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A Navigation Constitution for Autonomous Nanocarriers Crossing Biological Barriers under Uncertainty, Off-Target Risk, and Human Oversight

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ABSTRACT

Nanocarriers designed to alter their behavior in response to biological conditions create a safety problem that extends beyond conventional formulation quality and passive targeting. Their sensed inputs may influence transport, surface exposure, cellular entry, intracellular trafficking, or payload release, allowing uncertainty at one stage to propagate into later and potentially irreversible actions. This Original Governance and Control Theory Article proposes a navigation constitution for organizing such condition-dependent behavior without assuming cognition, unrestricted agency, or validated autonomous performance. The architecture separates sensing, barrier-state estimation, uncertainty assessment, authorization, material action, consequence verification, logging, and human intervention. It establishes distinct permissions for observation, route adaptation, and drug release; contracts the permitted action set when evidence is uncertain or contradictory; and gives prohibited-state signals priority over therapeutic mission signals. Biological-barrier recognition is treated as a probabilistic and revisable estimate because biodistribution, protein-corona evolution, cellular uptake, and intracellular release can vary across compartments and contexts. Traceability requirements connect formulation identity, observed cues, inferred states, authorized actions, deviations, and consequences, while intervention rights preserve human authority to stop, redesign, or withdraw a system. Preclinical evaluation is organized around nominal, ambiguous, conflicting, off-target, failure, and rescue scenarios. Manufacturing assessment must determine whether scale-up and lot variation preserve conditional behavior rather than only conventional particle attributes. The proposed constitution is an original conceptual synthesis requiring product-specific computational, experimental, manufacturing, and translational validation. It does not establish clinical safety, regulatory acceptance, universal applicability, or deployment readiness.

Key words: *Nanocarrier, Nanomedicine, Targeted drug delivery, Biological barriers, Intracellular release, Biodistribution*

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INTRODUCTION

Nanomedicine seeks to coordinate material design, payload protection, biodistribution, tissue access, cellular interaction, and therapeutic exposure. These functions are interconnected: optimization of circulation or accumulation does not necessarily establish delivery to the intended cell, intracellular compartment, or

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pharmacologically relevant site. Precision delivery therefore requires integration of carrier engineering with biological context, while heterogeneous disease environments and development constraints continue to limit translation [1-3].

Responsive nanocarriers extend this problem by linking biological or externally applied cues to changes in carrier behavior. Such systems may alter shielding, adhesion, penetration, membrane interaction, intracellular trafficking, or payload release. Yet responsiveness alone does not demonstrate that a signal accurately identifies a biological state, that the resulting action is appropriate, or that the same relationship will persist across patients, models, manufacturing lots, and disease stages.

This article defines adaptive nanocarrier autonomy narrowly as predesigned material state transitions that occur without contemporaneous human command. The term does not imply consciousness, general reasoning, moral agency, or unrestricted decision-making. It describes bounded conditional behavior encoded through physicochemical, biological, or biohybrid components. Because these transitions may be sequential and partly irreversible, they require governance at the level of permissions, evidence thresholds, prohibited actions, traceability, and intervention.

The objective is to propose a navigation constitution that separates what a carrier can detect from what it may infer and what it may do. The constitution organizes sensing, navigation, release, abstention, fail-safe behavior, logging, and human oversight within a unified supervisory architecture. It is an original non-empirical contribution intended to generate testable propositions and validation requirements, not a clinical guideline, regulatory standard, or claim that present nanocarriers already satisfy the proposed controls.

Why adaptive nanocarrier autonomy changes the safety problem

Conventional nanocarrier safety assessment commonly begins with composition, critical material attributes, dose, biodistribution, degradation, payload exposure, and toxicity. These remain essential, but a condition-dependent carrier introduces an additional question: whether its next action is justified by its present evidence. Safety therefore depends not only on what the product is, but also on the sequence of states through which it moves and the rules connecting observations to actions.

The biological environment does not provide an unambiguous navigation map. Nanoparticles may enter solid tumors through mechanisms that differ from simplified permeability assumptions; bulk tumor accumulation may not correspond to substantial exposure of intended cancer cells; and the acquired protein corona can change cellular internalization pathways [4-6]. These findings support the broader conclusion that administered identity, destination-level accumulation, and realized cellular behavior are distinct evidence domains.

