



DESIGNING THE DEPOT BACKWARD FROM A TARGET EXPOSURE PROFILE FOR LONG-ACTING INJECTABLE MEDICINES

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ABSTRACT

Long-acting injectable medicines are commonly developed by selecting a depot platform, adjusting formulation variables, and then evaluating the resulting release and pharmacokinetic behavior. This forward sequence can produce technically sophisticated formulations while leaving the governing therapeutic question incompletely specified: what depot behavior is required to generate an intended exposure trajectory across realistic patients, administration conditions, and manufacturing variation? This article develops Exposure-Constrained Depot Inverse Design, a proposed theory for designing the depot backward from a multidimensional target exposure specification. The approach decomposes the desired concentration–time behavior into admissible drug-input functions; maps those functions to molecular, material, formulation, administration, and process variables; represents depot formation, transformation, local tissue response, and systemic uptake as coupled dynamic processes; applies feasibility and manufacturability constraints before candidate acceptance; and requires forward evaluation across virtual populations and perturbation scenarios. The central contribution is a shift from maximizing a single output, such as nominal duration or cumulative release, toward identifying a robust feasibility envelope in which exposure requirements, depot physics, physiological variability, analytical observability, and product-development constraints remain simultaneously compatible. The theory distinguishes systemic exposure from in vivo input, intrinsic material behavior from the in vitro measurement system, and computational prioritization from experimental confirmation. Its principal limitations are non-uniqueness of the inverse problem, incomplete observability of depot states, model-form and parameter uncertainty, platform dependence, and limited human injection-site evidence. The proposed architecture may support more traceable formulation hypotheses and more informative validation studies, but it does not constitute a validated predictive model, clinical dosing framework, manufacturing control strategy, or regulatory decision tool.

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Introduction

Long-acting injectable medicines can reduce dosing frequency, sustain drug input, and create treatment options that are difficult to achieve with short-acting dosage forms. Their development, however, is not reducible to extending apparent half-life or maximizing the duration of measurable drug release. A clinically meaningful product must coordinate molecular potency and dose burden, depot-forming behavior, drug release, local absorption, systemic disposition, administration practicality, analytical characterization, process reproducibility, and exposure variability. Development experience with complex long-acting injectables shows that formulation composition, manufacturing, product characterization, release testing, and in vivo

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performance constitute interdependent scientific problems rather than separable optimization tasks [1]. A product may therefore achieve an attractive result for one isolated measure while remaining unsuitable when the complete exposure and product requirements are considered.

The inadequacy of single-measure optimization is especially evident in polymeric and phase-transforming depots. In poly(lactic-co-glycolic acid) systems, nominal polymer composition does not independently determine performance because particle-formation conditions, internal structure, drug distribution, and degradation behavior intervene between the selected material and the observed release profile [2]. In situ forming depots introduce additional transformations because the injected formulation may undergo solvent exchange, phase inversion, precipitation, gelation, hydration, erosion, and continuing structural reorganization after administration [3]. Consequently, the administered formulation is only the initial condition of a dynamic depot system. The pharmacokinetic trajectory emerges from the evolving relationship among the drug, the formulation, the transforming depot, the surrounding tissue, and systemic disposition.

The intended treatment context further narrows the set of acceptable depot designs. Injection volume, needle dimensions, route, administration frequency, care setting, device compatibility, patient acceptability, and the practical consequences of an extended terminal tail may all constrain what can reasonably be formulated and administered. Patient-centric analyses of long-acting platforms emphasize that route, usability, administration burden, and industrial implementation must be addressed together with pharmacological duration [4]. These constraints are not secondary commercial considerations that can always be added after release optimization. They determine whether the exposure target itself is realistic and whether a mathematically attractive drug-input function can correspond to an administrable pharmaceutical product.

The unresolved problem is therefore architectural: current evidence describes many relationships among formulation variables, release tests, depot behavior, and pharmacokinetics, but it does not by itself supply a general theory for moving backward from an intended exposure profile to a bounded set of depot-design requirements. Contemporary analyses of long-acting injectable suspensions continue to identify incomplete integration among particle attributes, formulation composition, release testing, injection-site processes, and translational evaluation [5]. This article addresses that gap by proposing Exposure-Constrained Depot Inverse Design, an original theoretical construct in which a multidimensional exposure specification is translated into admissible drug-input behavior, candidate depot variables, mechanistic depot-state hypotheses, feasibility constraints, and forward-evaluation requirements. The contribution is intended to organize design reasoning and future validation, not to claim that one formulation platform, inverse algorithm, mechanistic model, or exposure target is universally applicable.

From Target Exposure to Depot-Design Requirements

Backward depot design must begin with a target exposure specification that is richer than a desired duration or average concentration. Depending on the pharmacological context, the specification may include the required onset of exposure, an upper peak boundary, a maintenance band, a minimum effective exposure, acceptable peak-to-trough fluctuation, intended duration, repeat-dose accumulation, terminal-tail behavior, missed-dose resilience, and the tolerable probability of violating these conditions across patients. The first inverse-design operation is to determine what family of drug-input functions could generate that systemic behavior under an explicitly stated pharmacokinetic model. Analytical work linking pharmacokinetic and physicochemical properties to depot-formulation requirements supports the general feasibility of reasoning from systemic disposition and drug properties toward the release or absorption behavior required of a long-acting formulation [6]. The result should nevertheless be treated as an admissible family rather than a uniquely identified input function because different local mechanisms can produce similar plasma profiles.

The target specification must also be reconciled with the intended molecule, therapeutic context, and route of administration. A profile that appears pharmacokinetically desirable may imply an impossible drug load, excessive injection volume, unstable solid form, unrealistic release duration, or a terminal exposure tail that is difficult to manage. Clinical translation of long-acting delivery systems depends on the combined suitability of the drug, delivery platform, administration route, development pathway, and use context [7]. Exposure requirements should therefore be expressed as conditional design objectives. For example, a prolonged maintenance interval is meaningful only if the required mass of drug can be incorporated into an administrable product and if the resulting residual exposure remains acceptable when treatment is changed, delayed, or discontinued. The inverse process must be permitted to reject the original target or request its reformulation when the target cannot be reconciled with molecular and product constraints.

