS prospective cohort registry clearly support a conclusion that the use of autologous PRP, produced by devices cleared by the FDA for this purpose, for chronic diabetic foot ulcers significantly and reliably improves the rate of complete healing in the Medicare population. Based on these data, some of which were not available to CMS when the PDM was issued, we ask CMS to issue a positive coverage determination for use of autologous PRP, produced by an FDA-cleared device for the production of PRP, for chronic diabetic foot ulcers.

II. CMS Should Not Deny Coverage of Autologous PRP for Other Chronic, Non-Healing Wounds

A. CMS Should Reverse the Current Non-Coverage Decision for the Use of Autologous PRP for Other Chronic, Non-Healing Wounds and Allow Coverage at Contractor Discretion

At the time it issued the current NCD, CMS found "no evidence that focused on the use of platelet rich plasma in chronic, cutaneous non-healing wounds."[27] For this reconsideration, CMS identified seven studies on the use of autologous PRP in these wounds, including the Driver study regarding the treatment of chronic diabetic foot ulcers discussed above. These

[23] Letter from K. Mohan to S. Phurrough, Formal Coverage Reconsideration Request for CAG-00190N, June 20, 2007, Appendix D.
[24] Data on file, Cytomedix.
[25] Id.
[26] Letter from G.J. Holder, Director, CHS, Office of the Chief Medical Officer, Oklahoma City Area Indian Health Service, October 13, 2005.
[27] Decision Memorandum for Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190N), December 15, 2003.

studies, in addition to the data discussed above from the Friese and Saldalamacchia studies and the IHS prospective cohort registry, discussed above, provide sufficient evidence to reverse the current non-coverage decision and allow Medicare's contractors discretion to cover the use of autologous PRP in chronic non-healing wounds.

The studies of treatment of diabetic foot ulcers with autologous PRP are relevant to the analysis for coverage of other chronic, non-healing wounds because both groups of wounds share a common mechanism of healing. FDA guidance regarding studies of treatment for chronic cutaneous ulcers states, "if a scientific rationale and clinical data support clinical activity 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."[28] In the PDM, CMS also acknowledges that although some elements of treatment for different wound types vary, some treatments and strategies are common for all wound types.[29] We agree that all chronic wounds share certain common treatment elements, such as debridement to remove devitalized tissue, appropriate off-loading, and treatment for any infection that might be present. Once the wound bed has been prepared, the clinical data discussed below indicates that use of autologous PRP is an effective treatment for all chronic wounds. CMS also states that studies using a definitive outcome, such as complete healing, allow for "confident generalization of evidence across studies, different types of studies, different types of wounds, and to the Medicare population."[30] Given that complete wound healing was measured in diabetic foot ulcer studies discussed above, positive findings in these studies can be generalized to other chronic wounds.

Moreover, CMS recognized the similarities between diabetic foot ulcers and other chronic wounds in a prior NCD, in which it concluded that evidence on treatment of one type of wound is sufficient to support coverage of the same treatment for other types of wounds. In the Decision Memorandum regarding coverage of electrical stimulation for the treatment of chronic wounds, CMS analyzed clinical trials involving venous ulcers and pressure ulcers, but the coverage decision applies to four types of chronic ulcers: venous ulcers, pressure ulcers, arterial ulcers, and diabetic ulcers.[31] Thus, there is precedent for CMS to accept the data from studies of the use of autologous PRP on diabetic foot ulcers as evidence of the utility of this therapy for other chronic wounds.

When all of the available evidence on chronic wounds is reviewed, we believe it is sufficient to overturn the current non-coverage decision. In total, there are three prospective, randomized, controlled, and blinded studies; one retrospectively controlled study; several uncontrolled, unblinded studies; several case reports; and the data from the Cytomedix/IHS prospective cohort registry. In light of unique challenges inherent in researching treatment of chronic wounds with autologous PRP, CMS should recognize the significant value of these

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[28] Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment, FDA, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Center for Devices and Radiological Health, June 2006.