Adaptive behavior can amplify this separation. A false cue interpretation may expose a targeting ligand in the wrong compartment, increase retention in an off-target tissue, promote uptake by an unintended cell population, or initiate premature release. The consequence may then alter later observations, creating feedback between carrier action and biological state. This sequential dependence differs from a fixed formulation whose major behavior is specified before administration.

The proposed interpretation is therefore that autonomy changes safety from a predominantly property-based question into a bounded control problem. The relevant unit of evaluation becomes an evidence–state–permission–action–consequence chain. Alternative explanations, including nonspecific adsorption, passive transport, stochastic release, assay interference, or disease-related heterogeneity, must remain viable until excluded. A responsive outcome cannot be attributed to successful navigation merely because it is consistent with the intended design.

Proposed navigation constitution

A navigation constitution is proposed as a set of prior constraints governing what an adaptive carrier may sense, infer, and execute. Its mission envelope specifies the indication, administration route, intended destination, payload, acceptable exposure conditions, prohibited tissues, and anticipated biological transitions. Actions outside that envelope are not treated as exploratory successes; they are deviations requiring abstention, fail-safe behavior, or redesign.

The constitution contains twelve linked constructs: observable cue, signal-quality assessment, barrier-state estimate, uncertainty state, sensing permission, navigation permission, release permission, authorization gate, abstention state, prohibited state, fail-safe state, and human intervention right. A traceable event record connects these constructs to formulation identity and observed consequences. Minimum reporting, reproducible

characterization, and integration across bio–nano domains are necessary because an adaptive action cannot be interpreted when its material and biological context cannot be reconstructed [7-9].

The proposed control sequence is: sense, qualify, estimate, quantify uncertainty, test authorization, act or abstain, verify, log, and permit intervention. Observation is deliberately separated from interpretation, and interpretation from permission. A detectable cue may justify recording a signal without justifying route adaptation. Likewise, evidence sufficient for a reversible surface transition may remain insufficient for irreversible payload release.

Authority is hierarchical. Prohibited-state evidence overrides a positive mission signal. Greater uncertainty contracts rather than expands the available action set. Crossing a materially different biological compartment triggers renewed state estimation because evidence generated in blood, tumor interstitium, an endosome, or another environment may not remain transportable. Human investigators and accountable product developers retain authority to interrupt evaluation, revise the mission envelope, invalidate a decision rule, or withdraw the system.

Figure 1 presents the original conceptual synthesis for navigation constitution for autonomous nanocarriers, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

