WHITE PAPER

NONCLINICAL FORMULATION DEVELOPMENT - JUNE 2026

Nonclinical Formulation Strategies

for Early-Stage to First-In-Human Small Molecule Programs

- Solubility & pH
- Tox Formulations
- Solid Form
- IV Safety Risks

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Executive Summary

Sound and timely formulation decisions are foundational to generating consistent pharmacology and toxicology data, protecting program timelines, and bridging nonclinical work to a clinically viable drug product. This white paper offers a high-level overview of Integrated Pharma Consulting's approach to nonclinical formulation strategy for small molecule programs, from early discovery through first-in-human (FIH) studies.

Key topics covered include the formulation development continuum, solubility classification and pH optimization, solid form considerations, toxicology formulation objectives, excipient selection, and IV-specific assessments. Full formulation guides and excipient lists are available to clients upon engagement.

KEY INSIGHTS

▶ Formulation strategy must evolve in a phase-appropriate manner from discovery through FIH.

▶ Solubility, solid form, and stability are foundational; characterize early and track changes across batches.

▶ Toxicology formulations must maximize exposure without introducing extraneous safety signals.

▶ IV formulations require assessment of sterility, osmolality, hemolytic potential, and precipitation risk.

▶ pKa-guided pH optimization is often the most effective, and overlooked, solubilization strategy.

1. The Formulation Development Continuum

Formulation strategy is not a static decision. It must evolve as programs advance from discovery through registrational development. Each stage carries distinct objectives, constraints, and regulatory expectations. Failing to plan for this evolution is a common and costly source of program delay.

Stage-Appropriate Goals

- **Discovery / Proof-of-Concept (POC):** A general, highly solubilizing vehicle enabling SAR comparisons across compound series and reference compounds.
- **IND-Enabling Toxicology:** A compound-specific formulation maximizing systemic exposure without excipient-related signals.
- **FIH / Phase I–II:** A human-suitable formulation aligned with the Target Product Profile (TPP) and intended clinical route.
- **Phase III / Registrational / Commercial and Post-Marketing:** The final drug product (DP) formulation, optimized for manufacturability, stability, dose schedules and strengths, patient convenience, and regulatory compliance. Post-marketing formulation changes may be driven by market and clinical feedback, including changes in route of administration, dose schedules, improved bioavailability, stability, or ease of manufacture. These are outside the scope of this white paper.

Why This Matters for Your Program

Transitions between formulation stages require formal bridging activities — including head-to-head or crossover PK studies, dissolution testing, and in vitro compatibility assays for IV-administered drugs. Regulatory agencies may require demonstrated exposure comparability between nonclinical enabling formulations, particularly those from formal toxicology studies, and the intended clinical formulation. IPC can help teams plan and execute these bridging activities efficiently.

2. Solubility: Classification, pH Dependence & Developability Risk

Solubility is the single most important physicochemical property governing formulation feasibility. Understanding a compound's solubility early, and interpreting it correctly, is essential for making informed formulation decisions and setting realistic developability expectations.

Key Distinctions Programs Often Overlook

- Kinetic solubility (common in discovery screening) can overestimate true solubility and should be interpreted with caution.[1]
- Thermodynamic solubility, measured from solid compound at equilibrium, is the relevant value for formulation development and should be correlated with the solid form.[1]
- For ionizable compounds, pKa-guided pH optimization can achieve target concentrations with minimum, if any, excipients, often the simplest and most elegant solution.

Perspective

Under the Biopharmaceutics Classification System (BCS), compounds with low aqueous solubility (e.g. Classes II and IV) present the greatest formulation challenge. Practitioners often describe these informally as "brick dust" (high lattice energy) or "grease balls" (excess lipophilicity), both of which represent the highest formulation risk profiles.[2] Integrated Pharma Consulting helps teams identify these liabilities early and engage with medicinal chemistry teams before candidate nomination, when course correction is still practical.

Case Study Highlight

An oral formulation consisting of 20% HPβCD (toxicology risk) in water at neutral pH was used for discovery. Prior to tox studies, the HPβCD suspension (which settled over time) was replaced by a stable, clear solution using 0.5% MC via simple pH adjustment based on pKa.

3. Solid Form Considerations

Solid form encompasses polymorphs, salts, co-crystals, solvates, hydrates, and amorphous material. The solid form directly affects dissolution rate, apparent solubility, and formulation reproducibility. While often treated as a late-stage CMC concern, solid form has direct and significant implications for nonclinical work.

What Teams Often Miss

- Amorphous-to-crystalline transitions between early R&D and CMC batches can produce >10-fold solubility differences, collapsing a working formulation overnight.[3]
- Non-solvated polymorphs of the same compound typically exhibit ≤2-fold differences in solubility, though exceptions with substantially greater differences are documented in the literature.[4]
- IV formulations are especially vulnerable: a batch change that reduces solubility can render a previously functional formulation inadequate at the start of an IND-enabling study.
- A brief XRPD characterization of early R&D batches, even for informational purposes only, creates a baseline that prevents time-consuming surprises at candidate nomination.

Case Study Highlight

An IV formulation that met concentration targets with an R&D batch failed when the process chemistry batch arrived. A >4× solubility drop traced entirely to a solid form change and last-minute modifications to the formulation were required. XRPD of the original batch, had it been collected, would have flagged the risk weeks earlier.

4. Formulation for Toxicology Studies

Toxicology studies represent the most formulation-intensive phase of nonclinical development. The primary objective is to administer sufficient compound to characterize the pharmacological and toxicological dose-response, without the formulation itself confounding the readout.

