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High-Concentration Protein Formulations Under Injection Constraints: A Critical Review of Reversible Self-Association, Viscosity, Interfacial Damage, and the Trade-Off Between Dose Volume and Deliverability

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ABSTRACT

High-dose subcutaneous protein administration places pharmaceutical formulation under competing constraints: dose volume, solution flow, physical stability, device capability, and patient-facing delivery requirements. Concentrating a biologic may reduce injection volume while amplifying molecular crowding, reversible self-association, viscosity, and susceptibility to process- or container-associated stress. This critical review examines how those mechanisms are observed and interpreted, focusing on the distinction between protein interaction measurements, rheological responses, interfacial particle formation, and actual drug-product delivery. Evidence from colloid models, scattering, diffusion assays, protein-specific formulation experiments, and device-oriented reviews supports a conditional account: concentration-dependent rheology is strongly dependent on protein sequence and solution conditions, whereas particle formation under interfacial stress follows partly separate pathways. Shortcomings include assay-specific observability, incomplete cross-study comparability, and limited direct coupling of molecular measurements to complete injection-system outcomes. Consequently, selection between high-concentration/low-volume and lower-concentration/larger-volume presentations should be assessed at the level of the integrated formulation–container–device combination, without treating any single molecular predictor as a universal deliverability criterion.

Key words: *High-concentration monoclonal antibodies, Reversible self-association, Non-Newtonian viscosity, Subcutaneous injectability, Interfacial protein aggregation, Combination-product deliverability*

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INTRODUCTION

Subcutaneous (SC) dosing can offer a practical alternative to intravenous infusion for selected biologics, but the route creates an engineering problem when the required protein mass must be administered within a constrained volume and acceptable injection experience. Greater concentration places more molecules in the same solvent volume and commonly raises formulation viscosity; this may complicate filling, filtration, expulsion through a needle, and reliable administration. The current high-dose SC literature therefore links protein engineering, formulation, manufacturing, analytical characterization, and device selection, rather than viewing concentration as an isolated product attribute [1].

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Recent pharmaceutical discussions emphasize strategies to accommodate large biologic doses through excipient selection, alternative physical presentations, and injection technologies [2]. Yet a central comparison must remain open. A high-concentration, low-volume formulation may require higher driving force and more stringent physical-stability control, while a lower-concentration, higher-volume option shifts constraints toward tissue accommodation, administration time, and delivery hardware. These alternatives are explicitly considered in analyses of SC protein presentations [3].

Combination-product strategy adds further non-equivalence. Device architecture, container interaction, treatment bridging, and handling conditions can affect whether a product that is analytically acceptable can actually be delivered as intended. Recent formulation/device reviews treat these dependencies as interconnected development decisions [4]. The increased dose demanded by some biologics also requires care in translating benchtop syringe force, injection duration, and clinical tolerability into a single measure of success [5]. Accordingly, this review asks which physical mechanisms have direct evidence, which proxies are conditional, and where design choices redistribute rather than eliminate burden.

The specific critical contribution is to separate three propositions commonly compressed into one narrative: reversible protein association can modify concentrated-solution rheology; a viscous solution can raise mechanical delivery demands under defined device conditions; and interfacial exposure can generate particles through processes not explained adequately by bulk viscosity alone. A decision may be robust on one proposition and weak on another.

Review scope, literature identification, and critical evaluation approach

This is a critical review of recent peer-reviewed mechanistic, analytical, pharmaceutical, and delivery literature, interpreted alongside earlier foundational studies. The work draws on topic-directed searches of publisher-indexed and PubMed-visible records, supplemented by DOI-level examination. It was not based on a completed systematic database export, duplicate-resolution file, or reconciled full-text screening ledger. Accordingly, no comprehensive coverage, quantified inclusion count, formal risk-of-bias aggregate, or PRISMA-style selection estimate is claimed. Reference allocation is a writing constraint and is not treated as a population of eligible experimental studies.