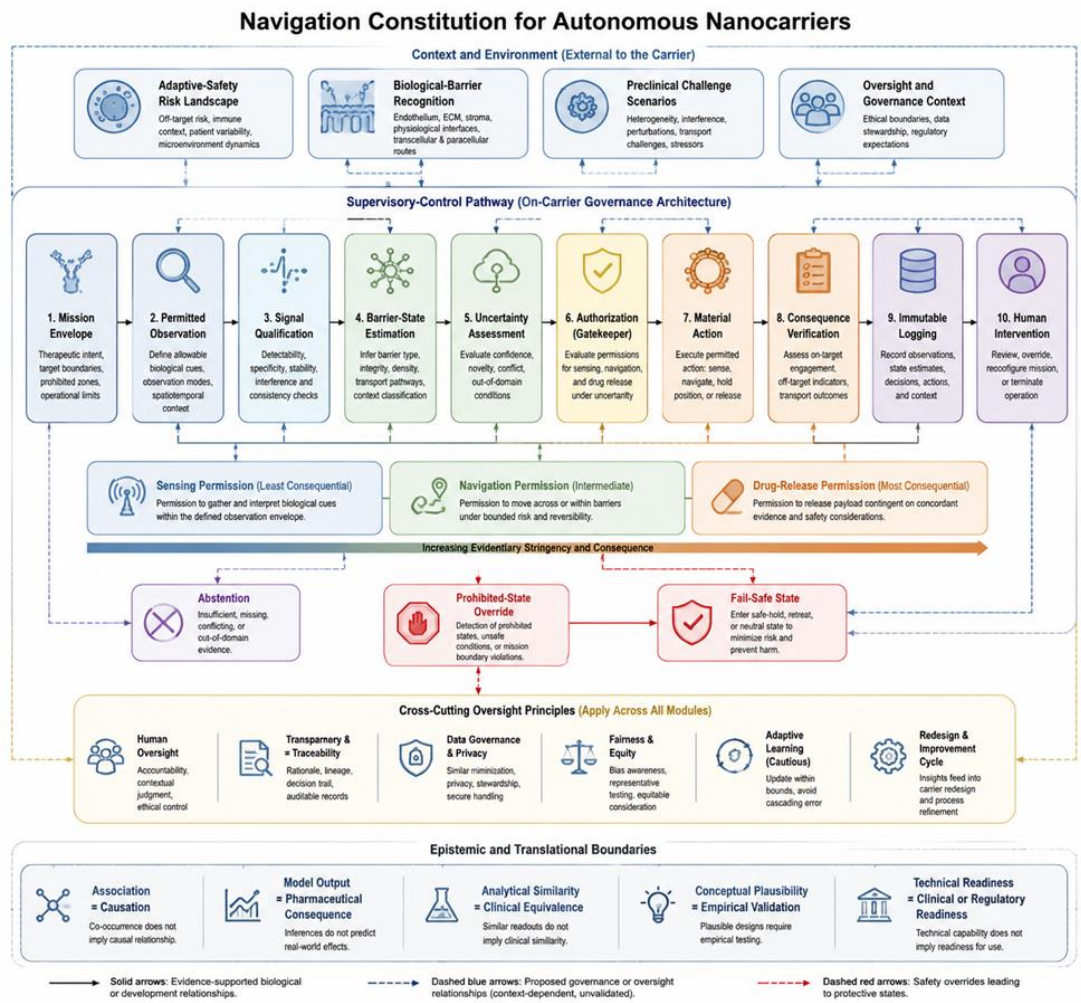

Figure 1. Navigation Constitution for Autonomous Nanocarriers

The figure should be read as a constitutional map rather than a mechanistic claim about a particular platform. Some links—such as biological identity influencing uptake or stimuli influencing material transitions—are supported by existing evidence. The permission hierarchy, uncertainty-contraction rule, barrier-transition reset, prohibited-state dominance, and intervention architecture are newly proposed relationships that require independent validation.

Permitted sensing and response functions

Permitted sensing functions may include detection of pH, redox state, enzymes, metabolites, temperature, light, magnetic or acoustic input, membrane interactions, cellular products, or elapsed time. Stimuli-responsive systems demonstrate that such cues can be coupled to changes in carrier structure or payload exposure [10]. However, a measurable response establishes only that the system reacts under specified conditions; it does not prove accurate tissue recognition or appropriate therapeutic authorization.

Response functions should be classified by consequence. Lower-consequence functions include observation, signal reporting, or maintenance of the existing state. Intermediate functions include reversible shielding changes, altered adhesion, bounded penetration, or modified intracellular trafficking. High-consequence functions include membrane disruption, substantial retention changes, and drug release. Multistage nanoparticles illustrate that several environmental conditions can be linked to sequential penetration and therapeutic functions, but their product-specific performance does not establish a universal navigation rule [11].

Biohybrid and membrane-coated carriers may introduce biological interactions, immune-evasive properties, or recognition-associated functions. They also create dependencies on cell source, membrane composition, preparation, stability, and lot consistency [12]. Such interfaces should therefore be treated as variable sensing or interaction components rather than as self-validating evidence of tissue identity.

The constitution permits an action only when its evidence is proportional to its reversibility and potential harm. Conflicting, missing, unstable, or out-of-domain signals require abstention or a less consequential action. Release cannot be authorized merely because a cue is detectable, and an external trigger cannot substitute for confirmation that carrier location and payload exposure remain compatible with the mission envelope. These are proposed decision rules requiring product-specific testing.

Biological-barrier recognition and navigation rules

Biological-barrier recognition should be treated as probabilistic state estimation rather than direct knowledge of location. A nanocarrier may encounter plasma proteins, vascular endothelium, extracellular matrices, immune cells, tumor-associated compartments, cellular membranes, endosomes, lysosomes, or cytosol. Each transition may alter the carrier's accessible surface, local cue profile, transport behavior, and interaction partners. The constitution therefore prohibits equating one biomarker or environmental signal with definitive compartment identity.

