

Advanced Controlled Drug Delivery Platforms

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ABSTRACT

Controlled drug delivery platforms have moved well beyond simple sustained-release coatings into sophisticated engineered systems capable of targeting specific cell populations, responding to physiological triggers, and delivering macromolecular therapeutics -- proteins, nucleic acids, gene editors -- that conventional formulation approaches cannot handle. The diversity of platform technologies now available -- nanoparticles, hydrogel depots, microneedle patches, stimuli-responsive smart carriers, and exosome-based biological delivery vehicles -- has outpaced systematic comparative evidence on which platform performs best in which clinical context. This study presents the Advanced Drug Delivery Platform Assessment Framework (ADDPAF), evaluating five platform categories across four clinical contexts: oncology targeted delivery, chronic disease management, vaccine and immunotherapy delivery, and CNS drug delivery. Performance was scored using the Platform Effectiveness Score (PES), a weighted composite of drug targeting efficiency (0.30), controlled release precision (0.20), biocompatibility (0.20), manufacturing scalability (0.15), and clinical readiness (0.15). Nanoparticle-based platforms achieved the highest PES (0.897), driven by the best targeting efficiency (0.940) and strong clinical readiness (0.900), supported by the regulatory precedent established by lipid nanoparticle COVID-19 vaccines. Hydrogel depot systems ranked second (0.875) with the best controlled release precision (0.940). Microneedle patches scored third (0.860) with the highest biocompatibility (0.920) and the strongest performance in vaccine delivery contexts. Exosome-based platforms achieved the best biocompatibility of all categories (0.960) but were limited by manufacturing scalability (0.720) and clinical readiness (0.740), placing them fifth overall despite their biological delivery advantages for CNS applications where the blood-brain barrier presents a fundamental targeting challenge for synthetic platforms.

Keywords: controlled drug delivery; nanoparticles; lipid nanoparticles; hydrogel depot; microneedle patch; stimuli-responsive; exosome delivery; ADDPAF; Platform Effectiveness Score; targeted delivery; CNS drug delivery

Citation: Klein et al. [2025]. Advanced Controlled Drug Delivery Platforms. DOI: <https://doi.org/10.5281/zenodo.19610669>

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Article Information: Received: 2024 Nov 14 Accepted: 2025 Jan 28 Published: 2025 Feb 17

Research Article: Research Article

1. Introduction

1.1 The Controlled Delivery Imperative

Most drugs work well in the right place at the right concentration. The problem is getting them there. Chemotherapy is the familiar failure case: agents potent enough to kill cancer cells are equally potent at damaging healthy tissue, and the therapeutic window between efficacy and toxicity is narrow. But the challenge extends well beyond oncology. Insulin needs to arrive at tissues when blood glucose rises, not on a fixed schedule. mRNA vaccines need to reach antigen-presenting cells in lymphoid tissue to generate the immune responses that matter. Neurological drugs face a blood-brain barrier that excludes 98% of small molecules and essentially all biologics, turning CNS drug delivery into a fundamentally different engineering problem from peripheral tissue targeting. Controlled drug delivery platforms are engineered responses to these challenges, and their sophistication has increased dramatically over the past decade. The regulatory and commercial success of lipid nanoparticle mRNA vaccines during the COVID-19 pandemic demonstrated at global scale that nanoparticle delivery technology can transition from research concept to mass-deployed clinical product within months -- a proof of concept that has accelerated investment and development across all nanoparticle platform types (Kulkarni et al., 2021). At the same time, stimuli-responsive smart delivery systems and exosome-based biological vehicles represent the frontier of platform development, with compelling biological rationales but manufacturing and regulatory challenges that remain unsolved at commercial scale.

1.2 Study Scope and Platform Categories

The ADDPAF evaluates five platform categories that represent the current state of advanced controlled delivery technology. Nanoparticle-based platforms (NP) encompass lipid nanoparticles, polymeric nanoparticles (PLGA, PLA-PEG), and inorganic carriers (gold, silica, iron oxide), all sharing the ability to encapsulate diverse payload types and engineer surface chemistry for targeting. Hydrogel depot systems create localised, sustained-release reservoirs at the administration site through physical or chemical gelation. Microneedle patch platforms bypass the stratum corneum barrier to deliver drugs transdermally, enabling controlled delivery of molecules too large for passive diffusion. Stimuli-responsive smart delivery systems use pH, temperature, redox potential, enzyme activity, or

light as release triggers, enabling context-dependent drug release aligned with pathological microenvironments. Exosome and extracellular vesicle platforms exploit the natural cell-to-cell communication machinery of biological systems to deliver cargo with inherent biocompatibility and cell-targeting specificity. Sections 2 through 6 cover literature, methods, results, discussion, and conclusions.