The comparative unit is an experimental or interpretive claim under specified conditions: molecule or protein class, concentration, pH, ionic environment, excipient composition, history of agitation or interfacial exposure, assay timescale, and measurement endpoint. Studies of concentrated monoclonal antibodies, for example, link macroscopic viscosity to several biophysical determinants, but dependence on formulation and measurement procedure makes unrestricted generalization inappropriate [6]. Molecular-descriptor approaches to viscosity are useful for identifying candidate correlates, yet their fitting data and endpoint definitions determine what they can legitimately predict [7].

Newer computational and machine-learning studies combine molecular dynamics or surface descriptors with measured developability attributes [8]. Complementary biophysical accounts of antibody-cluster distributions indicate that apparently similar viscosity outcomes can emerge from distinct association dynamics [9]. The critical questions are whether the comparator and physical state match, whether multiple assays converge, and whether an alternative physical explanation could reproduce the signal.

Scientific foundations of high-concentration protein formulations

Concentration changes the relative importance of excluded-volume effects, anisotropic electrostatics, short-range attractions, and crowding. For Y-shaped immunoglobulins, a scalar net charge does not describe the spatial pattern of complementary surface patches. A colloid-inspired experimental and theoretical analysis illustrates how anisotropic interactions and antibody geometry can jointly account for concentration-dependent osmotic compressibility, diffusion, and zero-shear viscosity [10].

Protein subclass and molecular orientation also matter. A comparative study of related antibody subclasses links modeled region-specific attraction to clustering and high-concentration viscosity, arguing against classification by concentration or net charge alone [11]. This mechanistic specificity is important for developability: two molecules formulated at the same mass concentration may exhibit different interaction landscapes.

Diffusion measurements create an additional interpretive challenge. Short-time collective diffusion, long-time self-diffusion, and bulk shear response probe different observables. A coarse-grained simulation of concentration-dependent antibody diffusion illustrates departures from simple diffusion over particular simulated time windows,

followed by behavior consistent with ordinary diffusion at longer windows [12]. Such results offer a mechanism to test, not direct proof of a corresponding dynamic regime in every injectable formulation.

Formulation ingredients can modify these interactions by altering solvent conditions or preferential association. Experimental assessment of salts, sugars, polyols, and amino acids alongside an extended-DLVO treatment provides evidence that excipient identity and concentration change apparent intermolecular interaction measures in a model protein system [13]. That work used bovine serum albumin, so an inferred improvement in antibody injectability would require confirmation in the relevant therapeutic protein. Throughout the following sections, concentration, chemical environment, thermal/mechanical history, and measurement timescale are treated as explicit context variables, not incidental laboratory details.

Evidence on reversible self-association and concentration-dependent protein interactions

Reversible self-association refers here to protein–protein contact assemblies whose population changes with solution conditions and which can dissociate without necessarily generating persistently damaged protein. In Fc-fusion proteins, experimentally measured electrostatic attraction and reversible oligomerization changed with pH and ionic strength; interactions assigned to different domains were additionally explored by coarse-grained simulation [14].

Greater local specificity comes from hydrogen–deuterium exchange and in-silico analysis of a diabody–interleukin fusion protein, which identify a candidate reversible association interface [15]. For antibodies carrying pronounced charge anisotropy, combined scattering, mobility, microrheology, and colloid-theory analysis show why a spherical effective-charge approximation can reproduce some population averages and still obscure orientation-dependent interactions [16].

Multiscale scattering extends this argument into dynamics. A study combining neutron spin-echo and small-angle neutron scattering across multiple antibodies relates short-lived cluster populations and diffusion to concentrated-solution viscosity [17]. A separate SAXS/molecular-dynamics analysis across concentrations connects fitted short-range attractive interactions, reversible cluster structures, and viscosity trends for a particular antibody [18].

Not all association-related signals establish the same physical state. Investigations of antibody interactions and liquid–liquid phase separation ask whether concentrated solutions approach regimes in which mesoscopic heterogeneity accompanies, or differs from, reversible oligomer populations [19]. Phase separation, reversible association, and irreversible aggregation must be specified independently. At earlier development stages, asymmetric-flow field-flow fractionation and polyethylene glycol precipitation have been evaluated as low-material screens for unfavorable solution behavior [20].

