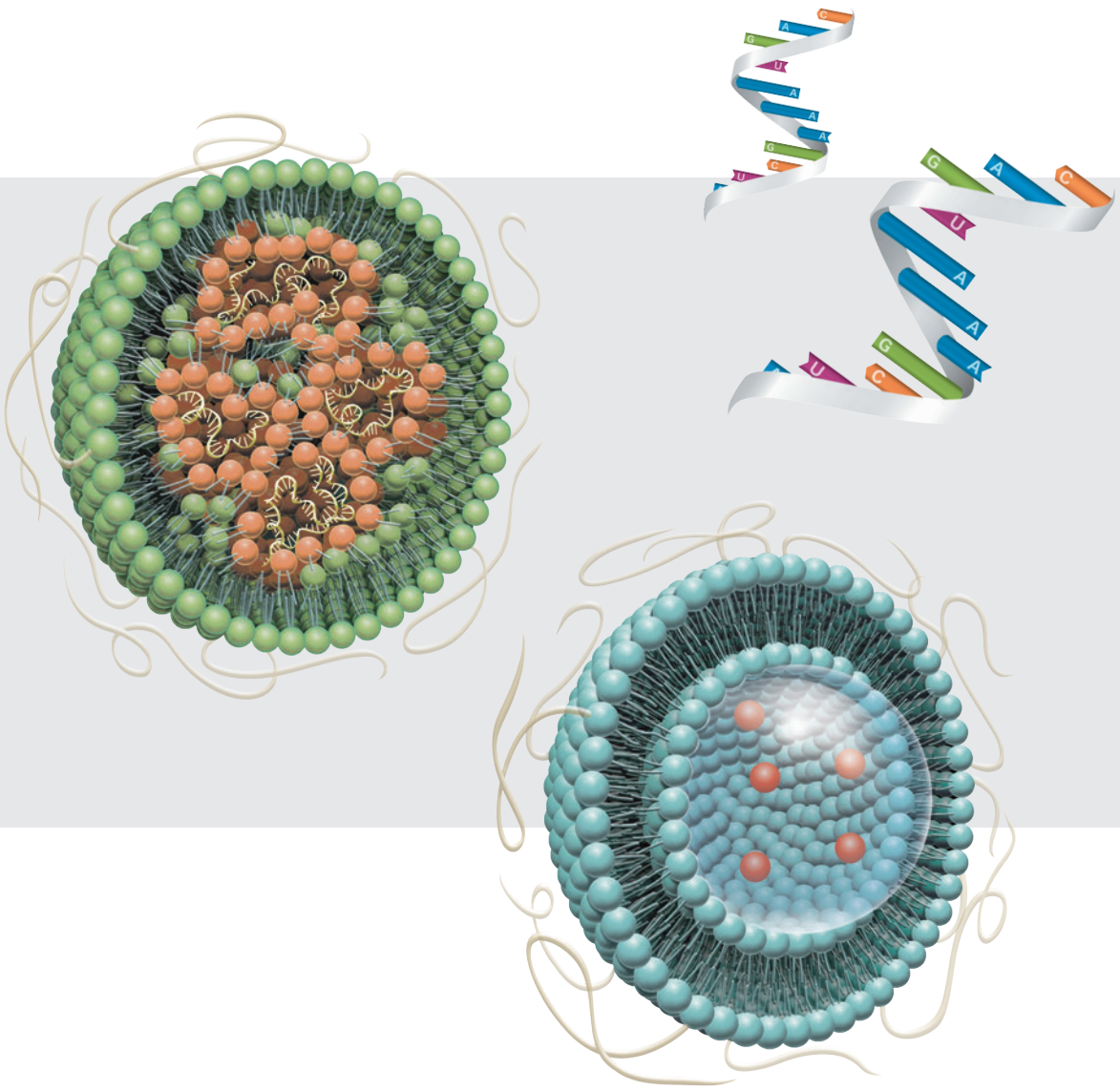
FUJIFILM
Value from Innovation

mRNA/LNP/Liposome CDMO Services and Technologies

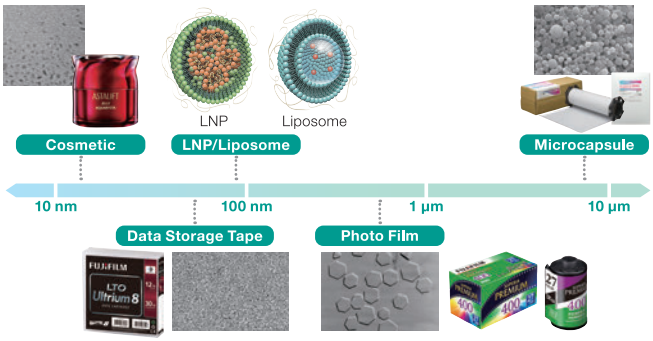


Background

Fujifilm's core technologies and FFTC's experiences

Throughout its 80-year history of research and development in the photographic film business, Fujifilm has cultivated precision chemistry and process technologies to control the properties of complex chemical materials at the nanoscale level. One of the fields in which Fujifilm's technologies and expertise can be applied is Drug Delivery Systems such as those for Lipid nanoparticles (LNP) and liposomes.
Fujifilm Toyama Chemical Co., Ltd. (FFTC), a Fujifilm group company, has launched many drugs, mainly in the field of infectious diseases, and has a long track record of manufacturing pharmaceutical products, including sterile preparations.
Applying these technologies and experiences, FFTC launched CDMO services for LNPs and liposomes in 2020.