[29] PDM, at 2.

[30] Id. at 4.

[31] Decision Memorandum for Reconsideration of Electrostimulation (Electrical Stimulation) for the Treatment of Chronic Wounds (CAG-00032R), December 17, 2003.

studies and not disregard them because they do not employ the strongest methodological designs. The Driver and Friese studies, summarized above, are particularly persuasive because they are prospective, randomized, controlled, and blinded clinical trials that measured rates of complete wound healing, a "definitive outcome" that "allows for a confident generalization of available evidence across different types of wounds." The Saldalamacchia study, also summarized above, further shows that autologous PRP accelerates healing in a type of chronic wound, diabetic foot ulcers. The other studies described in the PDM complement these studies by showing high rates of wound closure among patients with other types of chronic, non-healing wounds who received autologous PRP. For example, the retrospectively controlled study by Mazzucco et al. measured time required to achieve adequate tissue regeneration to undergo reconstructive surgery instead of complete wound healing, but nonetheless it found a statistically significant improvement among the patients who received autologous PRP when compared to conventional treatment. The patients who received autologous PRP experienced sufficient wound area reduction to have reconstructive surgery in 15.0 weeks, compared to 35.5 weeks for patients in the control group ($p<0.0001$).[32]

The prospective, uncontrolled studies by Barrett, Crovetti, and McAleer also reported high rates of success at achieving wound closure in chronic wounds treated with autologous PRP.[33] These results are complemented by the data from the Cytomedix/IHS prospective cohort registry, which found that 91% (42/46) of wounds treated with PRP derived from the AutoloGel™ System healed.[34] In our reconsideration request, Cytomedix provided data from additional unpublished studies that corroborate the findings discussed above. For example, a case review of 102 chronic wounds of various types found that 70% of all wounds achieved a volume reduction of 50% or greater in 28 days.[35] Of the 62 pressure ulcers included in the review, 67% achieved a volume reduction of 50% or greater in 28 days.[36] In a long-term care facility, 7 chronic pressure sores had experienced no significant reduction in volume after an average of 43.1 weeks of standard care. Once treated with AutoloGel™, 71% (5/7) of these wounds had significant volume reduction in an average of 9.3 weeks.[37] A retrospective analysis of 10 chronic, non-healing wounds of various types found that all 10 wounds healed completely in an average of 6.2 weeks after treatment with AutoloGel™.[38] A review of 17 chronic wounds of various etiologies in long-term care facilities found that 89% of the wounds achieved 50% or greater volume reduction and 47% achieved complete healing in 3.5 weeks.[39] Finally, among 7

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[32] Mazzucco L et al., The Use of Autologous Platelet Gel to Treat Difficult-to-Heal Wounds: A Pilot Study, Transfusion 2004;44:1013-1018.

[33] Barrett SL, A New Approach to Using Growth Factors in Wound Healing, Podiatry Today 2003;1:44-50; Crovetti G, et al., Platelet Gel for Healing Cutaneous Chronic Wounds, Transfusion and Apheresis Science 2004;30:145-151; McAleer JP, et al., Efficacy of Concentrated Autologous Platelet-Derived Growth Factors in Chronic Lower-Extremity Wounds, Journal of the Podiatric Medical Association 2006;96(6):482-488.

[34] Letter from K. Mohan to S. Phurrough, Formal Coverage Reconsideration Request for CAG-00190N, June 20, 2007, Appendix D.

[35] Id., Appendix G.

[36] Id.

[37] Id., Appendix E.

[38] Id., Appendix F.

[39] Id., Appendix H.

high-risk, largely minority patients identified by their physicians as being at risk for amputation, all 7 achieved wound volume reduction of 89% or greater, including complete healing in 4 patients, and were able to avoid amputation.[40]

Although CMS does not define how much evidence is "sufficient" for its coverage determinations, this substantial and consistent body of evidence justifies reversing the current non-coverage decision and allowing Medicare's contractors discretion to cover the use of autologous PRP for other chronic, non-healing wounds.