Surface-based tests introduce another trade-off. Quartz-crystal microbalance with dissipation detects a loosely associated antibody layer, and an antibody-panel study reports correspondence between this signal and solution-behavior ranking [21]. The assay measures interactions near an instrument surface; correlations with bulk viscosity require appropriate reference panels and orthogonal tests. The central critical inference is that self-association evidence becomes more convincing when concentration-relevant rheology is paired with independent structural/dynamic readouts, while any proposed injection consequence still requires formulation–device measurement. The different observables and their principal interpretation limits are distinguished in **Table 1**.

Table 1. Evidence-bearing measurements and inferential boundaries for reversible protein association at elevated concentration

Evidence unit / physical system	Directly interrogated condition	Observable or analytical technique	Supported interpretation	Interpretation that remains unproved
Fc-fusion protein comparison	pH- and ionic-strength-dependent solutions	Static/dynamic light scattering with coarse-grained calculations	Reversible association responds to electrostatic conditions	Same magnitude or mode of association in other antibodies
Diabody–interleukin fusion protein	Protein-specific formulation setting	Hydrogen-exchange mass spectrometry with molecular modeling	A plausible association-contact region can be localized	Exact syringe viscosity or patient injection performance
Charged IgG1 solution	Concentration and ionic-strength contrasts	Scattering, electrophoresis,	Charge anisotropy complicates	Uniqueness of a fitted molecular contact geometry

		microrheology, colloid modeling	effective-charge descriptions	
Multiple IgG1/IgG4 antibodies	Concentration- and temperature-varying formulations	Neutron scattering and dynamic analyses	Transient clusters and dynamics can contribute to high viscosity	Universal cluster lifetime or viscosity cutoff
Low-material antibody screening	Dilute or precipitant-challenged tests	AF4 and PEG precipitation	Tested panels can be ranked for unfavorable solution behavior	Complete prediction at the final injection concentration
Antibody adsorption comparison	Protein layers at a sensing interface	QCM-D loosely interacting-layer metric	A surface-sensitive correlate of self-association can be measured	Direct visualization of native bulk cluster distributions

Abbreviations: AF4, asymmetric-flow field-flow fractionation; PEG, polyethylene glycol; QCM-D, quartz-crystal microbalance with dissipation; IgG, immunoglobulin G. Statements are study-context interpretations, not pooled results.

Evidence on viscosity, injection performance, and pharmaceutical deliverability

Viscosity is the resistance of a fluid to deformation under a specified shear condition. Its relevance to injection is mechanical but conditional: pressure and force depend not only on solution viscosity, but also on needle dimensions, flow history, delivered volume, syringe geometry, and device operation. Protein solutions may depart from Newtonian behavior; a single viscosity reading therefore cannot describe every injection-rate regime. For a dose mass held constant, raising concentration reduces the nominal liquid volume, but the accompanying change in force or duration must be assessed in the intended delivery system.

Dilute-solution predictors are attractive because late-stage high-concentration tests require material and time. An investigation of diffusion-interaction-parameter measurement found that its relation with concentrated antibody viscosity depended on measurement conditions; modification of salt conditions improved prediction in the study's development panels [22].

Sequence-dependent surface chemistry may reshape that relationship. A study of four IgG4 antibodies reported divergent pH–viscosity patterns and associated them with differences in surface charge patches, solvent-exposed regions, and interaction measures [23]. Altering pH or salt may thus change flow properties, but it may also affect chemical stability, conformational state, or patient-compatible formulation composition. A poly(glutamic acid)-based additive was investigated as a route to reduce viscosity of a concentrated IgG formulation [24].

Scattering-based excipient studies further show the importance of examining viscosity together with structural and physical stability readouts rather than rewarding fluidity in isolation [25]. A different physical approach dispersed spray-dried monoclonal-antibody particles in a nonaqueous vehicle and reported lower suspension viscosity than a comparator concentrated solution under investigated laboratory conditions [26]. This result is especially informative because it changes the formulation's material state.

The practical distinction is summarized in **Table 2**. It places the measured domain beside the unmeasured device-level consequence, because improvement in a low-material screen or rheological property is insufficient to establish finished-product deliverability. The strongest development comparison would pair concentration-series rheology with the actual needle/device configuration and repeated performance tests following relevant storage and handling histories.