Core Objectives

- Maximize systemic exposure to enable characterization of potential adverse effects that might occur in a clinical setting.
- Avoid excipient-related signals that may mask or exacerbate test article effects. Common liabilities include surfactants (GI irritation), HPβCD (elevated liver enzymes with repeat dosing), DMSO (ocular effects with repeat dosing), and extreme pH or tonicity.[5]
- Achieve a complete solution or homogeneous suspension stable for ≥24 hours, using non-proprietary components that CRO staff can prepare reliably on-site.

! **IMPORTANT**

A toxicology formulation is NOT a “kitchen sink” of available solubilizers, nor is it necessarily the clinical formulation (NOTE: for ROAs other than oral, it is preferred to use the intended clinical formulation where feasible). Many excipients appropriate for single-dose PK studies are unsuitable for repeat-dose or GLP toxicology. Be aware of novel excipients, salt forms, or technologies planned for clinical formulation as these may need to be qualified during toxicology studies. Allow sufficient time for formulation development and PK bridging. This timeline must be built into program planning at candidate nomination.

5. Excipient Selection & Dose Parameters

Formulation screening follows a systematic cascade: starting with the simplest aqueous approaches (pH-adjusted water or buffered vehicle) and progressing through emulsifying agents, surfactants, co-solvents, and more complex solubilization strategies such as SDDs, HME, SNEDDS/SMEDDS, cyclodextrins, nanomilling, etc. only as needed.

Representative Excipient Limits

The table below highlights a selection of commonly used nonclinical excipients.[6] Integrated Pharma Consulting's full formulation guides, covering oral and IV routes with context-specific guidance, tolerability notes, and bioanalytical interaction flags, are available to clients upon engagement.

Excipient	Notes / Key Considerations
Methylcellulose 0.5% (PO)	Preferred suspending agent; well-tolerated across species
HPMC ≤2% (PO)	Emulsifying/suspending agent; suitable for repeat-dose studies
Tween 80 ≤0.2% (PO)	⚠ GI irritation risk at higher concentrations, particularly in dog
PEG 400 ≤40%	⚠ Bioanalytical interference risk (ion suppression in LC-MS/MS)
HPβCD ≤10% (IV)	⚠ Monitor ALT/AST with repeat dosing; may mask hepatic findings
DMSO ≤10% (IV)	⚠ Ocular effects reported with repeat dosing in some species
Normal saline ± pH (IV)	First-line IV vehicle; sterile; preferred starting point

pH & Dose Volume Guidelines

Formulations must fall within acceptable pH ranges and dose volumes to avoid confounding physiological effects. Values outside these ranges can cause GI injury, venous irritation, pain, or tissue necrosis.[7]

Species	PO pH	IV pH (bolus)[a]	IV Vol (mL/kg)	PO Vol (mL/kg)
Mouse / Rat	3–9	4–8	≤5	≤10
Dog / Cyno	3–9	4–8	≤2.5	≤5

[a] Slow infusion pH should be 7-8.

6. IV-Specific Safety Assessments

Because IV-administered materials enter systemic circulation directly, formulation-related adverse events are more immediate and potentially severe than for oral routes.[8] Four pre-study assessments are essential for any new IV formulation.

Required Assessments

- **Osmolarity/Osmolality/Tonicity:** These three terms are related but distinct and are frequently conflated. Osmolarity (Osmol/L) is temperature-dependent; osmolality (Osmol/kg) is temperature-independent and is the pharmaceutical standard, measured by osmometer with a target range of 280–310 mOsm/kg. Tonicity is a unitless measure of osmotic pressure across a semi-permeable membrane and should approximate physiological values. Values significantly outside range risk RBC crenation (>600 mOsm/kg) or hemolysis (<150 mOsm/kg). Note that the drug itself may contribute to osmolality at high concentrations.
- **Hemolytic Potential:** In vitro assessment using whole blood from the relevant species, with positive and negative controls and drug-only versus formulated drug comparisons across clinically relevant dilutions. In general, a hemolysis value >25% may be considered hemolytic while <10% would be considered nonhemolytic.[9]
- **Precipitation / Flocculation:** Assessment in isotonic phosphate buffer (0.067 M, pH 7.4), plasma, or whole blood at dilution ratios representative of anticipated in vivo exposure.
- **Sterility:** IV-administered formulations bypass the body's protective barriers and must be sterilized prior to dosing. Filtration through a 0.22 µm filter immediately before injection is the common nonclinical approach and has the added benefit of removing residual particulates that could cause embolism.

CAUTION

For dose escalation studies using novel IV formulations, a single ascending dose (SAD) design in higher-order species is strongly advisable. Integrated Pharma Consulting has designed and overseen these assessments across a range of compound classes and can help teams avoid common study design pitfalls before in-life work begins.

7. Closing Summary

Nonclinical formulation strategy is a discipline that requires deliberate planning, phase-appropriate execution, and proactive risk management. The key principles covered in this white paper, evolving formulation approach across development stages, early solubility and solid form characterization, excipient selection for toxicology, IV-specific pre-study assessments, and alignment with the Target Product Profile, are collectively foundational to generating reliable data and protecting program timelines.

Formulation decisions that are not aligned with the intended clinical plan risk generating nonclinical data that is difficult to bridge to the clinical formulation, or creating a development path inconsistent with the target label, triggering regulatory agency pushback. Engaging formulation expertise early, at or preferably before development candidate nomination, is among the highest-value investments an early-stage program can make. Integrated Pharma Consulting partners with teams at this critical juncture to build phase-appropriate formulation roadmaps aligned with clinical and regulatory objectives.

References

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If your program is approaching development candidate nomination, entering toxicology enabling studies, or planning a FIH study, reach out to Integrated Pharma Consulting at info@integratedpharmaconsulting.com to discuss formulation strategy support.

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