Allowing Medicare contractors the discretion to cover autologous PRP for other chronic wounds is similar to Medicare's treatment of other wound treatments and the coverage provided by other government health care programs. CMS currently has eight NCDs, including the NCD under reconsideration, that address wound treatments.[41] Coverage of all other wound treatments (e.g., Apligraf®, Dermagraft®) is left to contractor discretion. We ask CMS also to allow contractors discretion to cover autologous PRP produced by systems cleared by the FDA for production of PRP. This would allow Medicare beneficiaries to have access to a therapy that is already available for patients at IHS and Veterans Affairs facilities and is covered under certain state Medicaid programs.[42]

B. In the Alternative, CMS Should Consider Applying Coverage with Study Participation to the Use of Autologous PRP for Other Chronic, Non-Healing Wounds

If CMS determines that the evidence is insufficient to reverse the current non-coverage decision for other chronic, non-healing wounds, Cytomedix believes that there is at least sufficient evidence to warrant coverage of autologous PRP for non-diabetic ulcer chronic wounds under coverage with evidence development (CED), with a registry under the concept of coverage with study participation (CSP). As the CMS guidance on CED explains,

> CSP will allow coverage of certain items or services for which the evidence is not adequate to support coverage under section 1862(a)(1)(A) and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries.[43]

If CMS finds that the evidence is not adequate to support coverage at contractor discretion for non-diabetic foot ulcer chronic wounds, the agency should support the collection of data that would support a positive national coverage determination by allowing CSP with a registry. A

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[40] Id., Appendix I.

[41] National Coverage Determination Manual, Pub. 100-3, §§ 20.29, 270.1, 270.2, 270.4, 270.5, 270.6, and 280.8.

[42] See, e.g., Specialized Wound Therapy Authorization Form for Minnesota Health Care Programs (listing AutoloGel™ System among wound therapies for which prior authorization can be obtained); Letter from L.K. Lynn, Bureau of Comprehensive Health Services, Illinois Department of Public Aid, to D. Dees, Cytomedix, June 9, 2003 (stating that Illinois Medicaid will begin covering the AutoloGel Process Kit).

[43] Guidance for the Public, Industry, and CMS Staff: National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development, July 12, 2006, section V.B.

noncoverage determination would continue to stifle research regarding these therapies and would deny Medicare beneficiaries the opportunity to receive a therapy that has demonstrated efficacy. The use of a registry would allow beneficiaries to receive autologous PRP while facilitating the collection of additional data on its effectiveness. A registry also would permit physicians and providers to participate in research in a minimally burdensome manner. Through Cytomedix's collaboration with the IHS and our forthcoming registry for the FDA,[44] we have experience in designing and implementing registries, and we are willing to work with CMS to design a registry if CMS decides not to allow coverage at contactor discretion.

III. Conclusion

The available evidence, including the studies by Friese and Saldalamacchia that were not addressed in the PDM, is now adequate to conclude that the use of autologous PRP for chronic diabetic foot ulcers, when compared to conventional wound care, significantly and reliably improves the rate of complete healing in the Medicare population. We strongly encourage CMS to allow Medicare beneficiaries to receive this important therapy. We ask CMS to issue an NCD that establishes coverage for the treatment of chronic diabetic foot ulcers with autologous PRP produced by a device cleared by the FDA for the production of PRP. The evidence for the use of autologous PRP produced by an FDA-cleared device for other chronic, non-healing wounds is substantial and is sufficient to reverse the current non-coverage decision and allow coverage at contractor discretion. In the alternative, Cytomedix asks CMS to consider coverage with study participation using a registry for other, chronic nonhealing wounds.

Thank you for your consideration. We look forward to meeting with you to discuss this matter further. Please contact Mr. Stuart Langbein of Hogan & Hartson at (202) 637-5744 or me if you have any questions.

