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CLINICAL TRIALS

Wharton's Jelly in Regenerative Joint Therapy: A Case for IND-Exempt Inclusion in Randomized Controlled Trials

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Abstract

Platelet-Rich Plasma (PRP) and Wharton's Jelly (WJ) remain two of the most widely explored biologic injectables for the treatment of degenerative joint disease. To date, only PRP is permitted in Randomized Controlled Trials (RCTs) without FDA oversight under an Investigational New Drug (IND) application. This regulatory disparity persists despite the fact that WJ, particularly in its acellular or lyophilized form, shares critical biological, biochemical, and biomechanical functions with PRP-including anti-inflammatory, viscoelastic, and Extracellular Matrix (ECM) remodelling properties.

This article re-examines the native role of WJ during fatal development-where it withstands physiologic strain, undergoes active remodelling, and supports vascular integrity-as the appropriate frame through which to assess its clinical utility in adult joint degeneration. When used intra-particularly, WJ performs the same basic structural and reparative functions required of cartilage matrix support, making its exclusion from homologous use designation a contradiction under the FDA's own regulatory logic.

We argue that WJ, when minimally manipulated and applied for the structural repair of degenerated joints, qualifies as a homologous-use allograft under 21 CFR 1271.3(c). As such, it should be exempt from IND requirements in the context of randomized, controlled, or comparative clinical trials. Enabling such studies is not only scientifically and ethically justified-it is essential to fulfil medicine's obligation to pursue truth through evidence. RCTs are the cornerstone of clinical validation, and they must be equally accessible for all biologic candidates with plausible mechanistic parity. At stake is not just regulatory fairness, but the future of non-operative care for millions of Americans suffering from joint degeneration.

Introduction

Randomized Controlled Trials (RCTs) remain the highest standard in determining therapeutic efficacy and guiding clinical decision-making [1]. In regenerative orthopaedics, few biologics have generated as much interest-or confusion-as Platelet-Rich Plasma (PRP) and Wharton's Jelly (WJ). Both are under active clinical investigation for the treatment of cartilage loss, yet they occupy entirely different regulatory categories. PRP, derived autologous, qualifies as a minimally manipulated, homologous-use biologic and may be studied in RCTs without an Investigational New Drug (IND) application [2,3]. WJ, despite being similarly processed and biologically relevant, is classified as a Section 351 product, prohibiting even controlled clinical trials unless IND clearance is granted.

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This review examines whether that distinction remains valid in light of evolving evidence. Specifically, it evaluates the biological and functional roles of WJ in the fetal environment, the compositional and mechanical parallels to articular cartilage, and the immunologic safety of decellularized or lyophilized WJ. Taken together, these findings support a regulatory reevaluation of WJ as a homologous-use structural allograft. RCT access, under IND exemption, should be extended to this class of biologics-on par with PRP-to allow for objective determination of clinical superiority.

Historical and regulatory overview of HCT/P classification

The U.S. Food and Drug Administration (FDA) classifies human cells, tissues, and cellular and tissue-based products (HCT/Ps) under one of two regulatory frameworks: Section 361 or Section 351 of the Public Health Service Act. Products regulated under Section 361-codified at 21 CFR 1271-are exempt from premarket review when they meet four essential criteria: (1) they are minimally manipulated; (2) intended for homologous use; (3) not combined with other drugs or devices (with limited exceptions); and (4) do not rely on systemic effects or the metabolic activity of living cells for their primary function [4].

PRP is considered intended for homologous use because its function in the recipient-supporting clot formation and tissue repair-mirrors its natural role in the donor's blood. This classification aligns its therapeutic effect with its inherent biological function, which can reduce regulatory oversight compared with non-homologous applications. However, WJ has been designated a Section 351 product on the grounds that its use in joints constitutes non-homologous application. In turn, WJ must undergo thorough premarket review and prolonged testing to meet extensive requirements. This designation reflects a narrow, static interpretation of homologous use that does not consider the dynamic structural, anti-inflammatory, and mechanotransductive roles that WJ performs during fetal development [5-7]. Such roles directly parallel the functional demands of degenerative joint environments.