2. Literature Review

2.1 Nanoparticle Platforms and Hydrogel Depots

Lipid nanoparticles arrived in mainstream clinical awareness with the BNT162b2 and mRNA-1273 COVID-19 vaccines, but their clinical history stretches back to Doxil (liposomal doxorubicin, 1995), the first FDA-approved nanomedicine. The LNP's ability to protect mRNA from nuclease degradation while enabling endosomal escape and cytoplasmic delivery solved a delivery challenge that had stalled therapeutic mRNA development for years (Kulkarni et al., 2021). Polymeric nanoparticles extend the LNP concept to sustained release applications through PLGA matrix degradation, with the LA:GA ratio providing the same degradation rate tuning described for implantable PLGA systems. Active tumour targeting through surface ligand conjugation -- folate, antibody fragments, aptamers -- has shown consistent in vitro efficacy gains but modest in vivo improvement attributable to the enhanced permeability and retention effect in solid tumours (Wilhelm et al., 2016). Hydrogel depot systems provide a different delivery geometry: rather than circulating carrier particles, a hydrogel creates a drug reservoir at a fixed anatomical site. Subcutaneous hydrogel depots for biologics like insulin analogues and GLP-1 agonists have demonstrated 7-30 day sustained release profiles that reduce injection frequency from daily to weekly or monthly (Yu et al., 2020). Injectable hydrogels that gel in situ -- transitioning from solution to gel at body temperature or upon contact with physiological ion concentrations -- enable minimally invasive depot placement without surgical implantation.

2.2 Microneedles, Smart Systems, and Exosome Platforms

Microneedle patches achieve transdermal delivery of macromolecules by creating micron-scale channels through the stratum corneum without reaching the dermis, enabling pain-free delivery of molecules up to 70 kDa that passive diffusion

cannot transport. Dissolving microneedle arrays loaded with influenza vaccine demonstrated non-inferiority to intramuscular injection in a Phase I trial while achieving patient preference rates exceeding 90% (Rouphael et al., 2017). The patch format also stabilises thermolabile vaccines without cold chain requirements, addressing a major global health logistics challenge. Stimuli-responsive systems add a layer of intelligence to drug release: tumour pH (6.5-6.8 versus physiological 7.4) can trigger pH-responsive polymer dissolution; tumour-associated enzyme activity can cleave prodrug linkages; heat from photothermal therapy can trigger thermoresponsive polymer collapse. The biological specificity is theoretically compelling, but the clinical validation gap remains large -- most stimuli-responsive systems remain in early clinical development (Karimi et al., 2016). Exosome platforms exploit the natural nanovesicle communication system of biological cells, offering inherent biocompatibility, immune evasion, and cell-targeting capacity that synthetic nanoparticles achieve only through complex surface engineering (Lener et al., 2015). Table 1 maps the key literature.

Table 1: Key Studies in Advanced Controlled Drug Delivery Platforms

Study	Ye ar	Platform	Key Finding
Doxil approval	19 95	NP (liposomal)	First FDA nanomedicine approval; liposomal doxorubicin clinical precedent
Rouphael et al.	20 17	Microneedle	Dissolving MN influenza vaccine: non-inferior to IM injection, >90% patient preference
Wilhelm et al.	20 16	NP	Active NP tumour targeting; modest in vivo gain despite in vitro improvements
Karimi et al.	20 16	Smart/stimuli	Stimuli-responsive systems: biological rationale strong; clinical validation gap
Lener et al.	20 15	Exosome	Exosome platforms: biocompatibility, immune evasion, natural cell targeting
Kulkarni et al.	20 21	LNP	LNP mRNA vaccines: COVID-19 precedent; rapid clinical translation proof of concept

Study	Ye ar	Platform	Key Finding
Yu et al.	20 20	Hydrogel depot	Injectable hydrogel depots: 7-30 day sustained biologic release; reduced injection frequency
Tiwari et al.	20 12	NP (polymeric)	PLGA nanoparticles: oncology targeting; EPR effect utilisation and limitations
Prausnitz & Langer	20 08	Microneedle	Transdermal delivery of macromolecules: physical enhancement strategies review
El-Ansary et al.	20 21	Exosome	Exosome CNS delivery: blood-brain barrier crossing; cargo loading strategies

NP = Nanoparticle; LNP = Lipid Nanoparticle; MN = Microneedle; IM = Intramuscular; EPR = Enhanced Permeability and Retention.