Barrier passage may change the carrier itself. Protein-corona composition has been shown to evolve across the blood–brain barrier, indicating that biological identity established in one compartment may not remain stable after transition to another [13]. The proposed barrier-transition reset therefore downgrades previous state estimates whenever the carrier enters a materially different biological environment. Continued navigation then requires renewed signal qualification rather than automatic continuation of the preceding action sequence.

Cellular uptake must also be distinguished from successful intracellular delivery. Internalization may lead to endosomal sequestration, degradation, recycling, or incomplete payload access rather than cytosolic exposure. Endosomal escape is a separate and difficult-to-measure barrier, and evidence of uptake alone cannot authorize a claim of intracellular delivery [14]. Release rules should therefore specify the required intracellular compartment and include orthogonal evidence for payload availability at the intended site.

Computational models may help connect systemic transport, vascular passage, tissue penetration, cellular uptake, and intracellular trafficking, but their outputs remain dependent on assumptions, parameter quality, and domain coverage [15]. Model-supported navigation should include uncertainty estimates, sensitivity analysis, and out-of-domain detection. Simulation consistency may justify further testing, but it does not establish biological recognition, causal mechanism, or pharmaceutical consequence.

Evidence thresholds for route adaptation and release

Authorization should be proportional to action consequence. Observation or signal recording may require analytical detectability and specificity. Reversible route adaptation requires evidence that the inferred state is credible and that the action remains bounded. Irreversible payload release requires the strongest evidence because incorrect authorization may generate off-target exposure that cannot be recalled.

Carrier geometry is one determinant of transport, uptake, circulation, and biological interaction. Shape effects vary with material, size, surface, flow, tissue, and cell context, preventing a universal geometric rule from serving as an authorization threshold [16]. The constitution therefore requires product-specific evidence linking a material attribute to the proposed action in the relevant biological environment.

Evidence must also isolate interacting material variables. Controlled comparisons show that nanoparticle core composition can alter cellular uptake and cytotoxicity even when shape, size, and surface chemistry are constrained [17]. A response attributed to a targeting ligand or stimulus may therefore arise partly from unmeasured material differences. Authorization rules should be supported by factorial or otherwise discriminating experiments that separate cue response from composition-dependent behavior.

Predictive models may support barrier-state estimation or biodistribution hypotheses. Supervised learning based on nanomaterial-associated biological signatures has demonstrated the possibility of predicting aspects of in-vivo fate [18]. Nevertheless, model output should influence action only within a defined domain, with calibration, external testing, uncertainty assessment, and abstention under unfamiliar conditions.

Table 1 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for definitions, components, relationships, and intended uses in a navigation constitution for autonomous nanocarriers crossing biological barriers.

Table 1. Definitions, components, relationships, and intended uses in A Navigation Constitution for Autonomous Nanocarriers Crossing Biological Barriers

Component or scientific dimension	Problem addressed	Inputs or determinants	Proposed mechanism or relationship	Expected contribution	Evidence required	Failure or uncertainty risk	Boundary statement
Mission envelope	Unbounded interpretation of carrier behavior	Indication, route, payload, intended destination, prohibited tissues	**Proposed:** defines the permissible operational domain before testing	Constrains claims and actions	Product- and context-specific specification	Mission drift or post-hoc redefinition	Does not establish safety or efficacy
Observable cue	Confusion between detection and recognition	Chemical, enzymatic, physical, cellular, temporal, or external signals	Cue detection precedes state interpretation	Separates measurement from inference	Analytical specificity, stability, interference testing	Cross-reactivity, missing signal, assay artifact	A detectable cue does not prove tissue identity
Biological identity	Difference between administered and in-vivo carrier states	Protein adsorption, biomolecular exchange, compartment transition	Biological interfaces may alter uptake and transport [13]	Supports state reassessment	Dynamic characterization across relevant compartments	Corona drift and context dependence	Findings from one barrier cannot be generalized universally
Barrier-state estimate	Incomplete observability of location and transport state	Qualified cues, model inputs, biological context	**Proposed:** probabilistic estimate rather than direct knowledge	Supports bounded navigation decisions	Orthogonal measurements and uncertainty analysis	Misclassification or out-of-domain inference	Model output is not direct biological proof
Intracellular-delivery state	Equating uptake with functional delivery	Uptake, endosomal trafficking, escape, payload availability	Uptake and endosomal escape require separate evaluation [14]	Prevents premature release claims	Compartment-specific and functional assays	Sequestration, recycling, degradation	Internalization does not establish cytosolic delivery
Sensing permission	Automatic escalation from signal to action	Signal quality and relevance	**Proposed:** permits observation without route alteration	Preserves information while limiting harm	Validated sensing assay	False or unstable cue	Sensing is not therapeutic authorization
Navigation permission	Uncontrolled changes in transport or retention	State estimate, reversibility, geometry, off-target risk	**Proposed:** permits bounded route adaptation	Enables conditional behavior with limits	Mechanistic and biodistribution evidence [16]	Off-target adhesion, retention, or penetration	No universal material attribute guarantees navigation