Table 2. Where concentration–viscosity evidence does, and does not, reach injection-system performance

Intervention or evidence unit	Concentration / material-state contrast	Measured domain	Pharmaceutical question it informs	Device-level measurement still needed
Salt-adjusted diffusion interaction assay	Dilute interaction assay used to predict concentrated IgG viscosity	Dynamic-light-scattering interaction coefficient and high-concentration rheology	Which assay condition better forecasts viscosity within studied antibody panels?	Force–time profile in intended needle and syringe
IgG4 pH comparison	Related antibodies tested across formulation pH	Charge/surface descriptors, interaction, viscosity	Why can pH alter viscosity differently between antibodies?	Delivered dose and force after stability-qualified pH choice

Poly(glutamic acid) excipient approach	Concentrated IgG solution with candidate viscosity reducer	Formulation-dependent viscosity	Can a polymeric excipient change rheology in the tested system?	Needle flow, formulation compatibility, storage robustness
Excipient/scattering comparison	Antibody solutions with contrasting excipients	Small-angle scattering and physical stability/viscosity	Does reduced viscosity coincide with acceptable protein state?	Injection repeatability after process and storage exposure
Spray-dried antibody suspension	Concentrated particulate suspension versus solution comparator	Physical stability, binding-related assays, suspension viscosity	Can changing physical state alter the viscosity burden?	Suspension syringeability, dose uniformity, vehicle and device compatibility

The evidence units are analytically distinct; no universal acceptable viscosity, flow-rate, or force threshold is inferred. IgG, immunoglobulin G.

Interfacial damage, stability, and formulation-associated risks

Bulk self-association is not interchangeable with interfacial damage. Filling, pumping, transport, syringe handling, air bubbles, lubricants, and contact with container materials impose changes in interfacial area and composition. Proteins may adsorb, rearrange, and detach as particles, even when bulk measurements suggest acceptable colloidal behavior. A study of a high-concentration antibody found that the effectiveness of a polysorbate surfactant depended on protein concentration and air–liquid interfacial occupancy; under the highest investigated concentration, surfactant did not fully prevent subvisible particle formation [27].

Comparison across biological modalities sharpens this challenge. Measurements of surface activity and interfacial stress for an IgG and an Fc-fusion protein identified differences in adsorption behavior, interfacial film response, and particle formation, including altered behavior in the presence of polysorbate 80 [28]. Interfacial instability therefore reflects the protein and the evolving surface film, not just the presence or absence of an excipient. The relation between agitation history and particle burden depends on how surfaces are generated and disrupted, which complicates simple acceleration from a short shake test to shelf life or injection-use conditions.

Mechanistic modeling can help to dissect coupled steps. Experiments paired with molecular-dynamics simulations of peristaltic-pumping stress suggest that pH, ionic strength, protein adsorption, and detachment jointly modify interfacial particle formation [29]. That study included human growth hormone and lysozyme, so the detailed mechanistic attribution cannot be transferred automatically to high-dose IgG. Follow-on work compared mechanical stress at distinct compressible interfaces, including air–liquid and silicone–liquid contexts [30].

Packaging contributes additional, different sources of uncertainty. Investigation of the surface properties of primary packaging during reconstitution of lyophilized high-concentration antibody products concerned bubble behavior during *reconstitution* [31]. It must not be misrepresented as a direct demonstration of syringe injection failure. Conversely, an experimental agitation-stability comparison of marketed antibodies found that familiar developability parameters did not reliably track agitation-induced aggregation under its deliberately harmonized, surfactant-free test conditions, whereas interfacial-property measures were informative [32]. This is an important negative result for screening transferability, and a caution against using thermally oriented or dilute solution assays as exhaustive surrogates for interface tolerance.

Interactions with combination-product materials require separate attention. A study of zinc extraction from rigid needle shields examined metal leaching and subsequent interactions in a biologic formulation, linking material contact, time, temperature, and excipient context to an additional product-specific risk [33]. Other work on oleic-acid-induced antibody aggregation investigates fatty-acid-associated contamination or destabilization as a distinct chemical route [34].