Products based on Fujifilm's nanoparticle technology

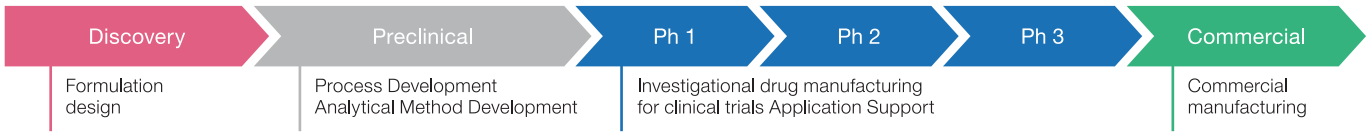


FFTC's marketed pharmaceutical products

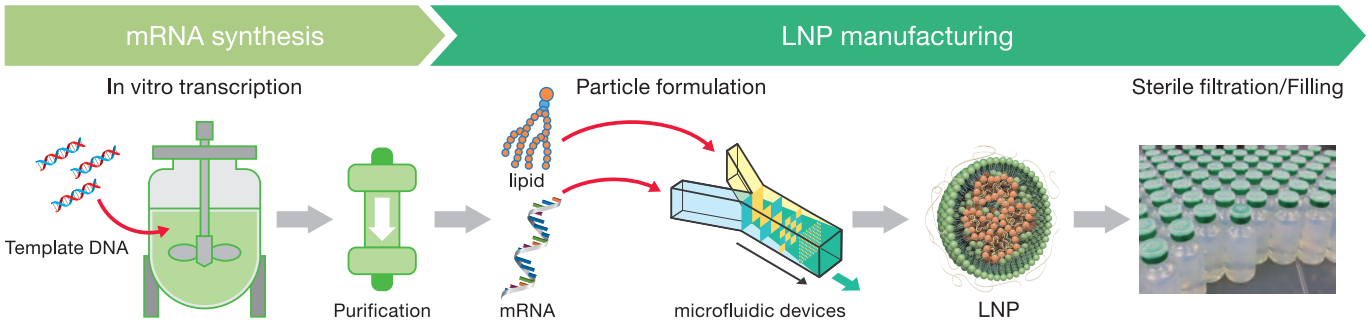
Platforms in FFTC's CDMO services

Features of FFTC's CDMO services

FFTC provides one-stop CDMO services from research use to commercial manufacturing, in alignment with the customer's R&D stage. By providing a one-stop service, we can reduce the technical risks associated with advancing to the next stage, and accelerate the customer's drug development.



- **End-to-end Services**
  - —FFTC can provide end-to-end services from mRNA synthesis to LNP manufacturing at one site.



FFTC's strengths as a CDMO

►LNP-CDMO service

- **Lipids**
  - —Fujifilm has proprietary ionizable lipids for LNP formulations for various types of nucleic acids, including mRNA, siRNA, DNA, and aptamers. And FFTC can provide using its lipids as LNP-CDMO services.
- **Formulation Design**
  - —FFTC can conduct feasibility studies based on its abundant experience, and design and prepare LNPs encapsulating the customer's API using Fujifilm's proprietary ionizable lipids or the customer's-own lipids.

►Liposome-CDMO service

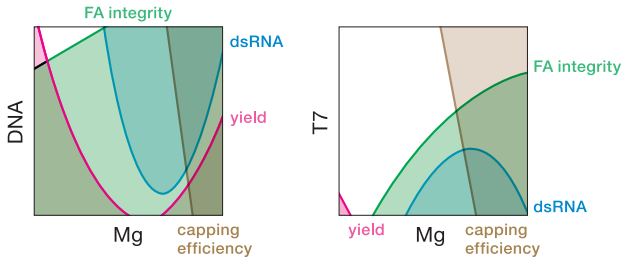
- **Lipids**
  - —Fujifilm has a versatile and proprietary liposome platform for small molecule compounds using DHSM (dihydrosphingomyelin), which can improve PK in plasma and delivery to the target. And FFTC can provide its platform as liposome-CDMO services.
- **Formulation Design**
  - —FFTC can also develop liposome formulations encapsulating the customer's-own small-molecule compounds.

mRNA

Process optimization study by DOE

One of the main challenges in mRNA production is improving purity. Therefore, FFTC applies a Design Of Experiment (DOE) approach to increase mRNA purity and yield.
In the in vitro transcription (IVT) process, we set target values for each parameter and predict the regions that will satisfy them. We use DOE to search for conditions that exhibit higher levels of predicted quality than the target values. The white areas in the figures below are the areas that meet the target quality.

Our DOE approach helps optimize the process in order to meet the customer's requirements for mRNA purity and yield.