			under defined evidence				
Release permission	Irreversible payload exposure	Concordant state evidence, payload risk, localization	**Proposed:** highest authorization burden	Reduces false release	Compartment-specific release and safety evidence	Premature or ectopic exposure	No generic cue establishes release readiness
Uncertainty state	Action under ambiguous evidence	Confidence, cue conflict, model domain, missing data	**Proposed:** increasing uncertainty contracts permissions	Supports abstention	Calibration and challenge testing [18]	Miscalibration or hidden distribution shift	Uncertainty estimates require independent validation
Prohibited state	Positive mission cues overriding safety	Immune, off-target, toxic, or unknown conditions	**Proposed:** safety signal dominates mission signal	Prevents escalation	Sensitive prohibited-state assays	Undetected hazard or false alarm	A proposed override is not validated until tested
Fail-safe state	Lack of response to unsafe conditions	Prohibited-state signal, failed gate, human command	**Proposed:** non-release, deactivation, sequestration, or clearance	Limits continued harmful action	Demonstrated activation and consequence	Fail-safe failure or added toxicity	A conceptual fail-safe is not an established rescue mechanism
Human intervention right	Loss of accountable control	Logs, monitoring, prespecified stopping criteria	**Proposed:** people retain stop, redesign, rescue, and withdrawal authority	Preserves accountability	Operationally feasible oversight	Delayed or ineffective intervention	Oversight cannot compensate for an intrinsically unsafe design

Off-target safeguards and fail-safe states

Off-target protection should be designed as an active constitutional layer rather than inferred from targeting performance. A carrier may accumulate outside the intended tissue, encounter a similar cue in normal physiology, activate immune pathways, or release payload after nonspecific uptake. Positive evidence of target interaction must therefore be interpreted alongside evidence for prohibited states.

Infusion reactions and immune activation are material risks for some nanomedicines and may depend on product, patient, dose, and administration context [19]. The constitution proposes that validated signs of a prohibited immune state override navigation or release permission. This rule does not specify a universal biomarker; each product would require justified indicators, detection windows, and intervention procedures.

Fail-safe states may include maintained non-release, loss of binding functionality, deactivation of a responsive element, sequestration, accelerated clearance, or termination of an external trigger. Their suitability depends on carrier chemistry, payload, route, and timing. Smart-carrier functions do not remove toxicity associated with the material, payload, degradation products, or off-target exposure [20].

A fail-safe claim requires more than demonstrating that a system can be switched under ideal conditions. Testing must examine delayed activation, partial activation, competing cues, biological fouling, manufacturing variation, and unintended effects of the safeguard itself. When no credible fail-safe is technically feasible, the mission envelope should narrow and the permissible action should remain less consequential.

Logging, traceability, and intervention rights

Adaptive behavior is interpretable only when the chain from formulation to consequence can be reconstructed. The proposed event record includes material identity, manufacturing lot, administration context, observed cues, preprocessing, inferred barrier state, uncertainty estimate, authorization outcome, material response, deviation, and measured consequence. Logging may be molecular, analytical, experimental, digital, or distributed across these forms.