Wharton's jelly and its native function in fetal development

WJ is a dense, viscoelastic connective tissue within the umbilical cord. It plays a crucial role in protecting fetal vasculature from compressive forces by dispersing mechanical load and facilitating hydration [8]. Its Extracellular Matrix (ECM) includes hyaluronic acid, collagens (types I, III, and VI), sulfated proteoglycans, and bioactive mediators such as Interleukin-1 Receptor Antagonist (IL-1RA), Transforming Growth Factor-beta (TGF-β), and Tissue Inhibitors of Metalloproteinases (TIMPs) [6,9]. These various components are critical for providing tensile strength and framework to the ECM, in addition to the network of macromolecules [10].

These molecules are not passive scaffolding; they participate in active remodeling, inflammation regulation, and repair signaling throughout gestation [6,11]. Importantly, WJ adapts to torsion, tension, and elongation as the fetus grows-demonstrating mechanoadaptive capabilities akin to those of adult articular cartilage under joint loading [12]. This dynamic reparative function places WJ well within the bounds of homologous use when applied to load-bearing joint tissues affected by osteoarthritis.

Saw SN, et al. [13] previously affirmed WJ's non-linear stress-strain, viscoelasticity, and load redistribution through ECM architecture mirror known adaptive responses in adult cartilage. The 2021 study emphasized the critical role of the gelatinous architecture of WJ in maintaining umbilical cord function under mechanical stress. The investigators highlighted the findings that when external pressure on the umbilical cord was increased by 30-50%, umbilical venous flow did not significantly decline. This finding underscores the protective, viscoelastic properties of the WJ matrix, which allow the vessel to deform, redistribute mechanical load, and preserve luminal patency. The gelatinous ECM provided both cushioning and a capacity for structural contortion, enabling continued venous return despite compression [13,14].

Biochemical and structural parallels with articular cartilage

The biomechanical advantages of WJ are paralleled in articular cartilage. In cartilage, proteoglycans with attached glycosaminoglycans absorb water and generate swelling pressure; however, this expansion is physically constrained by the surrounding collagen fibrillary network, conferring high compressive resilience [15]. Under increasing mechanical load, the repulsive forces between adjacent proteoglycans intensify as they are forced into closer proximity, while the tensile resistance of the collagen fibers further

restricts swelling [15]. This synergistic interaction between swelling pressure and collagen tension enables articular cartilage to withstand substantial compressive forces, often exceeding several times body weight. Importantly, the magnitude and pattern of mechanical loading experienced by cartilage vary by anatomical location, reflecting region-specific functional demands. Taken together, the structural and biomechanical features of WJ and articular cartilage mirror one another, as both tissues rely on hydrated, proteoglycan-rich matrices constrained by fibrous networks to redistribute load and preserve function under substantial mechanical stress.

Articular cartilage and WJ also share striking compositional and functional features. Both are avascular, aneural, and composed of dense ECM rich in collagen (types I and III), hyaluronic acid, and proteoglycans [16]. WJ and articular cartilage both contain type I and type III collagen, which support tensile strength, elasticity, and structural integrity of the ECM. This shared collagen composition underlies their load-bearing and load-redistributing properties, making WJ a promising scaffold for cartilage repair and other regenerative applications [17]. Both also rely on passive diffusion for nutrient exchange and serve roles in absorbing mechanical forces. Additionally, WJ's high hyaluronic acid content contributes to viscosity and lubrication-two core functional traits of synovial joints [18].

Furthermore, the presence of Insulin-like Growth Factor (IGF-1), Fibroblast Growth Factors (FGF), and Transforming Growth Factor beta (TGF-β) in WJ mirrors the signaling milieu of articular cartilage, promoting ECM synthesis, limiting catabolism, and modulating inflammatory cascades [19]. These similarities support WJ's classification as a structural analog to native cartilage tissue-particularly when used in its acellular, non-viable form.

Preclinical and clinical evidence supporting WJ for joint repair

Preclinical animal models have shown that intra-articular WJ promotes cartilage regeneration, reduces inflammation, and improves biomechanical parameters. In rodent studies, WJ-treated joints demonstrated reduced expression of degradative enzymes (e.g., MMP-13), increased glycosaminoglycan content, and visibly improved cartilage thickness compared to controls [20]. The results of this 2022 study suggest that WJ clinical applications offer therapeutic relief in the absence of cartilage tissue.

Early human studies-albeit small-are promising. Case series and pilot trials have shown that patients receiving WJ report improvement in joint pain, functional range of motion, and overall quality of life [21-23]. Importantly, these benefits were achieved without immunologic complications or adverse events. The growing body of data justifies further clinical trials-and those trials should not be hindered by regulatory structures that overlook WJ's functional homology to cartilage tissue.