Figure 1 separates the different paths from molecular interactions to bulk rheology, interfacial particle generation, and combination-product performance. Its cross-links are deliberately conditional: a molecular association measurement cannot substitute for particle counts, and a particle result cannot independently specify injection force.

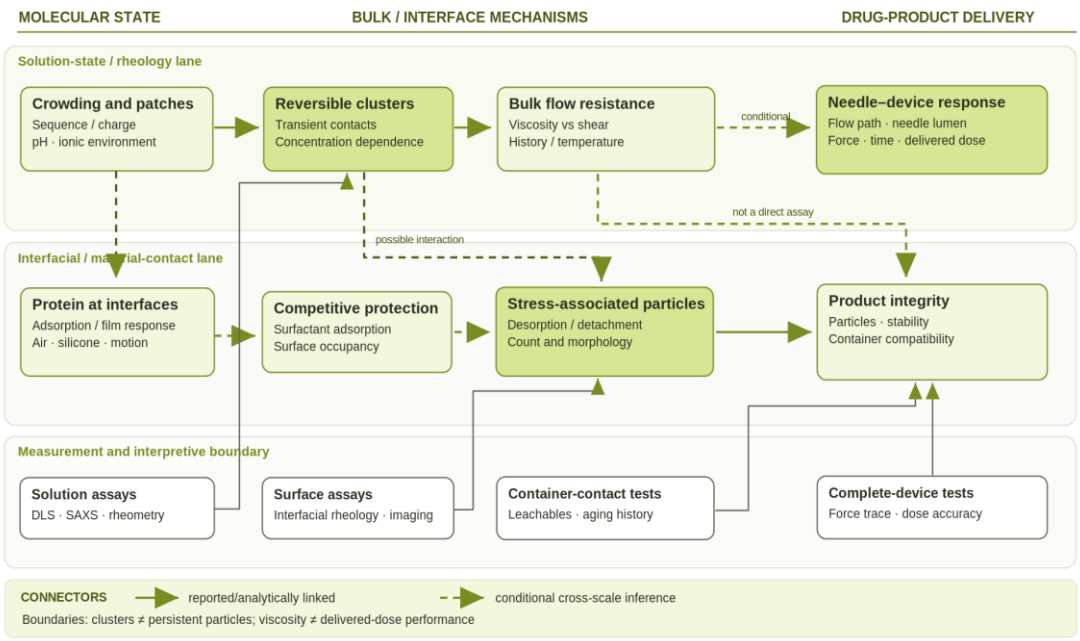


Figure 1. Concentrated protein delivery under coupled molecular, interfacial, and device stresses

Caption. A multiscale interaction map reads from molecular state at left through bulk-fluid and surface-associated mechanisms toward drug-product delivery at right. Solid connectors denote relationships directly addressed by the cited experimental literature; dashed connectors denote conditional extrapolations that still require linked experiments. Separate paths track reversible clustering and viscosity, interfacial adsorption and particle formation, and container-associated chemical exposure. Device force and delivered dose belong to the completed formulation–container–device system. The visual separation prevents identification of transient protein clusters with irreversible particles or of analytical viscosity with clinical administration outcomes. Abbreviations: DLS, dynamic light scattering; SC, subcutaneous.

Alt text. Wide, three-tier diagram. Left column shows molecular concentration, charge-patch attraction, and reversible clusters. Center upper lane runs toward bulk viscosity and rheological measurement; center lower lane shows air–liquid/silicone interfaces, adsorption and stress, with a separate material-leachables node feeding particle or stability risk. Right column contains needle/device flow resistance and dose delivery. Solid arrows connect measured phenomena within a level; dashed arrows connect cross-level steps requiring paired verification. Horizontal boundary bands distinguish molecular, formulation and device evidence, with a legend at bottom.

Comparative evaluation of formulation and delivery strategies

A formulation strategy changes several physical conditions at once. Preferential interaction computations for IgG1 with sorbitol, sucrose, and trehalose provide a molecular rationale for investigating sugar excipients, but calculated solvent preferences cannot independently establish manufacturability or shelf life [35]. Surfactant comparisons involving Kolliphor HS 15, Kolliphor ELP, polysorbates, and poloxamer broaden the choice of interfacial protectants; effectiveness must be checked against the particular protein, interface, and agitation protocol [36]. In a two-antibody excipient study, glutamate and methionine had contrasting effects across the antibodies examined, making a universal excipient ranking untenable [37].