Data should be findable, structured, interoperable, and reusable where feasible. FAIR assessment of nanosafety information demonstrates that metadata quality and community standards materially affect whether data can be reused and evaluated [21]. FAIRness, however, concerns accessibility and structure; it does not establish that the underlying experiment is valid or that a biological interpretation is correct.

Provenance should preserve transformations between raw observations and inferred conclusions. Curated nanomaterial toxicogenomic resources illustrate the importance of harmonized identities, exposure conditions,

biological context, and processing history [22]. An autonomous-carrier claim is weakened when the material tested, cue measured, state inferred, or action executed cannot be linked unambiguously.

Human oversight includes authority to challenge an inferred state, halt escalation, alter an external trigger, initiate rescue procedures, reject a manufacturing lot, revise the mission envelope, or terminate development. Intervention rights must be technically feasible within the time scale of the potential harm. A nominal right that cannot be exercised before irreversible release is not an effective safeguard.

Table 2 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for testable propositions, evidence requirements, and validation criteria for a navigation constitution for autonomous nanocarriers crossing biological barriers.

Table 2. Testable propositions, evidence requirements, and validation criteria for A Navigation Constitution for Autonomous Nanocarriers Crossing Biological Barriers

Architecture layer or process stage	Core function	Information or material flow	Interaction with other components	Validation criterion	Potential failure mode	Human or experimental responsibility	Readiness boundary
Mission specification	Define intended and prohibited operation	Product profile to testable mission envelope	Constrains all later gates	Prespecified, internally consistent, experimentally addressable	Post-hoc expansion of intended use	Define route, destination, payload, and exclusions	Specification alone does not establish readiness
Sensing gate	Detect a candidate cue	Biological signal to qualified observation	Feeds state estimation without automatic action	Specificity, stability, interference resistance, temporal relevance	False detection or missed cue	Validate assays and negative controls	Cue detection does not authorize navigation
State-estimation layer	Infer biological compartment or condition	Qualified observations to probabilistic state	Supplies uncertainty to authorization gate	Calibration, external challenge, out-of-domain detection	Misclassification or overconfidence	Test competing explanations and domain shift	Prediction is not direct measurement
Navigation gate	Permit bounded transport adaptation	State and uncertainty to reversible material response	Must remain subordinate to prohibited-state logic	Reproducible, bounded action with off-target assessment	Excess adhesion, penetration, or retention	Compare intended and unintended tissues	Technical response is not clinical benefit
Barrier-transition reset	Reassess after compartment change	New environment to updated state estimate	Invalidates unsupported prior assumptions	Demonstrated transportability or successful re-estimation	Carryover of obsolete state	Sample sequential compartments and time points	One-compartment validation is insufficient
Release gate	Permit payload exposure	Concordant state evidence to irreversible action	Highest-consequence gate	Localization, release specificity, payload safety, consequence verification	Premature or off-target release	Use orthogonal localization and functional assays	Preclinical authorization is not clinical authorization
Uncertainty-contraction rule	Reduce action under ambiguity	Confidence and conflict to narrower permission set	Applies to sensing, navigation, and release	Correct abstention under ambiguous and unfamiliar conditions	Escalation despite uncertainty	Include missing, noisy, and contradictory inputs	No universal confidence threshold is proposed
Prohibited-state override	Stop mission-directed escalation	Safety signal to abstention or fail-safe state	Overrides positive targeting evidence	Sensitive detection and reliable override	Missed hazard or inappropriate shutdown	Define safety triggers and stopping rules	Requires product-specific validation

Fail-safe layer	Limit continued harmful behavior	Failed gate or override to non-release or deactivation	Receives human and system stop signals	Specific activation without unacceptable secondary harm	Failure, delay, or added toxicity	Test rescue and failure conditions	Conceptual availability is not proven effectiveness
Immutable event record	Preserve traceability	Identity, evidence, decisions, actions, consequences	Spans all layers	Reconstructable evidence–state–action chain [21]	Missing provenance or incompatible formats	Maintain data governance and auditability	Logging does not compensate for invalid science
Human intervention layer	Preserve accountable authority	Monitoring and records to stop, rescue, or redesign	Can interrupt every authorization stage	Intervention is timely, feasible, and prespecified	Delayed recognition or ineffective control	Assign accountable roles and escalation procedures	Human oversight cannot validate unsafe autonomous behavior
Manufacturing comparability	Preserve conditional function across lots	Process inputs to material and behavioral attributes	Determines whether authorization evidence remains applicable	Comparable cue sensitivity, response, release, and fail-safe behavior	Policy drift despite similar mean particle properties	Link process changes to functional testing	Analytical similarity does not establish clinical equivalence