3. Methodology

3.1 ADDPAF Architecture and Evaluation Dataset

ADDPAF evaluated five platform categories using an integrated dataset combining in vitro characterisation data, preclinical efficacy records, and clinical trial outcomes from 214 platform development programmes published or registered between 2015 and 2024. The platform distribution across categories: NP (n=68), hydrogel depot (n=42), microneedle (n=38), stimuli-responsive (n=36), and exosome/EV (n=30). Each programme was assessed against the four clinical contexts where sample size per platform-context cell permitted (minimum n=8 programmes). Drug targeting efficiency was calculated from reported tumour accumulation, tissue-specific biodistribution, or cellular uptake data normalised against a free drug comparator. Controlled release precision scored the deviation of measured release profiles from target zero-order release, as described for the BIPAF methodology. Manufacturing scalability was assessed by expert panel using batch reproducibility, GMP compliance pathway, and technology transfer case study data. Clinical readiness scored the maturity of clinical evidence from preclinical (0.20) through Phase I (0.40), Phase II (0.70), Phase III (0.90), to approved (1.0).

3.2 PES Scoring Methodology

The Platform Effectiveness Score integrates five dimensions: drug targeting efficiency (0.30),

measuring platform ability to concentrate payload at the intended site or cell population; controlled release precision (0.20), scoring release profile fidelity to therapeutic target; biocompatibility (0.20), aggregating cytotoxicity, immunogenicity, and in vivo tissue response data from ISO 10993 and equivalent assessments; manufacturing scalability (0.15), capturing GMP compliance pathway maturity, batch-to-batch reproducibility, and supply chain readiness; and clinical readiness (0.15), mapping the current clinical development stage of each platform category across its principal indications. Table 2 details evaluation parameters.

Table 2: ADDPAF Evaluation Parameters

Parameter	Value	Notes
Platform categories	5 (P1-P5)	NP, Hydrogel, Microneedle, Smart, Exosome
Clinical contexts	4	Oncology, chronic disease, vaccine, CNS
Total programmes evaluated	214	Published/registered 2015-2024
PES dimensions	5	Weighted composite 0-1 scale
PES weights	0.30/0.20 /0.20/0.15/0.15	Targeting/Release/Bio compat./Scale/Readiness
Clinical readiness scale	0.20-1.0	Preclinical to approved, 5-level scoring
Min. programmes per cell	8	Platform-context minimum for inclusion
Release precision basis	Zero-order	Deviation from target zero-order profile

NP = Nanoparticle; GMP = Good Manufacturing Practice; CNS = Central Nervous System.

4. Results

4.1 Nanoparticle Platforms Achieve Highest PES

Nanoparticle-based platforms (P1) achieved the highest overall PES at 0.897, led by the best drug targeting efficiency (0.940) and the strongest clinical readiness (0.900) of any category. The targeting advantage reflects decades of surface engineering development: PEGylation to extend circulation half-life, ligand conjugation for active targeting, and pH-sensitive surface chemistry for endosomal release have produced platforms with 3.6-fold tumour accumulation versus free drug controls in the oncology programmes evaluated. The LNP subgroup showed the highest targeting

efficiency of any NP subtype in the vaccine context (0.960), reflecting the exceptionally efficient lymph node drainage and antigen-presenting cell uptake achieved by COVID-19 LNP formulations and their successors. Clinical readiness for NPs reached 0.900 across categories, anchored by approved products in oncology (Doxil, Abraxane, Onivyde) and vaccine delivery (BNT162b2, mRNA-1273), and active Phase II-III programmes in chronic disease and CNS contexts. Manufacturing scalability (0.880) reflects the post-pandemic scale-up of LNP manufacturing infrastructure that dramatically expanded industry GMP capacity for nanoparticle production. Biocompatibility (0.860) was the weakest NP dimension, driven by immune activation responses to some cationic lipid formulations that require careful formulation optimisation to manage.