Storage-focused studies expose a second axis of optimization. Four antibodies examined across formulation and incubation conditions exhibited non-Arrhenius aggregation-rate behavior; accelerated-temperature rankings were frequently misleading relative to refrigerated conditions in that experimental panel [38]. Sequence modification is yet another lever: anti-IL-8 IgG mutants were evaluated for manufacturability and critical quality attributes, illustrating how developability can change with molecular design while leaving syringe force and clinical administration unestablished [39].

At the drug-product level, the lower-concentration/higher-volume alternative changes delivery volume and patient-use demands [3]. Particle suspensions can change flow behavior by shifting the material state, while also introducing suspension uniformity and physical-storage questions [26]. Reduction of antibody-solution viscosity

using a polymeric additive offers a distinct formulation intervention [24]. None of these strategies removes the need to characterize the completed container and device. The most informative comparator is therefore a matched delivered protein mass, with force–time traces, volume accuracy, particles, and stability assessed under each candidate's relevant operating and storage conditions. **Table 3** compares the intervention's physical target with the failure modes requiring independent measurement.

Table 3. Formulation interventions cross-classified by the physical burden they relocate

Strategy / evidence setting	Directly changed feature	Evidence-bearing endpoint	Residual failure mode or comparator
Sugars and preferential solvation in IgG1	Protein–cosolute interaction environment	Modeled interaction preferences and experimental aggregation/viscosity context	Protein specificity; storage behavior requires validation
Surfactant substitution in antibody formulations	Air–liquid and other surface competition	Tensiometry, interfacial rheology and adsorption-related assays	Protein-specific film protection during relevant stresses
Individual excipients across two HIV antibodies	Formulation composition around different mAb surfaces	Contrasting stability and viscosity-related observations	Opposite excipient responses in distinct antibodies
Antibody sequence variants	Protein surface and manufacturability attributes	Variant-level quality/developability measurements	No direct inference about device force or clinical dose
Polymeric viscosity modifier or particulate suspension	Bulk rheology or material state	Formulation viscosity and physical-characterization measures	Syringeability, homogeneity, compatibility and shelf life
Lower concentration with larger volume	Dose-volume allocation	Delivery-option comparison in review literature	Tissue capacity, administration time and user acceptability

The comparisons are qualitative; no effect sizes are pooled and no intervention is ranked across untested proteins or devices.

Areas of evidence agreement, contradiction, and methodological uncertainty

A broad point of agreement is that the concentration–viscosity relationship depends on both protein molecular surfaces and solution conditions. Studies using scattering and colloid representations support association-sensitive rheology, although their fitted parameters and dynamic windows differ [10]. Direct work on antibody subclass and interaction patches emphasizes molecular specificity [11]. The inference is narrower than an equation that would transfer unchanged across unrelated therapeutic proteins.

Prediction studies expose disagreement about observability. A diffusion interaction coefficient measured in dilute solution can be useful within a calibrated antibody panel, yet the association with concentrated viscosity changed with salt conditions [22]. Surface-bound assays and precipitation screens can rank problematic proteins under chosen tests [20]. Their signals are not equivalent to the shear-dependent viscosity of a final fill, still less to expulsion force in a particular device. Similar caution applies to computational predictions trained on antibody panels, whose apparent portability depends on training coverage and assay matching [8].

Stability evidence adds a distinct methodological conflict. Interfacial studies show that particle formation responds to competitive adsorption, molecular identity, and mechanical exposure [27]. Accelerated aggregation at elevated temperature may reorder formulation preferences compared with refrigeration [38]. These results are compatible once the endpoints and histories are distinguished: a short-term bulk interaction measurement, an agitated particle count, and a refrigerated monomer-loss rate investigate separate risks. More informative comparisons would use the same protein batches, matched excipient compositions, common concentration units, explicit shear histories, and independent analytical techniques. Reporting uncertainty should include discordant or null measurements, not only successful predictions.