A second operation is to map the admissible input functions to classes of depot behavior rather than immediately to a single formulation recipe. A relatively rapid onset followed by sustained maintenance might require an initial accessible drug fraction combined with a slower matrix-controlled input, whereas a low-fluctuation profile could require suppression of early burst, control of transport-pathway formation, and resistance to abrupt changes in depot surface area. Experimental work with biodegradable in situ depots demonstrates that polymer architecture can be used to modulate depot formation and delivery kinetics within a defined material platform [8]. Fully synthetic injectable depots likewise show that drug-carrier association, depot chemistry, and composition can alter loading and pharmacokinetic persistence [9]. These studies support the existence of controllable mappings between material choices and drug input, but they do not establish that the same mapping applies across drugs, polymers, tissues, or administration routes.

A third operation is a molecular feasibility gate. Potency, projected dose, clearance, solubility, solid-state behavior, stability, and the relationship between pharmacological persistence and formulation persistence determine how demanding the depot must be. Evidence supporting lenacapavir as a long-acting injectable candidate illustrates how high potency and favorable

pharmacokinetic and physicochemical characteristics can reduce the formulation burden required to maintain prolonged exposure [10]. The proposed theory therefore does not assume that every molecule can be converted into a practical depot by increasing drug loading or slowing release. Instead, it classifies a target as provisionally feasible, conditionally feasible, or inconsistent with current molecular, material, administration, or manufacturing constraints. **Table 1** organizes the evidence, constructs, and interpretation boundaries needed to develop from target exposure to depot-design requirements within the article's central argument.

Table 1. Evidence domains, core questions, scientific requirements, and interpretation boundaries for from target exposure to depot-design requirements

Construct or evidence domain	Core question	Scientific basis	Role in the article	Failure or overclaiming risk	Boundary statement
Target exposure specification	Which features of the systemic concentration–time profile must be achieved or avoided?	Pharmacological objective, systemic disposition, regimen context, safety considerations, and intended use	Defines the multidimensional objective from which backward design begins	Reducing the target to duration, mean concentration, or one pharmacokinetic statistic	The specification is a proposed design input, not a clinical recommendation or validated therapeutic target
Exposure boundaries	Which peak, trough, maintenance, onset, and terminal-tail conditions are permissible?	Therapeutic and pharmacological reasoning expressed as ranges or constraints	Converts a general treatment intention into testable exposure conditions	Treating uncertain or context-dependent boundaries as fixed universal thresholds	Exposure boundaries remain conditional on the drug, indication, regimen, and supporting evidence
Systemic pharmacokinetic model	How would candidate drug-input functions be transformed into systemic exposure?	Distribution, clearance, compartmental or physiologically based structure, and repeat-dose behavior	Provides the forward operator required for inverse reasoning	Compensating for an incorrect depot model through flexible systemic parameters	The model must be qualified for its stated context and cannot prove the local release mechanism
Admissible input-function family	Which time-dependent depot inputs could produce the target exposure?	Convolution, deconvolution, mechanistic absorption modeling, and parameter constraints	Links the exposure target to provisional release and absorption requirements	Presenting one mathematically recovered input as the unique biological mechanism	Multiple input functions may remain compatible with the same systemic profile
Molecular feasibility	Can the drug support the required duration, dose, loading, and local persistence?	Potency, dose burden, clearance, solubility, solid state, chemical stability, and local tolerability	Rejects targets that impose implausible demands on the molecule or formulation	Assuming formulation engineering can overcome any molecular limitation	Molecular suitability does not establish developability, safety, or therapeutic value
Depot-behavior class	What type of local behavior could generate the admissible input?	Dissolution control, diffusion, degradation, erosion, phase transformation, reversible association, or combined mechanisms	Translates an input function into mechanistic depot hypotheses	Assigning a mechanism solely from the shape of the plasma profile	Mechanistic attribution requires independent local, material, and release evidence
Platform compatibility	Which suspension, microsphere, implant, gel, or other platform is compatible with the required behavior?	Platform-specific material properties, loading capacity, formation process, administration route, and duration	Narrows candidate technologies before detailed formulation search	Treating all members of a platform class as interchangeable	Platform selection is conditional and requires product-specific experimental confirmation
Administration requirements	Can the candidate be delivered using an acceptable route, volume, device, needle, and setting?	Injectability, viscosity, particle passage, route, site, administration technique, and patient-use considerations	Places practical boundaries around the theoretical depot design	Deferring administration feasibility until after release optimization	An exposure-effective depot is not viable when it cannot be administered reproducibly and acceptably
Uncertainty representation	Which requirements,	Parameter distributions,	Prevents nominal target matching	Reporting precise requirements	Model confidence must be

	parameters, and relationships are uncertain?	alternative model structures, scenario ranges, and evidence quality	from being mistaken for robust design	without propagating uncertainty	distinguished from calibrated uncertainty
Rejection and redesign conditions	When should the target, molecule, platform, or candidate formulation be reconsidered?	Constraint violation, implausible dose, unstable formulation, unacceptable tail, non-identifiability, or poor robustness	Creates explicit stopping and feedback logic	Continuing optimization after the underlying target has become infeasible	Rejection is a theory-guided research decision, not a regulatory or clinical determination

Linking Pharmacokinetic Targets to Release and Material Behavior

The central translation problem is not simply to match a target plasma curve with an *in vitro* release curve. Systemic exposure is generated by a sequence of processes that may include drug liberation from the formulation, dissolution or desorption, movement through an evolving depot, transport across local tissue, vascular or lymphatic uptake, and systemic distribution and elimination. For degradable microspheres, mechanistic analysis may require the simultaneous representation of polymer degradation and drug-release kinetics rather than a single empirical release-rate constant [11]. The inverse-design theory therefore separates at least three functions: the intrinsic liberation of drug from the material system, the effective *in vivo* input leaving the injection-site environment, and the systemic pharmacokinetic transformation of that input. These functions can coincide under restrictive assumptions, but they should not be treated as interchangeable by default.