Preclinical evaluation scenarios

Preclinical evaluation should examine the constitution as a sequence of claims rather than as a single efficacy endpoint. In-vitro measurements of cue response, transport, or release require an explicit relationship to in-vivo behavior and the intended decision. Nanomedicine in-vitro–in-vivo correlation remains context-dependent and cannot be presumed from apparent similarity between assays [23].

A nominal scenario tests the intended cue sequence in the intended model. More informative challenge scenarios introduce absent cues, excessive cues, competing signals, altered temporal order, off-target tissues, immune activation, endosomal trapping, and manufacturing variation. Relevant controls should distinguish passive accumulation, nonspecific uptake, spontaneous leakage, assay interference, and carrier-independent payload effects.

Preclinical study design should include relevant disease models, appropriate controls, biodistribution, target-cell exposure, intracellular localization, payload release, safety observations, and transparent reporting [24]. No single model can represent the full heterogeneity of human biological barriers. Evidence should therefore be framed according to the specific claim and model domain rather than aggregated into a generic success designation.

Rescue scenarios should test whether abstention, non-release, deactivation, or external interruption can function after partial progression through the authorization sequence. Negative results are informative because they identify where the constitution is technically infeasible. Passing a proposed preclinical gate would support only the prespecified experimental claim and would not establish clinical safety, regulatory acceptance, or patient benefit.

Manufacturing and translational constraints

Conditional behavior introduces critical quality questions beyond average particle size, loading, morphology, and release profile. Logic-bearing attributes may include cue-sensitive bonds, surface orientation, membrane composition, ligand accessibility, sensor density, response kinetics, payload distribution, and fail-safe functionality. These attributes must be linked to material and process variables through a risk-based development strategy.

Quality-by-design approaches can help connect critical material attributes, process parameters, analytical methods, and intended performance in nanomedicine development [25]. The proposed extension is that conditional permissions should also become part of the product-control strategy. A lot should not be considered constitutionally comparable merely because conventional summary attributes remain similar.

Scalable microfluidic manufacture has shown that defined nanomedicine attributes can be preserved from laboratory preparation toward GMP-oriented production in a bounded liposomal case study [26]. This evidence

supports the feasibility of systematic scale-up but not universal scale invariance. Mixing regime, raw materials, surface composition, sterilization, storage, and administration preparation may alter sensing or response behavior. Translation therefore requires lot-to-policy equivalence: evidence that manufacturing change has not altered the mapping between cue, state estimate, authorization, response, and fail-safe behavior. Analytical similarity remains distinct from clinical equivalence. A reproducible manufacturing process does not establish therapeutic readiness unless biological function, safety, monitoring, and intervention remain credible in the intended context.

Limitations and research priorities

The proposed constitution may be unnecessary for passive carriers or narrowly responsive systems that can be governed adequately through conventional specifications and release controls. Its value increases when a carrier performs sequential, context-dependent, or difficult-to-reverse transitions. Even then, the framework may add conceptual clarity without being technically implementable.

Current smart nanomedicine remains constrained by heterogeneous biology, limited delivery efficiency, variable target access, incomplete mechanistic understanding, and translational difficulty [27]. The constitution cannot remove these limitations. It may instead make unsupported assumptions more visible by requiring explicit states, permissions, uncertainty, and stopping conditions.

Research priorities include dynamic characterization of biological identity, calibrated state estimation, formal specification of forbidden transitions, multi-cue challenge testing, barrier-transition models, quantitative off-target assessment, independently testable fail-safes, and lot-to-policy equivalence. Translation should integrate material design, biological evidence, manufacturing, preclinical evaluation, clinical context, and implementation rather than treating isolated technical success as readiness [28].