Critical synthesis of formulation trade-offs

For a fixed prescribed protein mass, a higher concentration lowers nominal liquid volume. The physical feasibility of that adjustment remains contingent on the concentration-dependent fluid response, available drive pressure, needle and reservoir geometry, temperature, flow profile, and the required administration interval. A lower-

concentration option may simplify rheology while increasing volume-related constraints. The trade-off can therefore reverse when device capability, tissue accommodation, or stability differs between products [4].

A useful decision sequence separates three questions. First, does the molecular system remain sufficiently soluble and physically stable at the proposed concentration and over its realistic storage period? Second, can the target volume be expelled reproducibly within the intended force, flow and time operating envelope? Third, does the complete configuration maintain dose accuracy, particle control, and patient-facing usability across manufacturing, transport and handling histories? These are proposed comparative questions, not a validated scoring instrument. **Table 4** identifies which observations answer each question and where additional product-specific work is essential.

Table 4. Decision-relevant measurements for competing concentration–volume presentations

Development decision	Necessary direct observation	Common misleading shortcut	Discriminating comparison
Select a concentration	Solubility and concentration-series rheology at justified shear/temperature	Single dilute self-association number	Same molecule, controlled pH/excipients, multiple concentrations
Select a viscosity intervention	Flow curve plus physical/chemical stability of reformulated product	Lowest viscosity as sole criterion	Paired stability and syringe-flow tests after relevant aging
Select a container–device combination	Force–time trace, delivered-volume accuracy and compatibility	Bulk viscosity treated as injection outcome	Same drug mass through actual alternative configurations
Manage interfaces and contact materials	Particle profiles, contact/leachable studies and handling stress	Surfactant presence assumed fully protective	Relevant agitation, air exposure and container-contact controls
Choose accelerated studies	Storage-condition rank order and mechanism-sensitive assays	Elevated-temperature rank order taken as shelf-life truth	Refrigerated and accelerated conditions interpreted separately
Decide between low-volume and high-volume presentations	Integrated delivery feasibility and use-context evidence	Volume or concentration optimized alone	Matched-dose options with device and use-condition differences

Rows specify proposed development comparisons informed by the reviewed experimental domains; they do not claim prospectively validated acceptance limits.

Figure 2 maps the feasible choice as overlapping operating requirements: molecular stability, fluid transport, device performance, and the administered volume must all remain acceptable under the same product-specific conditions. Conditional connectors mark where published molecular or formulation measurements have not been jointly validated against final administration outcomes.