For crystalline suspensions, particle dissolution provides an especially clear example of the distinction. Intrinsic dissolution and thermodynamic solubility can influence the pharmacokinetic profiles produced by long-acting aqueous microsuspensions [12]. However, the *in vivo* consequence of dissolution depends on particle-size distribution, crystal form, wetting, aggregation, local fluid availability, sink conditions, tissue transport, and the removal of dissolved drug from the depot environment. A target exposure profile therefore cannot be translated into one nominal particle size without specifying the other conditions that determine effective surface area and dissolution. The relevant inverse-design object is a conditional relationship between a distribution of particle and formulation attributes and a distribution of possible *in vivo* input functions.

Observed *in vitro* release adds a measurement layer to this mechanistic chain. Formulation parameters can alter release measured from long-acting injectable suspensions, indicating that composition and particle-related variables must be represented jointly when interpreting performance [13]. Yet the apparent profile also depends on apparatus, medium composition, hydrodynamics, sampling, sink maintenance, and the physical disturbance imposed by the method. Development of discriminatory release methods for long-acting suspensions demonstrates that test design and operating conditions materially shape what can be observed and compared [14]. In the proposed theory, the *in vitro* experiment is consequently represented by a measurement model that acts on the formulation and its evolving state. A method may be repeatable or formulation-discriminating without being mechanistically equivalent to the injection site or quantitatively predictive of human exposure.

An *in vitro*–*in vivo* relationship should therefore be treated as a product-, method-, mechanism-, and context-dependent mapping that requires explicit evaluation. Current analysis of correlation development for PLGA-based long-acting injectables underscores the difficulty of assuming direct translation across heterogeneous products, release methods, and *in vivo* mechanisms [15]. Exposure-constrained inverse design uses *in vitro* data to test particular mechanistic propositions, rank candidate sensitivity, and update uncertainty; it does not designate the laboratory release curve as the target itself. Release behavior emerges from coupled degradation, dissolution, and formulation-dependent processes rather than from a single material constant [11-13]. The practical consequence is that backward design must identify not only the desired input profile but also the material mechanism capable of producing it, the analytical conditions capable of interrogating that mechanism, and the evidence needed to determine whether the inferred relationship survives transition to the physiological depot.

Inverse-Design Variables for Long-Acting Injectables

An inverse-design architecture requires a structured representation of variables rather than an undifferentiated list of formulation parameters. The proposed design vector is organized into six interacting layers: molecular properties, material properties, formulation composition, intermediate structure, administration conditions, and manufacturing-process variables. Quality-by-design analyses of PLGA- and PLA-based microspheres support a hierarchy in which critical material attributes and critical process parameters generate intermediate product structures and critical quality attributes that subsequently influence release and performance [16]. This hierarchy is important because the variables directly chosen by a formulator are not always the variables directly controlling exposure. Polymer grade, solvent ratio, mixing history, drying conditions, and drug loading may act through porosity, drug distribution, crystallinity, particle morphology, hydration, or degradation behavior. The proposed theory therefore treats intermediate structures as explicit state variables rather than allowing them to remain hidden inside an empirical formulation-to-release association.

Material identity must also be represented probabilistically rather than solely through nominal labels. Studies of PLGA variability show that polymers described by the same broad grade may differ in attributes capable of altering degradation and controlled release [17]. Such variation can arise from molecular-weight distribution, monomer sequence, end-group chemistry, residual monomer, branching, or manufacturing history. Internal microstructure adds another level of variability: three-

dimensional focused ion beam–scanning electron microscopy has demonstrated that pore architecture and structural organization within microspheres can be measured as potential critical quality attributes [18]. In the inverse-design engine, material inputs should therefore be expressed as distributions with defined uncertainty, while microstructure should be modeled as an intermediate consequence of material and process choices. A nominally optimal formulation is not robust when small, realistic changes in raw materials generate large shifts in internal transport pathways.

Interactions among variables are equally important. Polymer properties, active-pharmaceutical-ingredient characteristics, solvent exchange, matrix formation, and local precipitation may combine nonlinearly during in situ implant formation. Comparative evidence from injectable in situ forming implants indicates that polymer attributes and active-ingredient properties can jointly influence depot formation and release [19]. The proposed theory consequently rejects an assumption that every design variable contributes independently and additively. Interaction terms should be considered when they have a plausible physicochemical basis, including drug–polymer affinity, pH-dependent solubility, plasticization, crystallization within the depot, solvent–nonsolvent exchange, and drug-induced changes in polymer hydration or degradation. These relationships may be represented through mechanistic equations, empirical response surfaces, Bayesian hierarchical models, or hybrid structures, but the selected representation must remain traceable to its evidentiary basis.

Computational and machine-learning methods may assist candidate generation when the design space becomes too large for intuitive exploration. Models trained on polymeric long-acting injectable data have shown potential for predicting release behavior and prioritizing formulation candidates [20]. Within Exposure-Constrained Depot Inverse Design, however, machine learning is assigned a bounded role. It may interpolate within represented material and process domains, identify influential variables, estimate candidate rankings, or propose experiments that reduce uncertainty. It cannot establish that a generated formulation is synthesizable, stable, injectable, physiologically compatible, manufacturable, or capable of achieving the intended human exposure. Data availability must also be distinguished from data suitability: a dataset containing many release curves may still be unsuitable when methods, formulations, sampling schedules, and reporting conventions are inconsistent. The output of candidate generation is therefore a set of testable hypotheses accompanied by domain-of-applicability statements, uncertainty estimates, and explicit requirements for mechanistic and experimental evaluation.

Modeling Depot Formation, Transformation, and Physiological Variability

The administered product is the initial condition of the depot rather than the depot's complete identity. After injection, particles may redistribute, sediment, aggregate, hydrate, dissolve, or become incorporated into a local inflammatory response; in situ systems may spread before solidification, exchange solvent with tissue fluid, precipitate, contract, swell, erode, or fragment. Multimodal imaging of a long-acting cabotegravir formulation has demonstrated that depot distribution and local physical behavior can evolve after parenteral administration [21]. The theoretical implication is that a static descriptor such as injected volume, initial particle size, or nominal geometry cannot fully represent the source of systemic input. The proposed depot model must contain time-dependent states and transitions that connect the administered formulation to the continuously changing surface area, porosity, composition, drug distribution, and tissue interface.

