# Addressing manufacturing bottlenecks in small-volume GMP batches of mRNA-LNP products with the NANOme®

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## Introduction

This document outlines the potential of the NANOme® system, a next-generation GMP-compliant manufacturing technology developed by leon-nanodrugs, designed to support decentralized and point-of-care (PoC) manufacturing of nanoparticle-based advanced therapy medicinal products (ATMPs) and vaccines. As therapies such as autologous gene therapies and individualized mRNA immunotherapies become more prevalent, existing centralized GMP manufacturing models are proving increasingly inadequate. These traditional systems often lack the responsiveness required to deliver time-sensitive, patient-specific treatments or scale efficiently in emergency scenarios.

Recent regulatory initiatives — including the **Human Medicines (Modular Manufacture and Point of Care) Regulations 2025** and the **Draft Guidance on Individualised mRNA Cancer Immunotherapies** — reflect a growing recognition of the value and necessity of modular and near-patient manufacturing approaches. Despite this progress, the industry is currently facing several key challenges in the manufacturing of nanoparticle-based products intended for small batches (i.e., individual therapies (n=1), or groups of patients) (Table 1).

***Table 1**. Current challenges for manufacturing of small GMP batches of nanoparticle-based products.*

| Category | Challenge | How NANOme® alleviates/eliminates the challenge |
|---|---|---|
| Operational | Small batch size & fast turnaround needed | Enables rapid encapsulation of mRNA in sterile batches (50–1200 mL) in 10–20 minutes, ideal for personalized therapy timelines. |
| | Frequent changeovers & cleaning validation | Uses pre-assembled, single-use cassettes eliminating cleaning and cleaning validation, and reducing downtime and cross-contamination risk in the encapsulation step. |
| | Decentralized or PoC production requirements | Compact, benchtop system supports GMP-compliant encapsulation at hospital pharmacies, modular suites, or regional hubs, enabling proximity to patients. |
| Technological usability | Difficulty in miniaturizing encapsulation technologies | Provides closed, miniaturized GMP-compliant mRNA encapsulation, eliminating the need for large, customized LNP systems. |
| | Reproducibility in LNP formulation | Encapsulation is controlled via validated, predefined input parameters, improving batch-to-batch consistency even at n=1 scale. |
| | Sterility assurance during encapsulation | Fully closed and sterile design with gamma-sterilized cassettes ensures aseptic processing without cleanroom fill-finish dependencies for this step. |
| Cost-related | High cost due to manual or large-scale systems | Reduces cost by eliminating the need for cleaning, minimizing facility and equipment overhead, and streamlining encapsulation at point-of-need. |
| | Labor-intensive and error-prone manual steps | Operated via GMP-compliant software, reducing human intervention, training burden, and error rates during encapsulation. |
| Regulatory | Complex validation of encapsulation step | Predefined, validated parameters enable easier regulatory filing and batch release for encapsulation-specific operations. |
| | Facility compliance hurdles | Closed system reduces environmental requirements, easing GMP facility design for encapsulation in decentralized settings. |
| Data & Integration | Traceability and documentation gaps | Controlled by 21 CFR Part 11 GMP-compliant software, ensuring traceable, auditable encapsulation records suitable for regulatory submission. |

## The NANOme® system

The NANOme® is a single-use, cassette-based manufacturing system purpose-built for GMP-compliant decentralized and PoC manufacturing. Designed as a benchtop, fully closed system, it uses a pre-assembled cassette that is gamma sterilized and enclosed in triple-layer sterile packaging to ensure integrity and ease of integration. It supports both individualized batch sizes (n=1) and high-throughput vaccine production, within a compact and closed design suitable for hospital pharmacies, regional hubs, or modular GMP suites.

Key features:

- Production of sterile batches (50–1200 mL) in 10–20 minutes
- Pumpless system eliminating risk of shear-stress and degradation of materials
- Operated using 21 CFR Part 11 GMP-compliant software
- No cleaning or cleaning validation required between batches
- Process controlled by predefined, validated input parameters

The system accelerates production timelines and reduces operational complexity, making it well suited to the unique needs of ATMPs and mRNA-based therapies.

## Process development: From NANOlab® to NANOme®

Manufacturing workflows begin in the NANOlab®, where leon-nanodrugs' proprietary FR-JET® technology is used to formulate and characterize nanoparticle-based drug products. This includes lipid nanoparticles (LNPs), polymer nanoparticles, or liposomal formulations commonly used for mRNA or CRISPR-based therapies.

Stepwise process:

1. Formulation development in the NANOlab® using a stainless-steel or polymer FR-JET® modular mixer, composed of configurable pinhole nozzles and spherical mixing chambers
2. Identification and characterization of critical process parameters (CPPs) and critical quality attributes (CQAs)
3. A key CPP, the pressure output generated by the pumping system at defined flow rates, is recorded and serves as the only input value transferred from the NANOlab® to the NANOme®
4. In the NANOme® system, this pressure value is used as pressure input, which in turn defines the flow rate required to produce a GMP batch

This design enables a controlled and reproducible manufacturing process, based on the following parameters:

- Pressure input (derived from NANOlab® pressure output)
- Flow rate ratio (mRNA to lipid phase)
- Volume of bags containing the starting solutions (i.e., mRNA and lipids)
- FR-JET® nozzles and chamber dimensions
- Lipid concentration in ethanol
- mRNA concentration in buffer

These parameters are used to define and control the manufacturing process within a validated design space, enabling real-time release based on parametric process control rather than traditional end-product testing.

## Opportunity for regulatory innovation

The NANOme® system presents an opportunity to align manufacturing innovation with emerging regulatory frameworks. Its design supports practical implementation of decentralized GMP production models and provides a real-world basis for exploring:

- Parametric release models for nanoparticle-based medicinal products
- GMP aseptic processing for point-of-care and modular manufacturing facilities
- Broader acceptance of processes utilizing single-use and closed-systems
- Harmonization of regulatory pathways across EU member states for individualized therapies

These directions align with current policy shifts and provide a technological foundation to reduce bottlenecks in ATMP access while ensuring compliance with quality and safety standards.

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## Key takeaway

The NANOme® system represents a breakthrough in the encapsulation of mRNA for personalized and small-batch therapies by combining speed, sterility, and GMP compliance in a compact, closed format. Its single-use, cassette-based design eliminates the need for cleaning and validation, significantly reducing operational complexity and turnaround time. By enabling decentralized, reproducible LNP formulation, the NANOme® makes individualized mRNA and gene-editing therapies more feasible, scalable, and accessible.