Immunologic and safety profile of acellular WJ

The immunologic safety of any allogeneic product is paramount. When decellularized or lyophilized, WJ eliminates donor-specific antigens such as Major Histocompatibility Complex (MHC) molecules, while preserving ECM integrity. Studies across species have demonstrated favorable immunologic tolerance, with no meaningful incidence of graft-versus-host response or synovial inflammation [24].

The decellularization process of WJ involves the removal of cellular components while preserving the ECM structure. Techniques such as detergent-based methods, enzymatic digestion, and physical treatments are employed to achieve complete decellularization [25]. Standardization of these methods ensures reproducibility and consistency in the final decellularized WJ product. For instance, a 2022 study demonstrated the successful decellularization of WJ, preserving its biochemical composition and mechanical properties, which are crucial for its function as a scaffold in tissue engineering [25].

The concentration of components within decellularized WJ, such as glycosaminoglycans and collagen, is critical for its mechanical properties and suitability as a scaffold [25]. Standardized processing methods allow for the control of these concentrations, ensuring that the decellularized WJ maintains the necessary structural integrity to support tissue regeneration. Research has shown that decellularized WJ scaffolds can effectively support cell growth and tissue formation, indicating that the mechanical properties are preserved through standardized preparation [26].

The decellularization method employed for WJ significantly influences both its mechanical properties and biological signaling capabilities, which

are critical considerations for regulatory compliance and clinical application. Different decellularization protocols-ranging from detergent-based and enzymatic treatments to physical methods-can lead to variations in the scaffold's structural integrity, porosity, and retention of bioactive molecules. For instance, detergent-free decellularization has been shown to better preserve the ECM architecture and associated biological cues, which are essential for cell-ECM interactions and tissue regeneration. Conversely, harsher chemical treatments may compromise the mechanical strength and biological activity of the ECM, potentially affecting its suitability as a scaffold material [26,27].

Therefore, it is imperative to specify or critically discuss the decellularization methods used for WJ in regulatory submissions and clinical protocols. Detailed characterization of the decellularized WJ, including assessments of mechanical properties, biochemical composition, and biological activity, ensures that the material meets the necessary standards for safety and efficacy. Such thorough documentation not only facilitates regulatory approval but also supports the reproducibility and reliability of the scaffold in clinical applications.

Allogeneic decellularized WJ is considered safe for clinical applications when processed according to established protocols. A 2019 study assessed the safety of WJ-derived Mesenchymal Stem Cells (WJ-MSCs) administered via various routes, including intravenous, intrathecal, and intra-articular injections. The study found no serious adverse events associated with these administration methods. The only reported adverse effect was a mild headache in one patient following the first intrathecal injection, suggesting that WJ-MSC therapy is generally well-tolerated across different delivery routes [28].

In a 2020 multicentre safety review, Gupta A, et al. [16] reported no serious adverse events associated with intra-articular injection of acellular WJ. Thus, demonstrating both the safety of WJ applications in a clinical environment. Additionally, Gupta stated that the presence of Interleukin-1 Receptor Antagonist (IL-1RA) and Tumor necrosis factor-inducible Gene 6 protein (TSG-6) offers a biologically built-in anti-inflammatory buffer, further supporting the safety profile for joint injection. These findings collectively meet the threshold for biologic plausibility, biocompatibility, and clinical tolerability in human trials.

In summary, allogeneic decellularized WJ, when processed through standardized decellularization methods, demonstrates a favourable safety profile, consistent mechanical properties, and reliable performance as a scaffold in tissue engineering applications. These attributes make it a promising material for regenerative medicine.

PRP as regulatory precedent: A functional comparison

PRP has achieved IND exemption not because of anatomical homology to joint tissue, but because of functional congruence. It acts as a tissue modulator-promoting repair, limiting inflammation, and activating endogenous healing pathways. By those same standards, WJ performs equivalent functions, albeit in a fetal context.

Denying WJ the same regulatory latitude granted to PRP amounts to selective enforcement of function-based logic. If biologic function is the standard-and it should be-then WJ merits the same IND-exempt status in prospective clinical trials that aim to compare its efficacy to PRP.