Particle-scale properties interact with these post-injection states. Experimental evidence shows that particle size can influence the in vivo performance of long-acting injectable suspensions [22]. The relevant variable is rarely a single mean diameter; it is a distribution that may change through aggregation, dissolution, fragmentation, Ostwald ripening, or selective disappearance of smaller particles. Physiologically based pharmacokinetic modeling provides a means of connecting local intramuscular absorption processes to systemic disposition while retaining tissue and drug-specific structure [23]. In an inverse-design context, particle properties and physiological parameters should therefore be evaluated jointly. The same particle distribution may produce different effective inputs under different local perfusion, interstitial-fluid availability, muscle-to-adipose composition, lymphatic access, or systemic clearance conditions.

Local biology may alter the depot environment rather than merely contribute unexplained residual variability. Mechanistic modeling of intramuscular long-acting administration has begun to incorporate tissue response at the depot site, including processes that may influence transport and absorption [24]. A biologically responsive depot model could include inflammatory-cell recruitment, fluid influx, vascular change, extracellular-matrix remodeling, fibrosis, local pH, enzyme activity, and the formation of a tissue capsule. The evidence needed to parameterize these states remains limited, particularly in humans, and the importance of each process is likely to differ across suspensions, microspheres, implants, gels, drugs, injection sites, and species. The theory therefore treats tissue response as a candidate mechanistic layer with quantified uncertainty, not as a universally dominant determinant.

In situ implant evidence further illustrates why depot transformation must be observed independently of systemic pharmacokinetics. Studies of risperidone implant depots indicate that formation, degradation, mass loss, and physical transformation can jointly contribute to drug release [25]. A model that reproduces plasma concentrations while misrepresenting these local transitions may fit for compensatory reasons and fail when the formulation, dose, species, or tissue condition changes. Depot morphology, particle-scale properties, and site physiology jointly shape the observed exposure trajectory [21–23]. The proposed architecture therefore combines longitudinal depot-state evidence with systemic exposure, and it requires uncertainty to propagate from initial formulation attributes through local transformation and physiological uptake. **Figure 1** presents the target-exposure-to-depot inverse-design engine, showing how the article's key components and boundaries are connected within modeling depot formation, transformation, and physiological variability.

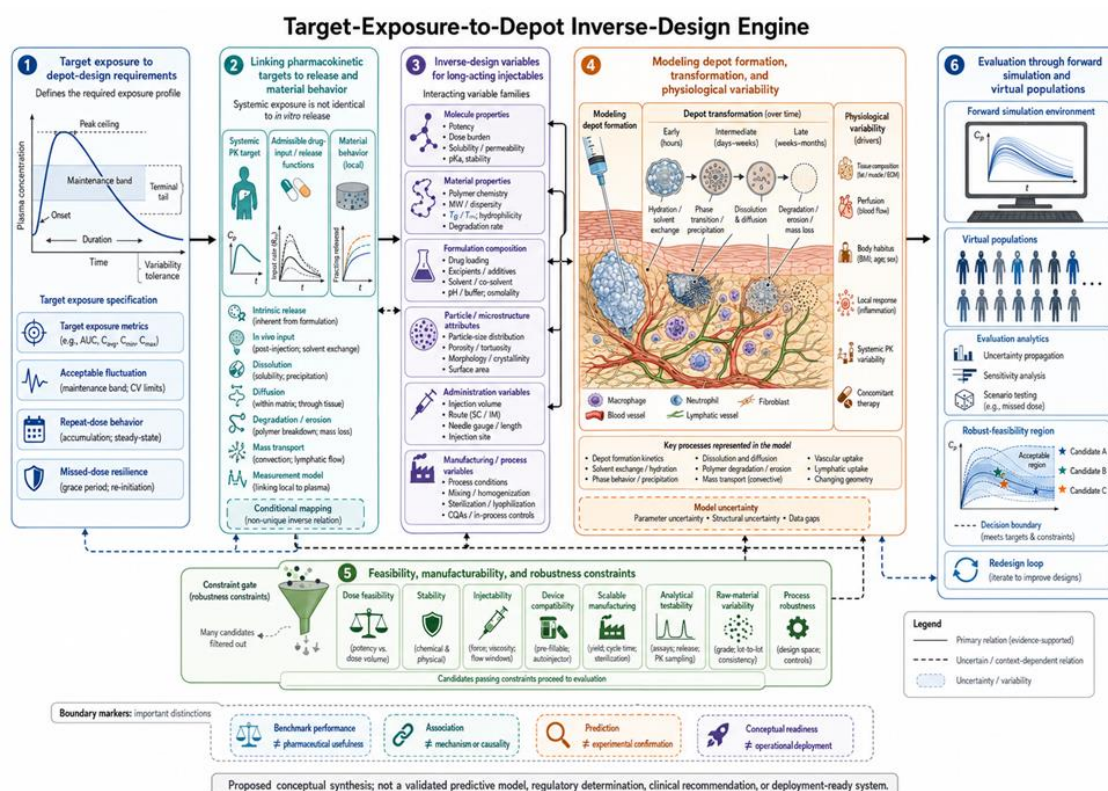


Figure 1. Target-Exposure-to-Depot Inverse-Design Engine.

The figure is an original conceptual synthesis that organizes the article's central contribution across target exposure to depot-design requirements, linking pharmacokinetic targets to release and material behavior, inverse-design variables for long-acting injectables, modeling depot formation, transformation, and physiological variability, modeling depot formation, physiological variability. Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, regulatory determination, clinical recommendation, or deployment-ready system.

