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Pharmacology GUIDELINE

The Innovation Drug Discovery

Clinical pharmacy management of emerging intra-articular drug delivery systems for knee osteoarthritis: A practical guideline

Jiang Liu,[1,2,7] Zhongqi Wang,[1,7] Hong Shen,[3,7] Taojin Feng,[1] Wei Wei,[4] Cong Wang,[5,6,*] and Yi Li[1,*]

[1]Institute of Orthopedics, Department of Orthopedics, The Fourth Medical Center of PLA General Hospital, National Clinical Research Center for Orthopedics, Sports Medicine & Rehabilitation, Beijing 100089, China

[2]Department of Orthopedics, The Second Affiliated Hospital of Harbin Medical University, Harbin Medical University, Harbin 150086, China

[3]School of Medicine, Nankai University, Tianjin 300350, China

[4]Department of Clinical Nutrition, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100730, China

[5]Department of Rehabilitation, Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200336, China

[6]Yuanshen Rehabilitation Institute, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

[7]These authors contributed equally

*Correspondence: wang.cong@shsmu.edu.cn (C.W.); yili730@126.com (Y.L.)

Received: June 30, 2026; Accepted: July 10, 2026; Published Online: July 14, 2026; https://doi.org/10.59717/j.xinn-drugdisc.2026.100025

Citation: Liu J., Wang Z., Shen H., et al. (2026). Clinical pharmacy management of emerging intra-articular drug delivery systems for knee osteoarthritis: A practical guideline. *The Innovation Drug Discovery* **1**:100025.

INTRODUCTION AND GUIDING PRINCIPLES

Emerging intra-articular drug delivery systems are being developed to improve local retention, controlled release, tissue distribution, or delivery of biological and nucleic acid payloads within the joint cavity. These products include sustained-release formulations, nanomedicines, injectable hydrogels, extracellular vesicle (EV) and engineered EV products, RNA delivery systems, and related local platforms. Although their composition differs, they share several practical problems: injection into a closed joint space, strict sterility requirements, device compatibility, release-dependent performance, and batch-to-batch variability.

This practical guideline is intended for early- to mid-stage knee osteoarthritis (OA), usually before surgical treatment is considered. It does not replace existing OA treatment recommendations, rank therapeutic efficacy, or support unapproved products as routine care. Its purpose is narrower: to describe how emerging intra-articular products should be qualified, stored, prepared, administered, traced, and monitored from a clinical pharmacy perspective.

The framework is organized as a simple workflow. Figure 1 starts with the clinical context, then moves to product classification, pharmaceutical qualification, preparation and administration, and post-injection safety monitoring.

METHODOLOGY AND EVIDENCE DEVELOPMENT

This Guideline Snapshot was developed through targeted literature review and expert discussion. PubMed, Web of Science, ClinicalTrials.gov, and public guidance or consensus documents from organizations including EULAR and ISEV were searched using terms related to knee OA, intra-articular therapy, drug delivery, sustained-release formulations, nanomedicine, hydrogels, EVs, RNA delivery, clinical trials, guidelines, and consensus. Evidence was organized by product type, regulatory status, quality attributes, administration, traceability, and safety. The multidisciplinary author group included expertise in orthopedics, rehabilitation medicine, clinical nutrition and medical management, and drug delivery/pharmaceutical sciences. Recommendations were based on available evidence and expert judgment, given the limited clinical evidence for many products.

Product classification and regulatory maturity

As shown in Figure 1, step 2, the first decision is product classification. Marketing-authorized sustained-release formulations should be used according to the approved label, local requirements, and institutional protocols. Off-label use should be justified and documented according to local policy.

Investigational nanomedicines, injectable hydrogels, RNA delivery systems, and related platforms should be used only in appropriately authorized and governed clinical studies until sufficient evidence of quality, safety, and clinical benefit is available.[1-3,5]

EV and engineered EV products require separate caution. They should be restricted to standardized clinical research settings with ethics approval, traceable source materials, release criteria, and clear informed consent.[4] Products marketed as "exosomes" should be described and evaluated as EV products unless their biogenesis has been adequately demonstrated. Before accepting an EV or exosome-labeled product, pharmacists or designated institutional personnel should verify source or donor information, source-cell screening, culture conditions, manufacturing batch records, isolation and purification methods, release testing, sterility, endotoxin, mycoplasma and viral safety data, storage and transport records, and batch-to-patient traceability. Commercial EV products lacking these documents should not be offered as routine treatment.

