Review Article
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# Autologous versus Non-autologous Exosomes: Immunological, Safety, and Regulatory Considerations in Regenerative Medicine

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## Abstract

Small extracellular vesicles (sEVs), commonly referred to as exosomes, have emerged as novel therapeutic tools in regenerative and esthetic medicine. A critical decision in their clinical application is the choice between autologous and non-autologous products, as this distinction directly impacts safety, immunocompatibility, efficacy, and regulatory compliance. This review analyzes the immunological profile and biological risks associated with exosomes' clinical use according to their cellular origin, addressing persistence, pathogen transmission, delivery routes, and regulatory classification. Furthermore, we highlight the strategic role of blood centers and biobanks in producing high-safety allogeneic sEVs, especially those derived from human platelets and mesenchymal stromal cells expanded in xenofree conditions. While autologous exosomes offer maximal immunological safety, standardized allogeneic strategies free from animal-derived components represent a scalable and regulatory-compatible alternative for modern regenerative therapies.

**Keywords:** Exosomes; Regenerative Medicine; Autologous Exosomes; Non-autologous Exosomes

## Introduction

Small extracellular vesicles (sEVs) are nano-sized vesicles (30–200 nm) secreted by most cell types and involved in intercellular communication via transfer of lipids, proteins, mRNAs, and microRNAs. These vesicles are enriched with bioactive cargo that reflects the physiological and molecular status of the parent cell. Due to their pivotal role in regulating inflammation, promoting tissue repair, and modulating immune responses, sEVs have garnered increasing interest as promising agents in cancer and regenerative medicine [1-5].

The origin of sEVs used in therapy is a crucial determinant of their biological behavior, clinical safety, and regulatory viability. Autologous sEVs, which are derived from the same individual who will receive them, ensure complete histocompatibility and minimize immunological risk. In contrast, non-autologous sEVs can be of allogeneic origin (from another human donor) or xenogeneic origin (from animal or plant sources). Each type of non-autologous sEVs has distinct advantages and limitations regarding immune compatibility, risk of pathogen transmission, and production scalability [6-8].

## Cellular Origin and Immunological Risk

The immunogenicity of sEVs is tightly linked to their origin and surface molecular composition (Table 1). Autologous sEVs are fully compatible with the recipient's immune system and therefore exhibit minimal risk of eliciting rejection or inflammatory responses. They persist longer in circulation and within target tissues, offering prolonged therapeutic effects without applying immunosuppressive strategies [6,7]. Allogeneic sEVs, although derived from the same species, carry membrane-bound proteins that may include donor-specific antigens and MHC class I/II molecules. While generally less immunogenic than whole cells, these vesicles may still trigger moderate immune responses, particularly upon repeated administrations. In this context, strategies such as donor selection, vesicle purification, and surface modification can help mitigate these risks [8-10]. Xenogeneic sEVs carry the highest immunological risk due to cross-species antigenicity. Their molecular pattern recognition by host innate immunity often leads to rapid clearance, inflammation, and adverse reactions. Consequently, xenogeneic sEVs are currently restricted to experimental or pre-clinical applications and are not approved for human use [10,11].

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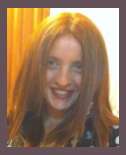
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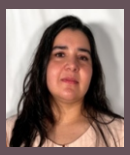
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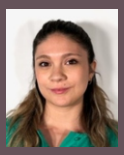
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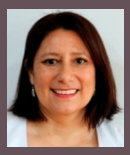
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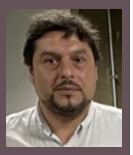
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**Table 1: Exosomes by cellular origin and species specificity: clinical, immunological, and regulatory differences among autologous (same individual), allogeneic (same species), and xenogeneic (different species) sEVs**

| Characteristic | Autologous | Allogeneic (Human) | Xenogeneic (Non-human) |
|---|---|---|---|
| Immunocompatibility | Complete | Partial | Very low |
| Risk of rejection | None | Moderate | High |
| Risk of infection | Very low | Low (with screening) | High (zoonotic potential) |
| Regulatory status | Injectable allowed | Topical use/trials | Not approved |
| Scalability | Limited | High (good manufacturing practice-compatible) | High (pre-clinical only) |
| Customization | High | Medium | None |