Feasibility, Manufacturability, and Robustness Constraints

Inverse design should not generate a pharmacokinetically attractive candidate and postpone feasibility assessment until late development. A candidate depot must pass constraints involving dose capacity, stability, injectability, sterilization, fill-finish, device compatibility, analytical characterization, process control, storage, and reproducible administration. Analyses of the gap between fundamental PLGA research and product development show that promising release behavior does not ensure that a formulation can be scaled, characterized, controlled, or manufactured consistently [26]. Exposure-Constrained Depot Inverse Design therefore incorporates a feasibility gate before a candidate is admitted to full forward evaluation. This gate is not merely a weighted objective that a superior pharmacokinetic score can offset. Some violations, such as chemically unstable drug, unacceptable injection volume, inability to sterilize the product, or uncontrolled phase separation, may constitute hard rejection conditions.

Feasibility remains platform specific. Current assessment of PLGA-based long-acting injectables emphasizes the interdependence of polymer properties, drug loading, particle production, degradation, release control, and product-development requirements [27]. Manufacturing studies of long-acting implants further show that process conditions can influence morphology and other critical quality attributes [28]. Accordingly, the inverse-design vector must contain both the desired final product attributes and the process route expected to realize them. A candidate requiring a narrowly specified microstructure is incomplete unless a plausible process can generate that structure with acceptable variability. Similarly, an exposure target that demands an implausibly precise release rate may be unsuitable when the available manufacturing process cannot maintain the necessary material and structural tolerances.

Particle-engineering routes provide a concrete example of process-constrained inverse design. Continuous antisolvent crystallization has been investigated as an integrated bottom-up approach for producing particles intended for long-acting injectable suspensions [29]. Such processes connect mixing, supersaturation, nucleation, crystal growth, agglomeration, and downstream handling to the final particle-size and solid-state distributions. In a backward design workflow, the desired particle state should therefore be translated into process-operating regions rather than a single ideal set point. The process model must also recognize correlations: reducing particle size may change filtration, drying, redispersion, suspension viscosity, surface-energy behavior, and physical stability. The theoretically preferred particle distribution may be rejected when its manufacturing or storage behavior is incompatible with the complete product requirement.

Manufacturing-platform selection can also change which release profiles are practically attainable. A microfluidic or related controlled-particle-production method may generate different distributions, morphologies, loading patterns, and release behavior from conventional emulsification or bulk-mixing processes. Development of long-acting microspheres using the IVL-DrugFluidic system demonstrates that the production platform itself can be linked to formulations intended for different delivery durations [30]. The proposed robustness criterion is therefore not that one nominal batch reproduces the target profile. A robust candidate should retain acceptable predicted exposure under plausible variation in polymer attributes, particle distribution, loading, microstructure, process settings, storage, injection technique, and patient physiology. The resulting feasible region is a conditional scientific construct, not a validated manufacturing design space or regulator-approved control strategy.

Evaluation through Forward Simulation and Virtual Populations

Backward derivation produces hypotheses; it does not demonstrate that the resulting depot will generate the intended exposure. Each candidate must therefore be returned to a forward model that begins with the proposed drug, material, formulation, process, and administration variables and predicts depot formation, transformation, release, local uptake, and systemic pharmacokinetics. Reviews of modeling and simulation in long-acting injectable development show that computational methods can connect formulation knowledge, preclinical evidence, clinical pharmacokinetics, and development questions across multiple stages [31]. The model's intended use must nevertheless be specified. A structure suitable for exploratory sensitivity analysis may not be sufficiently qualified for candidate rejection, formulation comparison, human translation, or a consequential bioequivalence decision.

Mechanistic in vitro–in vivo extrapolation offers one possible forward-evaluation architecture. Formulation attributes and preclinical observations may be integrated with mechanistic absorption and systemic models to generate human-exposure hypotheses [32]. For inverse design, the value of such a model lies not only in reproducing a central concentration–time curve but also in testing whether the candidate remains credible when mechanisms and parameters are perturbed. Evaluation should include alternative release mechanisms, uncertainty in depot geometry, variability in tissue conditions, uncertainty in systemic disposition, and disagreement among plausible parameter sets. Agreement with one calibration dataset is insufficient when multiple model structures can reproduce the same observation.

Decision uncertainty must also be propagated explicitly. Bayesian virtual comparative-trial frameworks show how uncertainty in model parameters and simulated comparisons can be incorporated into probabilistic assessments rather than hidden behind point predictions [33]. Virtual bioequivalence analyses of long-acting suspensions further demonstrate that formulation attributes such as particle size can be varied within physiologically based models to examine effects on population exposure, formulation variability, and statistical power [34]. In the proposed framework, a virtual population should include correlated physiological, pharmacokinetic, administration, material, and process attributes when evidence supports those relationships. The population is intended to stress-test candidate designs, not to serve as a synthetic replacement for clinical participants.

The final evaluation output should be a robust feasibility envelope rather than a single optimal candidate. Designs within this envelope satisfy the prespecified exposure and product constraints across stated uncertainty distributions and perturbation scenarios. Statistical investigation of Type I error and simulated safe spaces in long-acting injectable virtual bioequivalence illustrates that inferred decision regions depend on model validity, trial assumptions, formulation differences, power, and error control [35]. Credible forward evaluation requires mechanistic simulation, explicit model qualification, and calibrated decision uncertainty [31-33]. A candidate should be returned for redesign when its apparent success depends on one fragile parameter set, an unverified mechanism, unrealistic manufacturing precision, or an unrepresentative virtual population. **Table 2** organizes the evidence, constructs, and interpretation boundaries needed to develop evaluation through forward simulation and virtual populations within the article's central argument.