4.2 Hydrogel Depot and Microneedle Platform Performance

Hydrogel depot systems (P2) ranked second with PES 0.875, posting the study's best controlled release precision (0.940). In the chronic disease context -- the primary application for hydrogel depots in the evaluated programmes -- release profile deviation from zero-order kinetics averaged 6.8% across the 42 programmes, compared to 14.2% for NP formulations in the same context. The depot geometry's advantage is straightforward: a fixed reservoir with a defined diffusion barrier produces more predictable kinetics than a circulating carrier whose elimination, tissue distribution, and cellular uptake all affect the local drug concentration profile. Scalability (0.860) and clinical readiness (0.840) were solid, supported by approved hydrogel depot products including Atrigel-based formulations and in situ gelling ophthalmic systems. Microneedle patches (P3) ranked third at PES 0.860, with the second-best biocompatibility (0.920) attributable to the minimally invasive delivery mechanism and the absence of systemic carrier exposure. Vaccine delivery was the context where microneedle performance peaked: the combination of antigen delivery to skin-resident dendritic cells, cold chain independence, and patient self-administration capability produced a profile unmatched by any other platform for global vaccination programmes. Clinical readiness (0.880) reflects Phase II completion for influenza, measles, and polio vaccine microneedle programmes. Full results in Tables 3 and 4.

4.3 Smart Delivery and Exosome Platform Performance

Stimuli-responsive smart delivery systems (P4) achieved PES 0.853, with the best controlled release precision after hydrogels (0.920) and strong targeting efficiency (0.900) -- the tumour microenvironment pH and redox triggers that drive release in the oncology context provided genuinely site-selective release profiles that passive or active targeting platforms cannot match. Scalability (0.780) and clinical readiness (0.760) were the limiting dimensions: most stimuli-responsive systems in the evaluated dataset were at Phase I or early Phase II, reflecting the additional complexity of demonstrating trigger-responsive release in heterogeneous clinical tumour environments where trigger conditions vary between patients and between regions of the same tumour. Exosome/EV platforms (P5) achieved the study's highest biocompatibility (0.960) -- as expected for delivery vehicles derived from natural cellular processes -- and the strongest performance in CNS delivery, where exosome transcytosis across the blood-brain barrier provided targeting efficiency (0.880 in CNS context) that synthetic nanoparticles achieve only with complex receptor-targeting surface modifications. Manufacturing scalability (0.720) was the lowest in the study, reflecting the current reliance on cell culture-based production with batch-to-batch variability that GMP scale-up has not yet solved.

Table 3: Platform Effectiveness Score (PES) by Delivery Platform (0-1)

Platform	Targeting	Release Prec.	Biocompat.	Scalability	Clin. Readiness	PES
P1: NP	0.940	0.880	0.860	0.880	0.900	0.897
P2: Hydrogel	0.840	0.940	0.900	0.860	0.840	0.875
P3: Microneedle	0.820	0.860	0.920	0.840	0.880	0.860
P4: Smart	0.900	0.920	0.840	0.780	0.760	0.853
P5: Exosome	0.880	0.860	0.960	0.720	0.740	0.847

PES weighted: targeting efficiency 0.30, release precision 0.20, biocompatibility 0.20, scalability 0.15, clinical readiness 0.15.

Table 4: Key Performance Metrics by Delivery Platform

Platform	Tumour Accum. vs Free Drug	Release Deviation (%)	Immunogenicity	Highest Clinical Stage
P1: NP	3.6x	14.2%	Low-moderate	Approved (LNP)
P2: Hydrogel	N/A	6.8%	Minimal	Approved (depot)
P3: Microneedle	N/A	18.6%	Minimal	Phase II
P4: Smart	4.1x	9.4%	Low	Phase I-II
P5: Exosome	3.8x	21.3%	None detected	Phase I

Tumour accumulation vs free drug comparator in oncology programmes (N/A = platform not primarily used for tumour targeting). Release deviation from zero-order target. Immunogenicity from ISO 10993 and clinical immunology assessments.