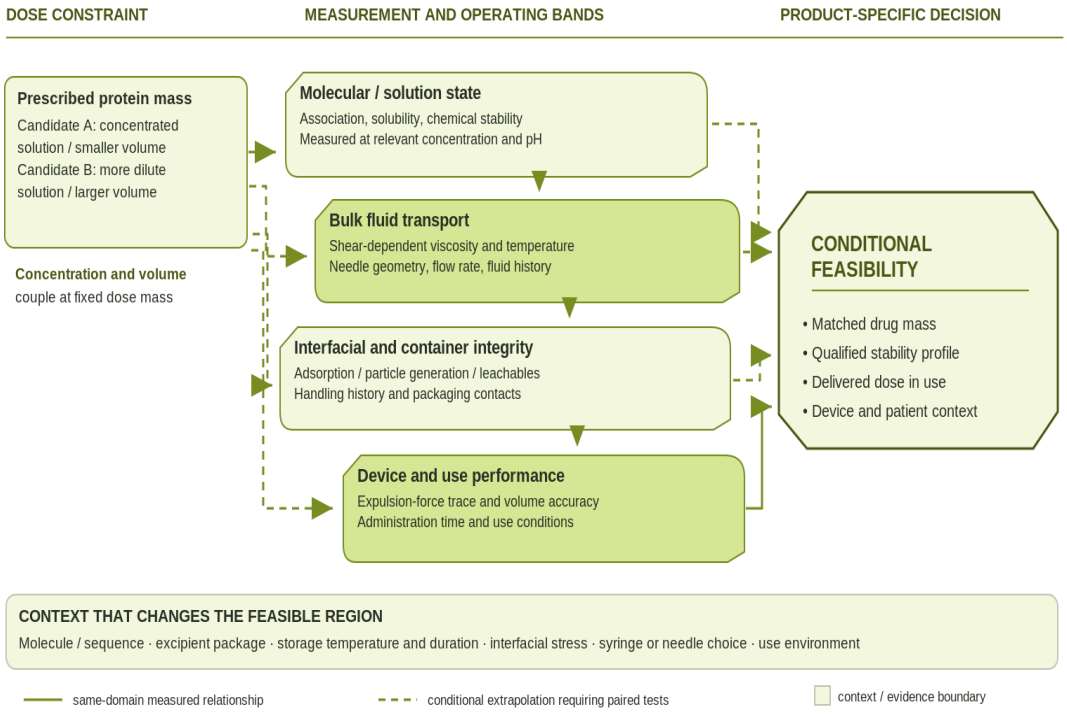


Figure 2. Feasibility of high-dose protein injection depends on overlapping formulation, interface, and device constraints

Caption. A conditional feasibility landscape reads from the matched-dose concentration/volume choice at left to intersecting assay, stability and delivery constraints in the middle, then to a product-specific feasibility assessment at right. Solid connectors represent relationships supported within named experimental domains; dashed connectors identify unvalidated cross-domain prediction. A separate uncertainty band denotes protein identity, excipients, storage history, temperature, interfacial stress and patient-use context. The diagram is a critical synthesis without numeric cutoffs or implied clinical validation. Abbreviations: SC, subcutaneous; mAb, monoclonal antibody.

Alt text. Landscape diagram. A left-hand panel shows a matched-protein-mass choice between concentrated/low-volume and dilute/high-volume presentations. The center has four vertically staggered bands for solution-state stability, shear-dependent flow, interfaces and particles, and device delivery. Solid lines link measurements within bands. Dashed crossing lines reach a right-hand product-specific feasibility region only when joint confirmation is needed. A lower boundary strip lists changing molecule, formulation, storage and use conditions; the legend distinguishes observations, conditional extrapolations and context boundaries.

Research gaps and future pharmaceutical development priorities

The most consequential gap is paired multiscale measurement. Studies that determine scattering-derived association or diffusion and then measure rheology on the same aged formulation should also obtain finished-device injection profiles. Such designs could test whether cluster descriptors add predictive information beyond a measured flow curve, and whether the advantage survives changes in protein sequence, pH, salt and excipient package. Prespecified, protein-disjoint external validation is particularly important for machine-learning developability metrics [7].

Interfacial robustness deserves a separate comparison across air–liquid, silicone–liquid and relevant packaging contacts, preferably tracking both particles and chemically altered species [30]. Storage experiments should distinguish refrigerated behavior from accelerated stress and relate aggregation mechanisms to clinical product specifications without extrapolating from one protein [38]. Finally, matched-dose studies across low- and high-volume presentations should report realistic force, duration, delivered mass, residual volume and usability outcomes. Such experiments would permit an actual pharmaceutical trade-off analysis; current evidence more often supplies isolated components.

Review limitations

The literature identification was topic-directed and did not produce a complete deduplicated screening ledger. The selected citations therefore support a critical account rather than estimates of prevalence, exhaustive study coverage or pooled effects. Some bibliography entries still require final author and publication-metadata verification. Comparability is also limited by heterogeneous proteins, concentration conventions, rheological devices, interface protocols, and storage histories. In several studies, measured molecular effects were only indirectly connected to injection mechanics. The proposed comparisons have not been prospectively validated and should not be interpreted as design specifications.

CONCLUSION

High-concentration protein formulation trades injection volume against a shifting combination of molecular interactions, viscosity, interfacial exposure, stability and device demands. Reversible protein clustering can contribute to resistance to flow, but its strength, dynamics and analytical observability depend on molecule and formulation. Particle formation and long-term deterioration follow partly distinct processes that can escape familiar early screening tests. Choosing a low-volume concentrated product over a larger-volume alternative consequently requires evidence from the entire formulation–container–device configuration and its intended storage and administration conditions. Matched-dose, cross-scale comparisons offer the clearest path toward defensible choices without presuming that one assay predicts every delivery outcome.

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