Table 2. Evaluation, implementation, and research priorities arising from Designing the Depot Backward from a Target Exposure Profile for Long-Acting Injectable

Component or layer	Inputs	Core function	Expected output	Uncertainty or limitation	Validation requirement
Target-exposure compliance	Target band, peak and trough boundaries, onset, duration, tail, dosing regimen, and systemic PK model	Determine whether a candidate produces the required exposure behavior	Predicted exposure trajectory and probability of requirement violation	Target uncertainty, systemic-model structure, parameter uncertainty, and non-unique input functions	External pharmacokinetic evaluation and confirmation that the target is clinically and pharmacologically justified
Molecular feasibility	Potency, dose burden, clearance, solubility, solid state, chemical stability, and local tolerability	Determine whether the molecule can support the intended depot burden	Feasibility classification and molecular failure conditions	Early estimates may be uncertain or indication dependent	Experimental physicochemical, pharmacological, stability, and tolerability evidence

Release-mechanism model	Dissolution, diffusion, degradation, erosion, phase transformation, and drug–material interactions	Translate formulation and depot states into time-dependent drug liberation	Mechanistic release-input hypothesis	Competing mechanisms, weak identifiability, and product dependence	Mechanism-discriminating experiments across formulations and conditions
Depot-state model	Initial geometry, particles, microstructure, solvent exchange, hydration, degradation, mass loss, and tissue interface	Predict post-injection formation and transformation	Time-dependent depot states and local concentration fields	Sparse longitudinal observations and uncertain model structure	Imaging, local sampling, histology, mass-balance, and physicochemical characterization
Measurement model	Release apparatus, medium, hydrodynamics, sampling, sink conditions, and analytical method	Distinguish intrinsic product behavior from observed laboratory output	Predicted in vitro observation and method-sensitivity profile	Discriminatory methods may not be biopredictive	Repeatability, discrimination, mechanism relevance, and prospective in vitro–in vivo assessment
Physiological absorption model	Local perfusion, tissue composition, lymphatic transport, inflammation, extracellular transport, and systemic disposition	Translate depot liberation into absorbed systemic input	Individual and population exposure predictions	Limited human injection-site data and compensatory parameterization	External physiological and pharmacokinetic datasets, including relevant covariate groups
Manufacturing feasibility	Raw materials, unit operations, scale, sterilization, fill-finish, device, and storage	Determine whether the candidate state can be produced and controlled	Process-operating region and predicted CQA distributions	Scale dependence, lot variability, process drift, and incomplete process models	Pilot- and production-scale process characterization and product testing
Administration robustness	Route, site, needle, volume, injection rate, depth, operator, and tissue condition	Test sensitivity to realistic administration variability	Exposure and depot-state distributions across administration scenarios	Clinical distributions may be poorly characterized	Human-factors studies and clinically representative administration evidence
Virtual-population ensemble	Physiological distributions, covariates, systemic PK, depot parameters, administration variation, and product variability	Stress-test candidate performance across plausible individuals and scenarios	Population distributions of exposure and failure probability	Virtual subjects may not represent clinical populations or tail behavior	Calibration and external evaluation against individual-level clinical observations
Uncertainty and sensitivity analysis	Parameter distributions, alternative mechanisms, prior information, and model ensembles	Separate influential uncertainty sources and identify fragile assumptions	Variance decomposition, sensitivity rankings, and value-of-information priorities	Results depend on chosen distributions and model alternatives	Prospective testing of high-value uncertainties and transparent uncertainty reporting
Statistical decision layer	Exposure criteria, equivalence or comparison rules, trial design, model uncertainty, and error thresholds	Quantify the stability and operating characteristics of a candidate decision	Decision probability, power, Type I error, and conditional feasible region	Statistical safe spaces may be model and product specific	Prespecified simulation studies and comparison with observed trial outcomes
Human review and governance	Model documentation, evidence lineage, assumptions, version history, uncertainty, and candidate trade-offs	Ensure that computational outputs remain within their intended context	Traceable candidate decision and documented rationale	Automation bias, unrecorded assumptions, and context expansion	Independent multidisciplinary review, change control, and explicit stopping rules

Limitations and Boundary Conditions

The principal conceptual limitation is the non-uniqueness of the inverse problem. A target systemic profile may be compatible with multiple local input functions, and each input may be compatible with several material or depot mechanisms. This

ambiguity cannot be resolved from plasma pharmacokinetics alone. Constraints based on physicochemical plausibility, imaging, release testing, local tissue observations, process knowledge, and prior evidence may narrow the solution space, but they do not guarantee identification of the true mechanism. The proposed architecture is therefore intended to generate an admissible and testable family of designs rather than recover one objectively correct formulation from an exposure curve.

The evidence base is also uneven across depot platforms and physiological contexts. Many mechanistic insights arise from product-specific experiments, animal models, PLGA systems, crystalline suspensions, or in situ implants. Injection-site biology is incompletely observed in humans, and parameters such as local perfusion, inflammatory response, tissue composition, lymphatic uptake, and depot geometry may be weakly identifiable. An apparent mechanistic relationship may fail when translated across species, injection sites, drugs, doses, materials, or manufacturing processes. The theory should therefore be implemented with modular platform-specific models rather than one universal depot equation. Absence of evidence for a mechanism should not be interpreted as evidence that the mechanism is negligible.

A further boundary concerns decision use. Computational fit, benchmark accuracy, or successful retrospective simulation does not establish prospective pharmaceutical usefulness. Model confidence is not equivalent to calibrated uncertainty, and a simulated feasible region is not automatically a validated product-design space. The framework cannot determine clinical utility, local safety, immunological acceptability, manufacturability, bioequivalence, or regulatory acceptability without fit-for-purpose experimental and clinical evidence. It may organize questions, prioritize experiments, expose hidden assumptions, and reject internally inconsistent candidates. It must not be used to issue dosing instructions, waive necessary studies, claim regulatory equivalence, or characterize a formulation as development-ready solely from simulation.

Research Agenda and Implementation Priorities

The first research priority is to formalize the target exposure specification and investigate the identifiability of its corresponding depot-input family. Studies should examine which combinations of onset, maintenance, fluctuation, duration, terminal tail, repeat dosing, and population variability can be estimated reliably under alternative systemic pharmacokinetic structures. Joint collection of systemic concentrations, depot imaging, local tissue measurements, polymer or particle-state information, and in vitro release data would permit stronger discrimination among competing mechanisms. Prospective blinded challenges should specify the target profile before candidate formulation design and should compare predicted depot states, release behavior, and systemic exposure with subsequent observations rather than evaluating retrospective fit alone.