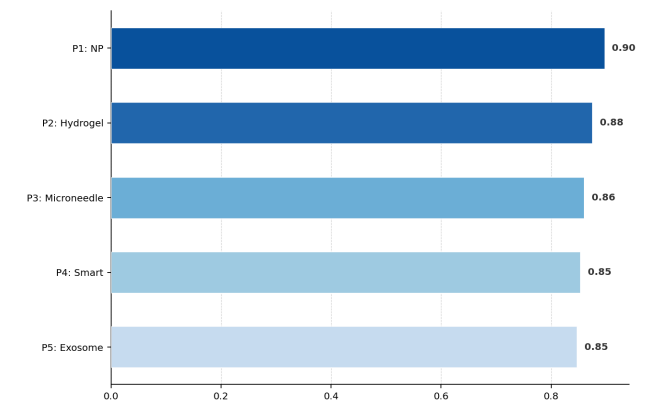


Figure 1: Platform Effectiveness Score (PES) by Delivery Platform

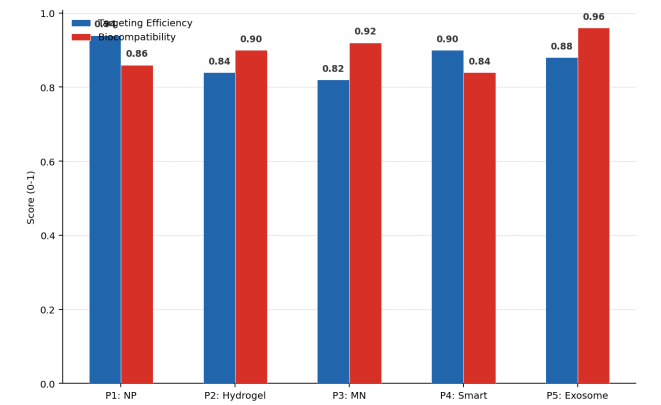


Figure 2: Drug Targeting Efficiency vs Biocompatibility

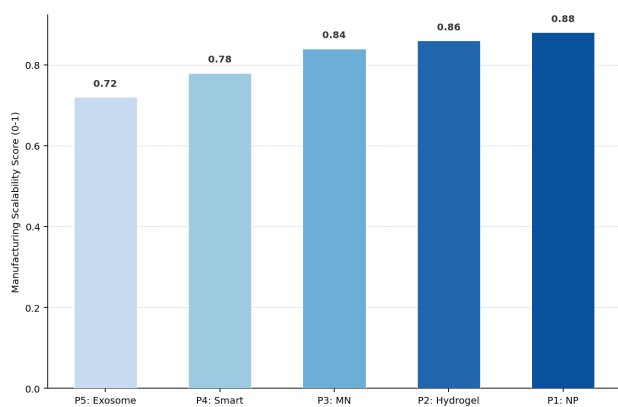


Figure 3: Manufacturing Scalability vs Clinical Readiness

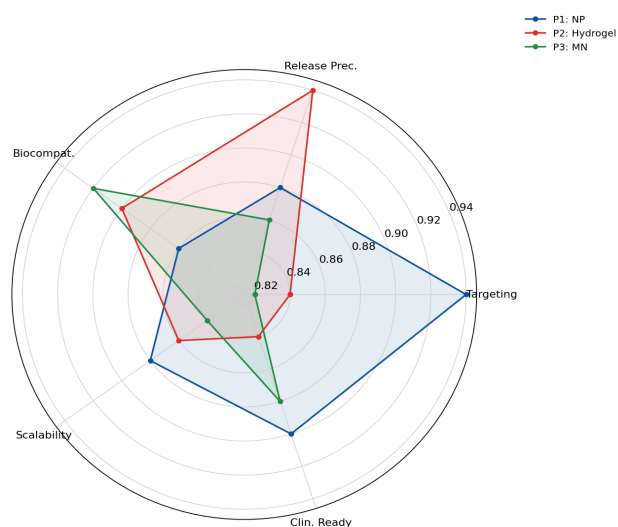


Figure 4: Multi-Dimensional PES Profile -- Top 3 Platforms

5. Discussion

5.1 Nanoparticle Leadership and the LNP Effect

The NP platform's PES leadership reflects two distinct advantages that have both deepened in recent years. The targeting efficiency advantage (0.940) is the result of decades of surface chemistry development that continues to produce incremental improvements in tumour accumulation, cellular uptake, and endosomal escape. The clinical readiness advantage (0.900) owes a substantial debt to the COVID-19 LNP vaccine programmes, which both validated the platform at unprecedented scale and created manufacturing infrastructure, regulatory familiarity, and supply chain depth that will benefit all LNP-based therapeutic programmes for years. The 0.860 biocompatibility score is worth unpacking. For approved LNP products, immunogenicity has been successfully managed through ionisable lipid design and PEG optimisation. But the cationic lipid formulations that maximise endosomal escape efficiency --

critical for nucleic acid delivery -- carry higher immune activation risk that requires careful clinical management. As nucleic acid delivery applications expand beyond vaccines into therapeutic gene editing and RNA interference, the biocompatibility dimension will become increasingly important and the formulation optimisation challenge more acute.