Sincerely,

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

Attachment

[44] Under this registry, Cytomedix will collect hematological and adverse event data from 300 patients at 3 sites receiving repetitive topical treatment of wounds with the AutoloGel™ System.

The use of autologous platelet concentrate activated by autologous thrombin (APC+) is effective and safe in the treatment of chronic diabetic foot ulcers – a randomized controlled trial

G. Friese[1], M. Herten[2], W.A. Scherbaum[1]
1 German Diabetes Center,German Diabetes Clinic, WHO Collaborating Center for Diabetes Leibniz Institute at the Heinrich-Heine-Universität Düsseldorf
2 Kieferklinik Heinrich-Heine-Universität Düsseldorf

Deutsche Diabetes-Klinik, Deutsches Diabetes-Zentrum, Leibniz-Institut an der Heinrich-Heine-Universität Düsseldorf

Fifth International Symposium on The diabetic foot
9-12 May 2007, Noordwijkerhout, The Netherlands

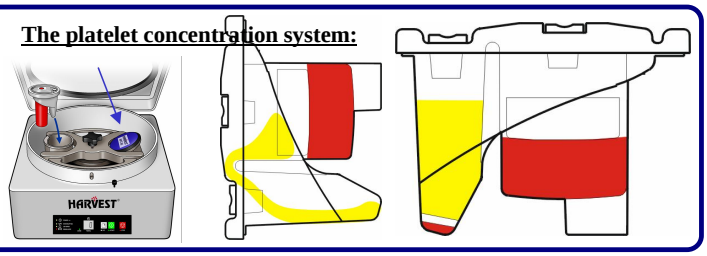
Introduction:

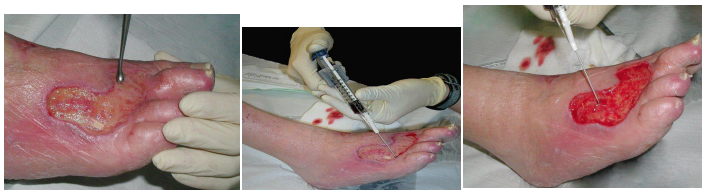
Diabetic foot wounds are difficult to heal and frequently lead to amputation despite optimal treatment. Natural healing is a complex procedure involving different growth factors, which may lack in chronic wounds. The effectiveness and safety of topical applied APC+ is investigated.

Methods:

A total of 59 patients suffering from chronic diabetic foot lesions with a duration > 6 weeks, Wagner stage 1-3, a size > 0,7 cm2 and attending the Ambulatory Foot Clinic were screened, 42 patients finishing a 14 days run-in phase and meeting the study inclusion criteria were randomized into two groups (n=21). Patients with active infection, compromised circulation (ABI < 0,7) or venous stasis were excluded. One patient of the test group dropping out for non-medical reason (transport costs) was excluded from the final analysis. Both groups were treated according to the International Consensus of the Diabetic Foot and received weekly debridement, cleansing, coverage with a polyurethane foam, regulary dressing changes and off-loading. Every two weeks the test group additionally received the topical application of APC+, which was produced from a small sample of patients whole blood and processed via the SmartPRePTM System (Harvest Technologies). Wound size and conditions were assessed weekly during the treatment period of 12 weeks and monthly during a 3 months follow-up. Primary endpoint was complete healing during the treatment period of 12 weeks. This study has been registered with clinical-trials.com (ISRCTN 28965380).