The second priority is infrastructure for interoperable, mechanism-oriented pharmaceutical data. Reporting should preserve raw-material characteristics, process conditions, formulation composition, particle distributions, internal microstructure, analytical methods, failed formulations, depot observations, physiological context, and individual pharmacokinetic data. Standardized schemas should distinguish directly measured quantities from inferred states and should document units, sampling schedules, censoring, preprocessing, and model assumptions. Negative and nonconfirmatory results are essential because candidate-generation systems trained only on successful formulations will underestimate failure regions. Shared benchmark datasets may support method comparison, but they should be designed around prospective pharmaceutical questions rather than generic prediction accuracy.

Implementation should proceed in stages. An initial stage may use the framework qualitatively to trace requirements and identify missing evidence. A second stage may introduce local mechanistic submodels for dissolution, degradation, particle transformation, or systemic pharmacokinetics. A third stage may couple these modules with manufacturing variability and virtual populations for prospective candidate comparison. More consequential uses require external validation, version control, uncertainty qualification, context-of-use documentation, audit trails, predefined stopping criteria, and multidisciplinary human review. Adoption should be judged by whether the framework improves experimental informativeness, reduces avoidable formulation dead ends, and produces more transparent decisions—not by whether it increases the apparent sophistication or automation of formulation development.

Conclusion

Exposure-Constrained Depot Inverse Design reframes long-acting injectable development as a constrained backward-and-forward reasoning problem. The proposed theory begins with a multidimensional target exposure specification, derives admissible drug-input requirements, maps them to interacting molecular, material, formulation, administration, and process variables, and represents the depot as a dynamic system embedded in variable physiology. Candidate formulations are filtered for feasibility and manufacturability before being challenged through forward simulation, uncertainty propagation, virtual populations, and perturbation analysis. The intended output is not a single nominal optimum but a robust feasibility envelope whose assumptions, uncertainties, and failure conditions remain visible. This architecture may support more coherent formulation hypotheses and more informative validation programs, but it does not establish mechanism, clinical benefit, manufacturing readiness, bioequivalence, regulatory acceptance, or universal applicability. Its value ultimately depends on prospective experimental evaluation, improved depot-state observation, qualified models, disciplined data practices, and sustained human scientific oversight.

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References

- O'Brien MN, Jiang W, Wang Y, Loffredo DM. Challenges and opportunities in the development of complex generic long-acting injectable drug products. *J Control Release*. 2021;336:144-58. doi:10.1016/j.jconrel.2021.06.017
- Park K, Skidmore S, Hadar J, Garner J, Park H, Otte A, et al. Injectable, long-acting PLGA formulations: Analyzing PLGA and understanding microparticle formation. *J Control Release*. 2019;304:125-34. doi:10.1016/j.jconrel.2019.05.003
- Pandya AK, Vora LK, Umeyor C, Surve D, Patel A, Biswas S, et al. Polymeric in situ forming depots for long-acting drug delivery systems. *Adv Drug Deliv Rev*. 2023;200:115003. doi:10.1016/j.addr.2023.115003
- Alidori S, Subramanian R, Holm R. Patient-centric long-acting injectable and implantable platforms—an industrial perspective. *Mol Pharm*. 2024;21(9):4238-58. doi:10.1021/acs.molpharmaceut.4c00665
- Malavia N, Burgess DJ. Insights into development of long-acting injectable suspensions. *J Control Release*. 2026;392:114721. doi:10.1016/j.jconrel.2026.114721
- Shah JC, Hong J. Model for long acting injectables (depot formulation) based on pharmacokinetics and physical chemical properties. *AAPS J*. 2022;24(3):44. doi:10.1208/s12248-022-00695-0
- Li W, Tang J, Lee D, Tice TR, Schwendeman SP, Prausnitz MR. Clinical translation of long-acting drug delivery formulations. *Nat Rev Mater*. 2022;7(5):406-20. doi:10.1038/s41578-021-00405-w
- Roberge C, Cros JM, Serindoux J, Cagnon ME, Samuel R, Vrlinic T, et al. BEPO®: Bioresorbable diblock mPEG-PDLLA and triblock PDLLA-PEG-PDLLA based in situ forming depots with flexible drug delivery kinetics modulation. *J Control Release*. 2020;319:416-27. doi:10.1016/j.jconrel.2020.01.022
- Ho DK, LeGuyader C, Srinivasan S, Roy D, Vlaskin V, Chavas TEJ, et al. Fully synthetic injectable depots with high drug content and tunable pharmacokinetics for long-acting drug delivery. *J Control Release*. 2021;329:257-69. doi:10.1016/j.jconrel.2020.11.030
- Subramanian R, Tang J, Zheng J, Lu B, Wang K, Yant SR, et al. Lenacapavir: A novel, potent, and selective first-in-class inhibitor of HIV-1 capsid function exhibits optimal pharmacokinetic properties for a long-acting injectable antiretroviral agent. *Mol Pharm*. 2023;20(12):6213-25. doi:10.1021/acs.molpharmaceut.3c00626
- Gao GF, Ashtikar M, Kojima R, Yoshida T, Kaihara M, Tajiri T, et al. Predicting drug release and degradation kinetics of long-acting microsphere formulations of tacrolimus for subcutaneous injection. *J Control Release*. 2021;329:372-84. doi:10.1016/j.jconrel.2020.11.055
- Nguyen TTV, Bevernage J, Darville N, Tistaert C, Van Bocxlaer J, Rossenu S, et al. Linking in vitro intrinsic dissolution rate and thermodynamic solubility with pharmacokinetic profiles of bedaquiline long-acting aqueous microsuspensions in rats. *Mol Pharm*. 2021;18(3):952-65. doi:10.1021/acs.molpharmaceut.0c00948
- Bao Q, Zou Y, Wang Y, Choi S, Burgess DJ. Impact of formulation parameters on in vitro release from long-acting injectable suspensions. *AAPS J*. 2021;23(2):42. doi:10.1208/s12248-021-00566-0
- Bao Q, Wang X, Zou Y, Wang Y, Burgess DJ. In vitro release testing method development for long-acting injectable suspensions. *Int J Pharm*. 2022;622:121840. doi:10.1016/j.ijpharm.2022.121840
- Wang Y, Otte A, Park H, Park K. In vitro-in vivo correlation (IVIVC) development for long-acting injectable drug products based on poly(lactide-co-glycolide). *J Control Release*. 2025;377:186-96. doi:10.1016/j.jconrel.2024.11.021
- Zhang C, Yang L, Wan F, Bera H, Cun D, Rantanen J, et al. Quality by design thinking in the development of long-acting injectable PLGA/PLA-based microspheres for peptide and protein drug delivery. *Int J Pharm*. 2020;585:119441. doi:10.1016/j.ijpharm.2020.119441
- Costello MA, Liu J, Kuehster L, Wang Y, Qin B, Xu X, et al. Role of PLGA variability in controlled drug release from dexamethasone intravitreal implants. *Mol Pharm*. 2023;20(12):6330-44. doi:10.1021/acs.molpharmaceut.3c00742
- Clark AG, Wang R, Qin Y, Wang Y, Zhu A, Lomeo J, et al. Assessing microstructural critical quality attributes in PLGA microspheres by FIB-SEM analytics. *J Control Release*. 2022;349:580-91. doi:10.1016/j.jconrel.2022.06.066
- Wang X, Wang R, Roy M, Kwok O, Burgess DJ. Long-acting injectable in situ forming implants: Impact of polymer attributes and API. *Int J Pharm*. 2025;670:125080. doi:10.1016/j.ijpharm.2024.125080
- Bannigan P, Bao Z, Hickman RJ, Aldeghi M, Häse F, Aspuru-Guzik A, et al. Machine learning models to accelerate the design of polymeric long-acting injectables. *Nat Commun*. 2023;14(1):35. doi:10.1038/s41467-022-35343-w
- Jucker BM, Alsaid H, Rambo M, Lenhard SC, Hoang B, Xie F, et al. Multimodal imaging approach to examine biodistribution kinetics of cabotegravir (GSK1265744) long acting parenteral formulation in rat. *J Control Release*. 2017;268:102-12. doi:10.1016/j.jconrel.2017.10.017
- Ho MJ, Jeong MY, Jeong HT, Kim MS, Park HJ, Kim DY, et al. Effect of particle size on in vivo performances of long-acting injectable drug suspension. *J Control Release*. 2022;341:533-47. doi:10.1016/j.jconrel.2021.12.011