sEVs: Small extracellular vesicles

## Biological Safety and Pathogen Control

Beyond immunogenicity, a paramount consideration is the risk of transmitting infectious agents. Autologous sEVs pose the lowest threat as they are derived from the patient's own biological material. In contrast, allogeneic and xenogeneic products require rigorous screening and quality control processes to ensure microbial safety [12,13]. Several studies have demonstrated that extracellular vesicles can serve as carriers for viral particles or pathogenic proteins, which may pose risks for transmission, including prions. To mitigate this risk, good manufacturing practice (GMP)-compliant facilities must perform sterility testing, endotoxin analysis, viral nucleic acid screening, and validation of removal protocols. Blood centers and biobanks are well-positioned to meet these standards, due to their established infrastructure and expertise in producing pathogen-free blood products. Their adoption of standard operating procedures and traceability systems makes them ideal for scaling up sEVs from human platelets or mesenchymal stromal cells (MSCs) in safe and consistent conditions [7].

## Regulatory Pathways and Routes of Administration

Regulatory agencies such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) differentiate sEV products based on their origin, manipulation level, and intended clinical use. Autologous sEVs, especially those obtained with minimal manipulation and reinjected without extensive processing, may be eligible for exemptions or reduced regulatory oversight. Conversely, allogeneic sEVs are typically classified as advanced therapy medicinal products and must undergo full pre-clinical and clinical evaluation [9,10]. Furthermore, sEVs that are genetically modified, loaded with drugs, or engineered to express targeting molecules are treated as gene therapy or combination products, demanding additional regulatory scrutiny [14]. At present, only topical formulations of allogeneic sEVs have been approved for commercial use, whereas injectable forms remain under clinical investigation.

To bridge the gap between safety and scalability, xenofree culture systems have been developed for producing allogeneic sEVs. These systems exclude animal-derived supplements, such as fetal bovine serum, using human platelet lysate (hPL) or chemically defined media instead. This minimizes immunogenic risk and the transmission of zoonotic agents. In addition, implementing 3D bioreactor platforms facilitates the continuous, high-yield production of reproducibly characterized MSC-derived sEVs. Studies have shown that culture conditions, such as oxygen concentration, passage number, and mechanical stimulation, affect the quality and composition of sEVs. Therefore, process standardization is essential to ensure therapeutic efficacy and regulatory compliance [14-16].

One example of this circular approach is the use of hPL and platelet-derived extracellular vesicles (PDEVs). Both can be obtained from discarded platelet units at blood centers. hPL is rich in growth factors such as platelet-derived growth factor, transforming growth factor beta, vascular endothelial growth factor, and epidermal growth factor. This makes hPL highly suitable for cell expansion and wound healing applications. Similarly, PDEVs carry a complex cargo of regenerative proteins and microRNAs that contribute to angiogenesis, immunomodulation, and tissue repair. Since these products originate from clinically validated, pathogen-screened platelet concentrates that would otherwise be discarded, they are a cost-effective, biologically potent source of therapeutic agents. Integrating them into compatible clinical workflows supports the development of allogeneic, injectable-grade biologics, reduces biomedical waste, and enhances health system sustainability.

## Conclusion

The decision to use autologous or non-autologous exosomes is crucial for the development of regenerative therapies. While autologous sEVs offer unmatched safety and immunological compatibility, their individualized nature limits scalability and broad clinical application. In contrast, allogeneic sEVs derived from xenofree and GMP-compliant conditions provide a feasible path to standardized, safe, and effective off-the-shelf products. Blood centers, with their expertise in pathogen screening and biologic processing, are uniquely suited to serve as platforms for allogeneic sEV production. Their established protocols, infrastructure, and regulatory oversight support the transition from experimental use to clinical-grade biologics. Meanwhile, the use of xenogeneic sEVs should remain confined to the research setting until further studies address their safety and efficacy in humans. This review emphasizes that successful clinical translation of sEV-based therapies requires not only scientific and technical validation but also strong institutional collaboration. Specifically, strategic partnerships between blood centers, academic research laboratories, and regulatory authorities are essential to establish a sustainable framework for the development and approval of clinically safe biologicals from various cellular sources. Such collaboration will enable the implementation of standardized protocols, pathogen screening systems, and traceability procedures necessary to meet the rigorous safety standards required for injectable human use.

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Conflict of interest:** Nil **Source of support:** None

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