phosphorex

# LNP Scale-Up Readiness Checklist

## 15 Questions to Answer Before Moving Beyond Bench Scale

PHOSPHOREX PRACTICAL DEVELOPMENT TOOL

A promising bench-scale LNP formulation is only the starting point. Early formulation choices, downstream unit operations, analytical strategy, and CMC planning can all influence whether particle performance is preserved as a program advances. Use these questions to identify potential scale-up risks before committing valuable time and material.

## Formulation Readiness

**1. Does the lead formulation extend beyond small-scale biological performance?**

Candidate selection should also consider manufacturability, stability, and whether the formulation can realistically progress to clinically relevant production.

**2. Is the LNP sufficiently defined, characterized, and understood?**

Document the composition and rationale, including the ionizable/helper lipids, PEG-lipid, cargo, buffers, and other components that may affect particle behavior.

**3. Have the critical particle attributes been identified?**

At minimum, understand attributes such as particle size, polydispersity, encapsulation efficiency, cargo integrity, stability, and other program-relevant CQAs.

**4. Is the formulation stable under conditions relevant to future processing and storage?**

Instability that appears in later development phases or scale-up can create significant delays and rework.

## Analytical Readiness

**5. Are fit-for-purpose analytical methods in place to assess the attributes that matter?**

Analytical methods should generate the data needed to evaluate physicochemical properties, stability, cargo integrity, and biological performance as the program advances.

**6. Can the analytical methods distinguish process-related changes in the LNP?**

Scale-up can alter particle size distribution, composition, encapsulation, morphology, or other CQAs. The analytical package should be capable of detecting meaningful changes.

**7. Is there a plan to increase analytical method rigor as development progresses?**

A stage-appropriate, risk-based strategy allows methods to evolve toward qualification and validation as the program moves closer to clinical development.

## Process & Downstream Readiness

### 8. Has the upstream mixing process been evaluated for scalability?

Assess the mixing approach using equipment and operating conditions that translate to larger, clinically relevant production scales.

### 9. Have clinically relevant downstream operations been considered early?

Purification, buffer exchange, concentration, and filtration can materially affect LNP quality and should not be treated as an afterthought.

### 10. Has the formulation been evaluated for shear sensitivity?

Some LNPs can aggregate or otherwise change downstream when scaled. Understand this risk before scale-up.

### 11. Are TFF parameters being developed around the specific formulation?

Membrane chemistry, MWCO, surface area, concentration factor, transmembrane pressure, feed flow, diafiltration conditions, and loading can all influence recovery and CQAs.

### 12. Has downstream buffer composition been optimized?

Buffer species, pH, and ionic strength can influence LNP size, morphology, and stability during downstream processing.

## CMC & Translation Readiness

### 13. Are CQAs linked to the process parameters that control them?

A scalable process development plan should demonstrate how formulation intent and critical quality attributes will be maintained as process conditions change.

### 14. Can the process be reproduced consistently with acceptable yield and material use?

Reproducibility and recovery become increasingly important when payload is limited or expensive and when material must support toxicology or clinical studies.

### 15. Is the program being developed with the future GMP operation in mind?

Early feasibility decisions should anticipate clinical and commercial manufacturing requirements to reduce redesign, repeated development, and tech-transfer risk.

## Ready to Move Forward?

If several questions remain unresolved, the program may benefit from additional formulation, analytical, process development, or CMC work before scale-up. Phosphorex integrates these disciplines to help preserve delivery performance while building a clinically viable path forward.

*Use this tool as a discussion framework, not as a substitute for program-specific scientific, quality, regulatory, or manufacturing assessment.*