23. Bettonte S, Berton M, Battegay M, Stader F, Marzolini C. Development of a physiologically-based pharmacokinetic model to simulate the pharmacokinetics of intramuscular antiretroviral drugs. *CPT Pharmacometrics Syst Pharmacol.* 2024;13(5):781-94. doi:10.1002/psp4.13118
24. Silva DA, Le Merdy M, Mullin J, Malavia N, Alam K, Tsakalozou E, et al. Mechanistic modeling of intramuscular administration of a long-acting injectable accounting for tissue response at the depot site. *AAPS J.* 2026;28(1):4. doi:10.1208/s12248-025-01171-1
25. Wang X, Wang R, Roy M, Wang Y, Qin B, Burgess DJ. Understanding drug release mechanisms of risperidone in situ forming implant depots in rabbits. *J Control Release.* 2025;383:113785. doi:10.1016/j.jconrel.2025.113785
26. Li X, Zhang Z, Harris A, Yang L. Bridging the gap between fundamental research and product development of long acting injectable PLGA microspheres. *Expert Opin Drug Deliv.* 2022;19(10):1247-64. doi:10.1080/17425247.2022.2105317
27. Park K. PLGA-based long-acting injectable (LAI) formulations. *J Control Release.* 2025;382:113758. doi:10.1016/j.jconrel.2025.113758
28. Costello MA, Liu J, Wang Y, Qin B, Xu X, Li Q, et al. Manufacturing dexamethasone intravitreal implants: Process control and critical quality attributes. *Int J Pharm.* 2023;647:123515. doi:10.1016/j.ijpharm.2023.123515
29. Nandi S, Padrela L, Tajber L, Collas A. Development of long-acting injectable suspensions by continuous antisolvent crystallization: An integrated bottom-up process. *Int J Pharm.* 2023;648:123550. doi:10.1016/j.ijpharm.2023.123550
30. Kim M, Kim JH, Kim S, Maharjan R, Kim NA, Jeong SH. New long-acting injectable microspheres prepared by IVL-DrugFluidic™ system: 1-month and 3-month in vivo drug delivery of leuprolide. *Int J Pharm.* 2022;622:121875. doi:10.1016/j.ijpharm.2022.121875
31. Siemons M, Schroyen B, Darville N, Goyal N. Role of modeling and simulation in preclinical and clinical long-acting injectable drug development. *AAPS J.* 2023;25(6):99. doi:10.1208/s12248-023-00864-9
32. Silva DA, Le Merdy M, Alam K, Wang Y, Bao Q, Malavia N, et al. Development of mechanistic in vitro-in vivo extrapolation to support bioequivalence assessment of long-acting injectables. *Pharmaceutics.* 2024;16(4):552. doi:10.3390/pharmaceutics16040552
33. Bois FY, Brochot C. A Bayesian framework for virtual comparative trials and bioequivalence assessments. *Front Pharmacol.* 2024;15:1404619. doi:10.3389/fphar.2024.1404619
34. Morris NM, Djehizian A, Mittapelly N, Telaprolu KC, Holland BW, McNally K, et al. Virtual bioequivalence assessment of long-acting injectable suspensions using PBPK modeling: Part 1. Impact of particle size on formulation variability. *AAPS J.* 2026;28(3):85. doi:10.1208/s12248-026-01213-2
35. Morris NM, Jamei M, Alam K, Tsakalozou E, Donnelly M, Feng K, et al. Virtual bioequivalence assessment of long-acting injectable suspensions using PBPK modeling: Part 2. Type I error and safe space analyses. *AAPS J.* 2026;28(3):86. doi:10.1208/s12248-026-01215-0