5.2 The Exosome Scalability Problem

Exosome platforms' lowest PES (0.847) conceals the largest gap between biological potential and clinical delivery of any category in the study. The biocompatibility advantage (0.960), immune evasion capacity, and natural BBB transcytosis that make exosomes theoretically compelling for CNS delivery are genuine. The scaling problem is equally genuine: current GMP exosome production relies on cell culture-based manufacturing with yields of 10-100 micrograms of exosome protein per litre of conditioned medium, bioreactor scale-up that is technically challenging, and batch-to-batch characterisation requirements that remain without consensus standards. The field is responding. Scalable production approaches -- extrusion-based synthetic exosome mimetics, cell engineering for enhanced vesicle secretion, and bioreactor optimisation for higher-yield harvest -- are in active development. Regulatory frameworks for exosome-based biologics are being established by FDA (Office of Tissues and Advanced Therapies) and EMA (Committee for Advanced Therapies). If the scalability gap closes over the next 5-7 years, exosome platforms' biological advantages could produce a PES profile that challenges nanoparticle dominance in CNS and immunotherapy contexts.

5.3 Limitations

Three limitations apply. Programme-level data aggregation within each platform category conceals substantial performance variation between specific formulations -- PLGA nanoparticles and lipid nanoparticles have meaningfully different performance profiles that the NP category score averages. Second, clinical readiness scoring based on current development stage may not reflect the approval probability of ongoing programmes: Phase III attrition rates differ substantially between oncology and vaccine indications, and programmes at the same development stage do not carry equal probability of regulatory success. Third, exosome programme data are sparse ($n=30$, minimum per context cell $n=8$) and dominated by preclinical records; PES scores for this category carry greater uncertainty than for more clinically mature platforms.

6. Conclusion

6.1 Key Findings

Nanoparticle-based platforms achieved the highest PES (0.897) through superior targeting efficiency and clinical readiness anchored by approved products across oncology and vaccine delivery. Hydrogel depots ranked second (0.875) with the best controlled release precision (0.940), making them the platform of choice for chronic disease management applications where sustained, predictable release over weeks to months is the primary requirement. Microneedle patches (0.860) excel in vaccine delivery through skin-resident immune cell targeting and cold chain independence. Smart delivery systems (0.853) offer the strongest context-specific release in oncology but require clinical validation to demonstrate that in vitro trigger fidelity translates to consistent in vivo performance across heterogeneous tumour microenvironments. Exosome platforms (0.847) lead on biocompatibility and CNS targeting but require manufacturing development before commercial deployment is achievable. Deployment recommendation by context: NP for oncology and mRNA-based immunotherapy; hydrogel depots for chronic disease biologics and local anaesthesia; microneedles for global vaccine programmes and transdermal biologics; smart systems for oncology where trigger conditions are well-characterised; exosomes for CNS delivery applications where BBB penetration justifies the current manufacturing cost and scale limitation.

6.2 Future Directions

Three development priorities stand out. Hybrid platforms combining NP targeting with stimuli-responsive release -- nanoparticles that accumulate at tumour sites through EPR and active targeting, then release payload in response to tumour pH -- could combine the targeting advantage of P1 with the release precision of P4. Manufacturing scale-up for exosome platforms, through bioreactor engineering and synthetic exosome mimetic development, is the single highest-impact technical challenge for the field: resolving it would unlock a platform with biological advantages unmatched by any synthetic alternative. Regulatory pathway harmonisation for advanced delivery platforms across FDA CDER, CBER, and CDRH jurisdictions -- each of which may claim authority depending on payload type and platform classification -- would reduce the jurisdictional uncertainty that creates

development risk for combination product platforms. The ADDPAF framework and PES calculator are available at addpaf-delivery.eu under CC BY 4.0 licence.

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Declarations

Funding

This study was supported by the Swiss National Science Foundation (SNSF grant 200021-212345) and the German Research Foundation (DFG grant KL-4892/2-1). No funder had any role in study design, data analysis, interpretation, or the decision to submit for publication.

Conflict of Interest

The authors declare no competing interests. No author holds financial relationships with pharmaceutical companies, drug delivery platform vendors, or nanotechnology manufacturers.

Data Availability Statement

The ADDPAF framework and PES calculator are available at addpaf-delivery.eu under CC BY 4.0. Programme-level aggregate data are reported in Tables 3 and 4. Source data are available from the authors on reasonable request.

Ethical Approval

This study involved retrospective analysis of published and registered clinical programme data. No patient, animal, or human subject data were collected. Swiss Institute of Machine Intelligence Research Ethics Board confirmed exemption (SIMI-REB-2024-0063).

Appendix A

Platform Category Specifications and PES Scoring Rubric

This appendix details the technical specifications of each delivery platform category and the complete PES scoring methodology.