Product qualification and key quality requirements

Figure 1, step 3 summarizes the product qualification process. Before lot release or clinical use, the basic product file should define the product identity, formulation type, active ingredient or cargo, concentration, appearance, pH, osmolarity, excipients, container or device compatibility, route of administration, storage condition, and release criteria. At the point of care, staff should verify product identity, batch record, storage status, appearance, and readiness before injection. Sterility and endotoxin control are essential for all intra-articular products. Mycoplasma testing is required when relevant, especially for cell-derived and EV products.

Each platform needs focused quality assessment. For nanomedicines, size/aggregation, surface properties, drug loading/free drug, release kinetics, dilution and storage stability, and batch consistency should be assessed; cationic particles, immune-active payloads, and repeated dosing require closer review because local irritation or systemic escape may alter safety.[2]

Injectable hydrogels and depots should be assessed for composition, gelation, rheology, injectability, device compatibility, degradation, release, residual reagents, sterility, endotoxin, and in-use stability.[3]

EV and engineered EV products should be evaluated for source, purification, particle number/size, EV-associated and purity markers, sterility/endotoxin/mycoplasma when relevant, stability, potency, and batch consistency; engineered EVs also require engineering method, cargo loading, residual reagents, and comparability assessment.[4]

RNA delivery systems require documentation of RNA integrity, carrier-RNA ratio, encapsulation, nuclease protection, release behavior, target engagement, immune activation when relevant, off-target distribution, stability, and batch comparability.[5]

Therapeutic performance assessment

Pharmaceutical quality alone is not enough. Emerging intra-articular products should also show reproducible therapeutic performance linked to their proposed mechanism.

Clinical and biomarker outcomes should be selected according to knee OA trial standards and the proposed mechanism.

Preparation, administration, and traceability

Figure 1, step 4 describes the common workflow before injection. At receipt and before use, pharmacists or trained personnel should verify product documentation, storage status, patient identity, consent, target joint, dose, route, and relevant contraindications.

Preparation should follow product-specific instructions under aseptic conditions. Thawing, reconstitution, mixing, dilution, equilibration, and maximum in-use time should be documented. Products should not be pooled, transferred, diluted, warmed, or combined with other agents unless compatibility has been demonstrated. The delivered product, batch, dose, joint, operator, device, and injection conditions should be recorded to maintain product-batch-patient traceability.

Image-guided administration should be considered when anatomical landmarks are uncertain, precise intra-articular deposition is important, or the protocol requires confirmation of placement. When image guidance is used or required, the imaging modality, operator, target joint, confirmation of intra-articular placement, delivered product, batch, dose, device, and injection conditions should be included in the administration record and traceability checklist.

