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

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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) remodeling properties. This article reexamines the native role of WJ during fetal development—where it withstands physiologic strain, undergoes active remodeling, and supports vascular integrity—as the appropriate frame through which to assess its clinical utility in adult joint degeneration. When used intra-articularly, 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 fulfill 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.

Keywords: Wharton's jelly; extracellular matrix; joint degeneration; investigational new drug

1. Introduction

Randomized controlled trials (RCTs) remain the highest standard in determining therapeutic efficacy and guiding clinical decision-making [1]. In regenerative orthopedics, 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 autologously, 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.

This review examines whether that distinction remains valid in light of evolving evidence. Specifically, it evaluates the biological and functional roles of Wharton's Jelly 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,

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should be extended to this class of biologics—on par with PRP—to allow for objective determination of clinical superiority.

2. 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.

PRP qualifies under this framework. 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 conclusion 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 [4-6]. Such roles directly parallel the functional demands of degenerative joint environments.

2.1. Wharton's Jelly and Its Native Function in Fetal Development

Wharton's Jelly 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 [7]. Its extracellular matrix (ECM) includes hyaluronic acid, collagens (types I, II, 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) [5, 8]. These various components are critical for providing tensile strength and framework to the ECM, in addition to the network of macromolecules hydrated [8].

These molecules are not passive scaffolding; they participate in active remodeling, inflammation regulation, and repair signaling throughout gestation [5, 9]. 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 [10]. This dynamic reparative function places WJ well within the bounds of homologous use when applied to load-bearing joint tissues affected by osteoarthritis. Saw et al. (2021) previously affirmed WJ's non-linear stress-strain, viscoelasticity, and load redistribution through ECM architecture mirror known adaptive responses in adult cartilage [11].

2.2. Biochemical and Structural Parallels with Articular Cartilage

Articular cartilage and WJ share striking compositional and functional features. Both are avascular, aneural, and composed of dense ECM rich in type II collagen, hyaluronic acid, and proteoglycans [12]. Both rely on passive diffusion for nutrient exchange and serve roles in absorbing mechanical forces. WJ's high hyaluronic acid content contributes to viscosity and lubrication—two core functional traits of synovial joints [13].

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 [14]. These similarities support WJ's classification as a structural analog to native cartilage tissue—particularly when used in its acellular, non-viable form.

2.3. Immunologic and Safety Profile of Acellular WJ

The immunologic safety of any allogeneic product is paramount. When decellularized or lyophilized, Wharton's Jelly eliminates donor-specific antigens such as Major Histocompatibility

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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 [15].

In a 2020 multicenter safety review, Gupta et al. reported no serious adverse events associated with intra-articular injection of acellular WJ [16]. Thus, demonstrating both the safety of WJ applications in a clinical environment. Additionally, Gupta stated that the presence of Interleukin-1 receptor agonist (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.

2.4. 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 [17]. The results of this 2022 study suggest that Wharton's jelly 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 [18-20]. 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.

2.5. 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.

2.6. 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 present a lower regulatory risk and can be safely integrated into a controlled research framework. 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.

3. Summary

Viewed through a developmental and functional lens, Wharton's Jelly—when decellularized or lyophilized—clearly meets the criteria for homologous use as outlined in 21 CFR 1271.3(c). It shares structural elements with articular cartilage, supports mechanical loading, mediates inflammation, and promotes ECM homeostasis. In this context, its use in the treatment of joint degeneration mirrors its native physiologic function.

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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 Wharton's Jelly has earned that consideration.

4. Discussion

Science must lead regulation—not the other way around. When a tissue-derived product such as Wharton's Jelly 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 randomized controlled trials—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 [21]. 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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