Figure 2 presents the original conceptual synthesis for authorization gates for sensing, navigation, and drug release, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

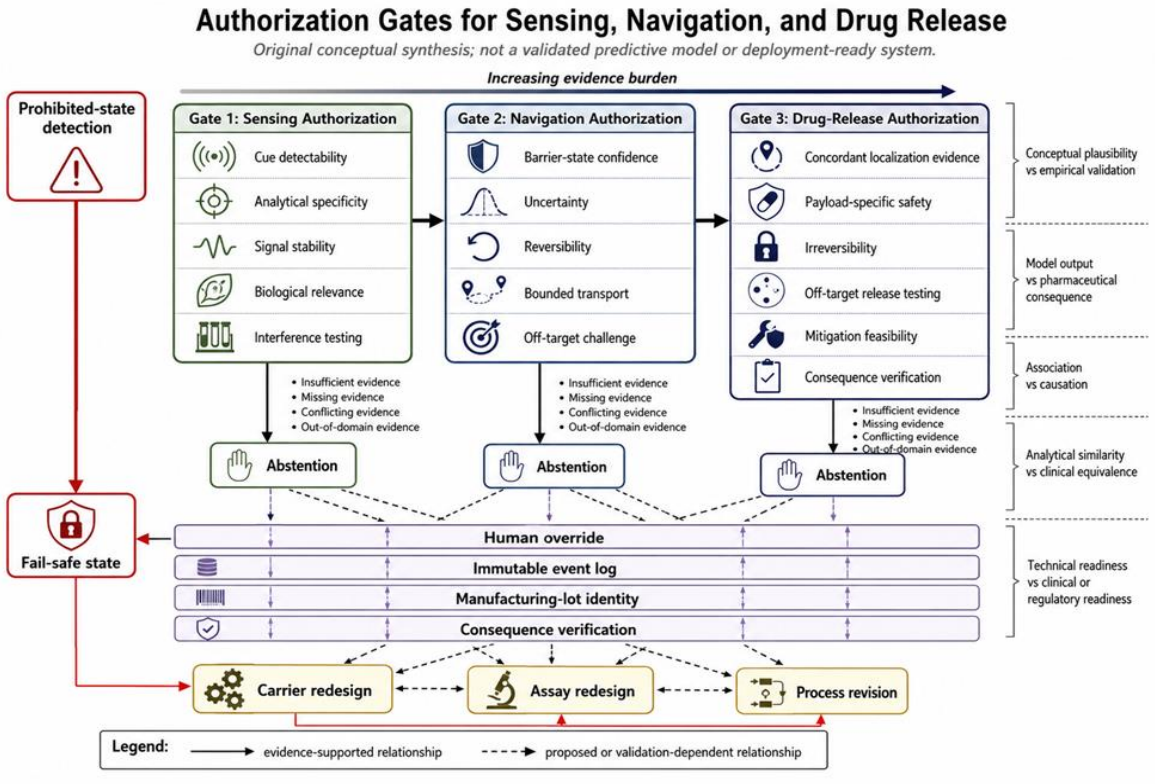

Figure 2. Authorization Gates for Sensing, Navigation, and Drug Release

The principal limitation is that the architecture governs how claims should be constrained; it does not prove that sensing, navigation, release, logging, or intervention can be implemented reliably in a particular carrier. Its propositions should be rejected, modified, or narrowed when product-specific evidence shows that states cannot be distinguished, actions cannot be bounded, or fail-safe behavior cannot be demonstrated.

CONCLUSION

Adaptive nanocarriers convert drug delivery into a sequential control problem when sensed conditions alter subsequent transport, intracellular behavior, or payload exposure. The proposed navigation constitution addresses this problem by separating observation, state estimation, uncertainty, authorization, action, verification, traceability, and human intervention. It establishes narrower permissions under uncertainty, treats biological-barrier recognition as revisable, distinguishes reversible navigation from irreversible release, and gives prohibited-state evidence priority over therapeutic mission signals. Its authorization gates, fail-safe hierarchy, event-log requirements, and lot-to-policy equivalence criterion are original conceptual constructs requiring product-specific validation. The framework does not establish clinical benefit, regulatory acceptability, universal applicability, or deployment readiness; its value lies in making permissions, assumptions, evidence needs, and decision boundaries explicit.

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