The platelet concentration system:



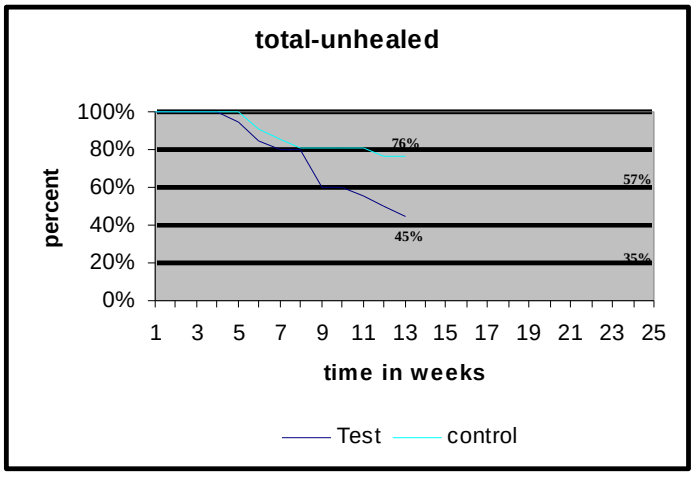


Treatment concept

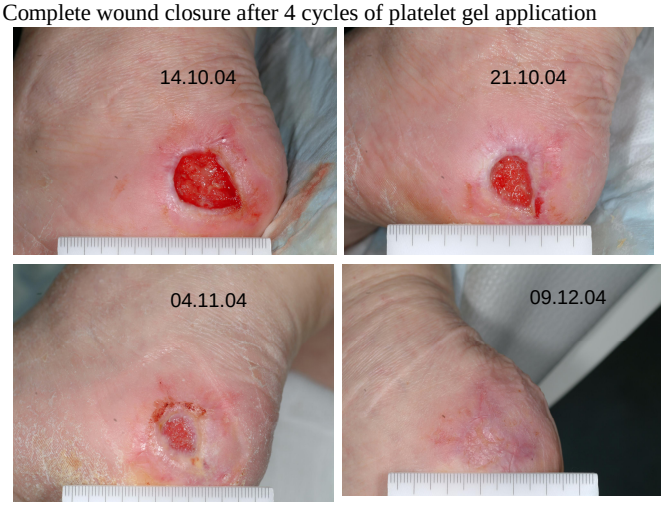
1. Debridement
2. The use of platelet gel
3. Platelet gel on the wound
4. Wound dressing with polyurethan foam

Results:

Within the treatment period of 12 weeks more patients in the test group (11 out of 20, 55%) than in the control group (5 out of 21, 24%) achieved complete wound healing (p<0,05). The rate of healing based on the time to complete closure is potentially faster in the test group (9,2 vs. 12,2 weeks). The frequency and severity of adverse events was significantly higher in the control group (9 vs. 2, p=0,02), of which the most common was infection and any vascular complication



Example: 67 years old female diabetic patient
Chronic non-healing ulcer of the heel (test group).
Complete wound closure after 4 cycles of platelet gel application



Conclusion:

The use of growth factors released from activated platelet concentrates (APC+) could lead to a higher proportion of healed wounds, potentially faster healing rates and reduced treatment related complications.

contact: Gerd.Friese@ddz.uni-duesseldorf.de DDZ Deutsches Diabetes-Zentrum Auf`m Hennekamp 65 D-40225 DÜSSELDORF

January 17, 2008

Beverly A. Lofton, MHA
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Centers for Medicare & Medicaid Services
7500 Security Blvd.
Woodlawn, MD 21244
Mail Stop: C1-09-06

Re: Comments on Proposed Decision Memo – "Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190R2)"

Dear Ms. Lofton:

I am writing to comment on the Centers for Medicare & Medicaid Services' Proposed Decision Memo for Autologous Blood-Derived Products for Chronic Non-Healing Wounds. I am the Chairman of the Department of Dermatology and Skin Surgery at the Roger Williams Medical Center and a Professor of Dermatology and Biochemistry at Boston University School of Medicine. My main area of expertise is chronic wounds and their treatment. I have co-authored numerous peer-reviewed papers on the efficacy of tissue engineering products, including Apligraf®, for venous stasis ulcers[1]. I also published numerous articles in leading journals on wound healing, including The Lancet and Wound Repair and Regeneration.