The role of ECM-based allografts in regenerative research

The regenerative medicine landscape increasingly favors ECM-based products. These scaffolds are not inert—they engage native tissue responses, direct cellular activity, and support biologic repair. WJ, in its decellularized form, is an exemplary ECM platform: biomechanically resilient, biochemically active, and immunologically inert.

Unlike pharmacologic agents or stem cell therapies, ECM allografts are primarily structural, acellular scaffolds that perform the same basic functions in the recipient as in the donor, which aligns with homologous use criteria. Because they lack live cells and are inherently low-risk, ECM allografts generally present a lower regulatory burden compared with cellular or gene-based therapies [29] (Table 1).

Decellularized ECM provides structural support, retains biomechanical function, and promotes tissue remodeling, all while exhibiting low immunogenicity and reduced risk of disease transmission. Its acellular nature and homologous use generally result in a lower regulatory burden, making it well-suited for controlled research frameworks. However, risks such as incomplete decellularization, processing

Table 1: Risks, benefits, and regulatory implications of decellularized ECM.

Category	Key Points
Benefits	▸ Provides natural structural support and maintains tissue architecture. ▸ Low immunogenicity due to removal of donor cells. ▸ Retains biomechanical function (e.g., cushioning, load redistribution). ▸ Supports host cell infiltration and tissue remodeling. ▸ Reduced risk of disease transmission compared to cellular grafts.
Risks	▸ Incomplete decellularization may leave residual antigens. ▸ Processing variability can affect mechanical properties and bioactivity. ▸ Potential for microbial contamination if sterilization is inadequate. ▸ Cannot fully replicate complex cellular functions (e.g., secretion, metabolism).
Regulatory Implications	▸ Often regulated as HCT/Ps under **21 CFR Part 1271** when minimally manipulated and used homologously. ▸ Lower regulatory burden for homologous use and acellular products. ▸ IND/IDE required if used non-homologously or in trials evaluating new therapeutic effects. ▸ Suitable for controlled research frameworks with standard ethical and safety oversight.

variability, and potential contamination must be managed, and regulatory oversight increases when the ECM is applied for non-homologous or novel therapeutic purposes.

Recognizing WJ as a homologous-use ECM scaffold would align regenerative research priorities with clinical and scientific feasibility, opening the door to direct, evidence-driven comparison studies with PRP and other injectables. Viewed through a developmental and functional lens, WJ—when decellularized or lyophilized—clearly meets the criteria for homologous use as outlined in 21 CFR 1271.3(c). Briefly, the FDA defines homologous use as requiring that the HCT/P in the recipient performs the same fundamental role it served in the donor, and is not redefined by new or different intended effects [4]. WJ functions in the umbilical cord as a hydrated, proteoglycan-rich matrix that cushions and redistributes mechanical load to protect the vessels. Articular cartilage performs an analogous role in joints, where its proteoglycan and collagen architecture enables load absorption and structural protection. Thus, when transferred, WJ preserves the same basic function in the recipient as in the donor, consistent with homologous use criteria. WJ maintains its intrinsic function of cushioning and redistributing mechanical load after transfer, regardless of the clinical context. Its intended use for joint support does not redefine this basic biomechanical role, so the tissue's function also remains consistent with homologous use criteria.

By contrast, continuing to treat WJ as a non-homologous biologic not only disregards current science-it limits our ability to pursue the comparative trials needed to determine whether WJ or PRP offers superior clinical outcomes. Regulatory consistency demands an evidence-based approach to exemption status, and WJ has earned that consideration.

Discussion & Future Implications

Science must lead regulation-not the other way around. When a tissue-derived product such as WJ demonstrates clear biochemical, mechanical, and immunologic alignment with native cartilage function, it deserves regulatory treatment that reflects that reality.

This is not a call for deregulation. It is a call for regulatory reform that enables clinical research-particularly RCTs-to proceed without unnecessary delay. The risk of abuse is real, and regulatory guardrails should remain. But denying RCT access to acellular WJ-based on a rigid misclassification of its function-ultimately undermines the very premise of evidence-based medicine.

More than 53 million Americans live with arthritis, with knee involvement being the most common presentation [30]. The cost-both personal and

societal–is staggering. Failing to explore every viable therapeutic avenue, particularly those grounded in biologic logic and promising early data, is both short-sighted and ethically untenable. If we are to claim allegiance to science, then our regulatory frameworks must reflect a willingness to test, compare, and let the data decide.

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