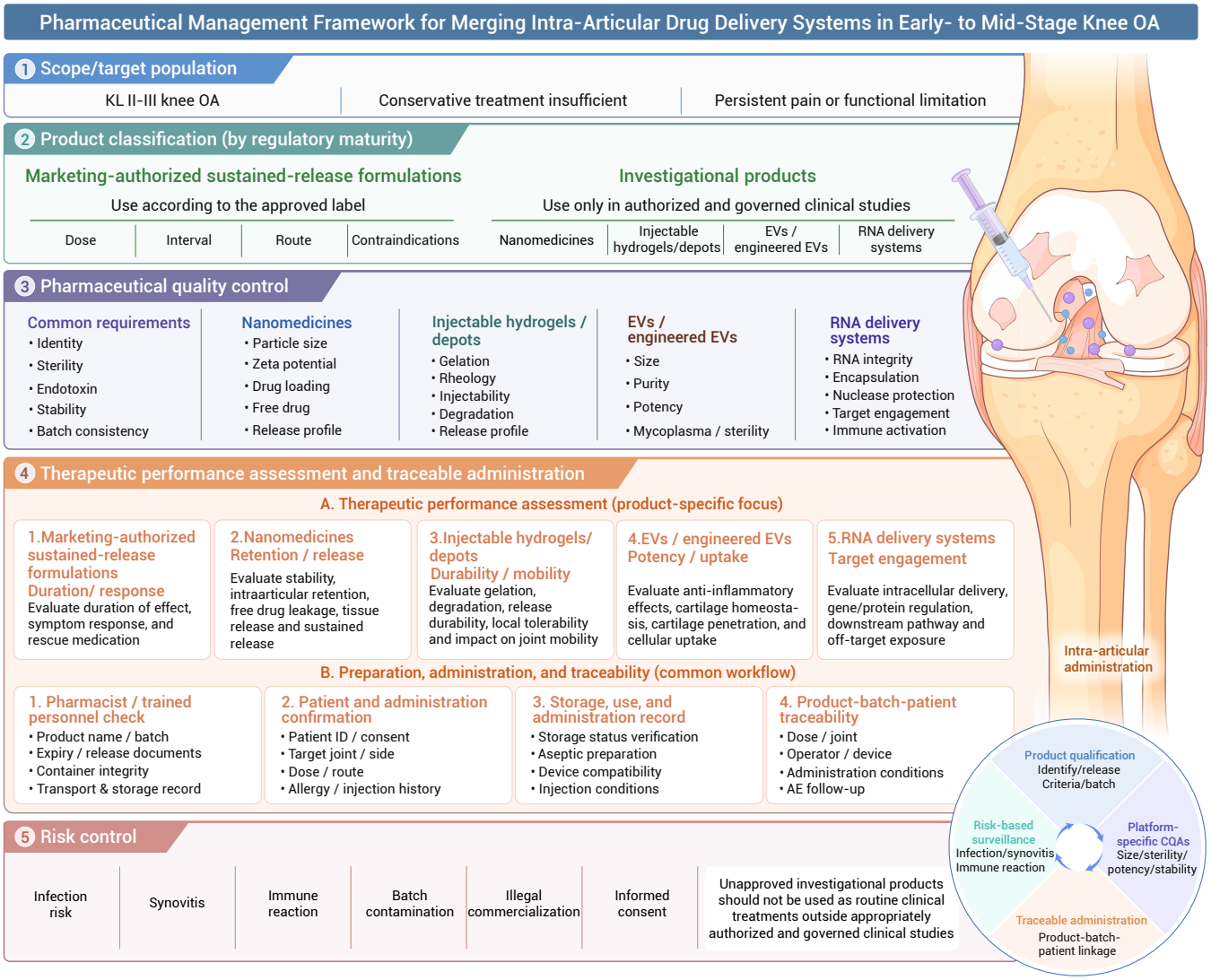

Figure 1. Pharmaceutical management framework for emerging intra-articular drug delivery systems in early- to mid-stage knee osteoarthritis The framework summarizes regulatory classification, product qualification, platform-specific quality attributes, therapeutic performance assessment, preparation and administration control, traceability, and risk-based pharmacovigilance. Investigational products should not be used as routine clinical treatments outside appropriately authorized and governed clinical studies.

Safety and pharmacovigilance

Figure 1, step 5 separates procedure-related and product-related risks. Procedure-related events include post-injection pain flare, bleeding, synovial irritation, extra-articular injection, and infection. Product-related risks include microbial contamination, residual reagents, formulation instability, immune activation, delayed synovitis, off-target exposure, and batch inconsistency.

Post-injection surveillance should monitor local pain, swelling, effusion, fever, allergy, infection, functional change, and delayed adverse events. Longer follow-up is needed for EV and engineered EV products, RNA systems, long-retention hydrogels, and repeated-dose nanomedicines when persistence, cargo activity, or immune risk is expected. Serious events should be reported. Products lacking traceability, release testing, storage records, or batch documentation should not be used.

CONCLUSION

Emerging intra-articular delivery systems for knee OA require management that goes beyond ordinary treatment selection. Clinical pharmacy management should verify whether the product is authorized or investigational, whether quality documentation is complete, whether preparation and injection are traceable, and whether safety monitoring is adequate. A clear product-risk-quality workflow can support safer and more consistent translation of advanced intra-articular therapies into clinical research and appropriately authorized clinical use.

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FUNDING AND ACKNOWLEDGMENTS

This work was supported by the Beijing Natural Science Foundation (L259080 to Y.L., 7254394 to W.W.). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.