I reviewed the Proposed Decision Memo and literature currently available on autologous platelet-rich plasma ("PRP") gel and I write to express my concern that the clinical studies, case reports, and case series analyzed by CMS fail to demonstrate adequately the product's safety and efficacy in healing diabetic foot ulcers, venous stasis ulcers, or pressure ulcers. Based upon my experience designing and implementing wound-healing clinical trials, the studies lack the necessary parameters to establish accurately and definitively the ability of PRP gel to heal a chronic, cutaneous wound. For example, the Mazzucco et al. trial[2] was nonrandomized, unblinded, and used a retrospective control group. The design further weakened the study's conclusions by evaluating multiple ulcers, including venous, arterial, and pressure ulcers, and involving only 31 patients. Finally, wound characteristics, such as area and volume, were not described and patient follow-up was limited only to the post-surgery period. As a result of these design deficiencies, it cannot be concluded, based upon the study, that PRP gel is safe and effective for healing chronic, cutaneous ulcers.

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[1] See, e.g., Falanga et al., *Rapid Healing of Venous Ulcers and Lack of Clinical Rejection with an Allogeneic Cultured Human Skin Equivalent*, Arch Dermatol (Mar. 1998); Falanga et al., *A Bilayered Skin Construct (APLIGRAF®) Accelerates Complete Closure of Hard-to-Heal Venous Ulcers*, Wound Repair and Regeneration (July-Aug. 1999).

[2] Mazzucco et al., *The Use of Autologous Platelet Gel to Treat Difficult-to-Heal Wounds: A Pilot Study*, Transfusion (July 2004).

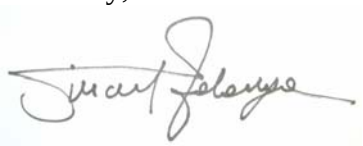
The Driver et al. study[3] also exhibited several significant design flaws. For example, an independent audit revealed numerous protocol violations, ultimately reducing the sample size to only 40 patients. The follow-up period was minimal, with only 22 of the 40 subjects completing follow-up. We cannot rely upon the results obtained from this limited patient follow-up. More study subjects are necessary to determine properly the safety and efficacy of PRP gel, and the incidence of premature wound opening and skin breakdown that results from use of this product needs further study. In addition to the protocol violations and limited patient follow-up, the results indicated that only 20 percent of control group patients had ulcers healed in 12 weeks, which is less than the healing rates using conventional therapies. In the end, this lower figure casts doubt upon the accuracy of the study and its results.

* * *

The clinical trials referenced in CMS' Proposed Decision Memo lacked adequate procedures for ensuring the quality of the studies and the final conclusions. As a result, the current available evidence fails to demonstrate that PRP gel is safe and effective for treating chronic, cutaneous wounds such as diabetic foot ulcers, venous stasis ulcers, and pressure ulcers. A final CMS decision to cover PRP gel will encourage physicians to use this product on chronic wounds, ultimately exposing patients to unproven and inappropriate treatment methods. As a clinician, I am always concerned that the use and payment of unproven therapies robs our patients of the opportunities to use treatments that have been properly tested in thorough clinical trials. Therefore, I recommend that CMS issue a non-coverage determination for autologous blood-derived products intended to treat chronic, non-healing wounds until the clinical studies accurately demonstrate the ability of this product to heal chronic wounds. The effectiveness of this product is yet to be determined, and more carefully designed and larger clinical trials are needed.

Thank you for considering my comments on the Proposed Decision Memo. If you have any questions, please do not hesitate to contact me at 401-456-2521 or by e-mail (vfalanga@bu.edu).

Sincerely,



Vincent Falanga, MD, FACP
Professor, Boston University
PI, NIH Center of Biomedical Research Excellence
Roger Williams Medical Center

[3] Vickie R. Driver et al., *A Prospective, Randomized, Controlled Trial of Autologous Platelet-Rich Plasma Gel for the Treatment of Diabetic Foot Ulcers*, 52 Ostomy/Wound Mgmt 68 (2006).