TriLink BioTechnologies CleanCap® mRNA

FFTC entered into a non-exclusive license agreement with TriLink BioTechnologies® for CleanCap® mRNA capping technology, and began providing TriLink's CleanCap® capping services. This agreement enables us to provide contracted mRNA manufacturing services using CleanCap® mRNA from preclinical to Phase III studies.
CleanCap® mRNA can be used as highly active mRNA with improved translation efficiency under in vivo conditions and a Cap-1 structure that lowers immune reaction in vivo.

TriLink BIOTECHNOLOGIES
part of Maravai LifeSciences

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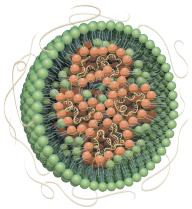
LNP

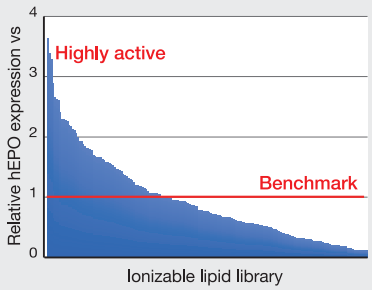


Proprietary ionizable lipids for LNP

LNPs are one of the promising carriers for mRNA delivery, and ionizable lipids are the most important factor in determining LNP performance. Fujifilm has discovered proprietary ionizable lipids showing a superior profile to conventional ionizable lipids.

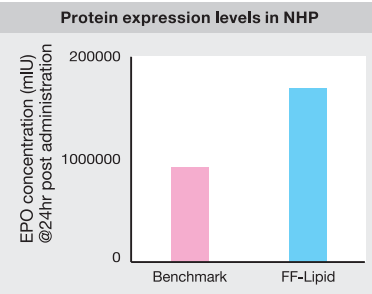
In vivo screening data shows that a variety of lipids discovered by Fujifilm have achieved higher mRNA expression than a benchmark lipid (the figure on the right).

In vivo screening of ionizable lipids



Some lipids have been evaluated in non-human primates (NHPs). EPO mRNA-encapsulated LNP was intravenously administered to NHPs. The EPO expression of Fujifilm's LNP was analyzed in parallel with that of a benchmark LNP (the figure on the right). FFTC's LNP showed a higher protein expression than the benchmark LNP. Also some lipids are already available for GMP-grade manufacturing. And we have filed several composition patents for lipids.

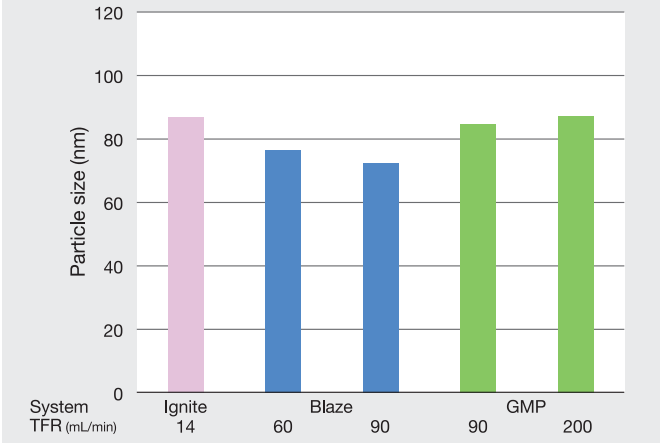
Protein expression levels in NHP



Process development for LNP

FFTC has installed the NanoAssemblr™ Platform under a partnership agreement with Precision NanoSystems Inc. for LNP-CDMO services. Process development from lab-scale sample production to GMP manufacturing can be carried out seamlessly, utilizing the lab-scale to GMP-scale NanoAssemblr™ machines (the figure on the below).

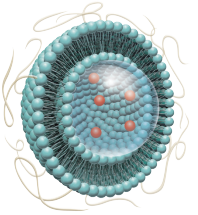
Seamless scale-up with NanoAssemblr™ Platform



FFTC has been closely working closely with many customers, supporting their design and manufacture of LNP formulations including clinical trial materials. Accordingly, our project manager will work closely with you to ensure that your timeline is kept and you achieve your milestones.

In addition, FFTC has also installed state-of-the-art equipment dedicated to formulation and process development. Particle Works' Automated Library Synthesis System (ALiS) allows for high-throughput screening of LNP formulations. Particle analysis such as nano-flow cytometry, Field Flow Fractionation (FFF), and cryo-TEM are also available to support LNP design.

Liposomes

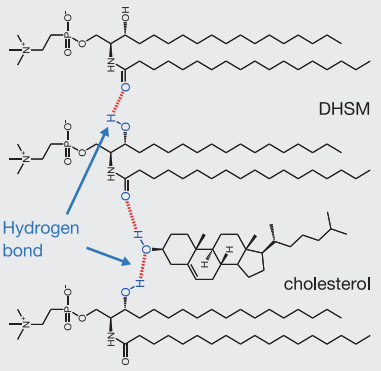


Features of CDMO services for liposomes

A liposome is a nanoparticle with a water phase inside a lipid bilayer.Liposomes have the potential to improve drug distribution, exposure and safety.

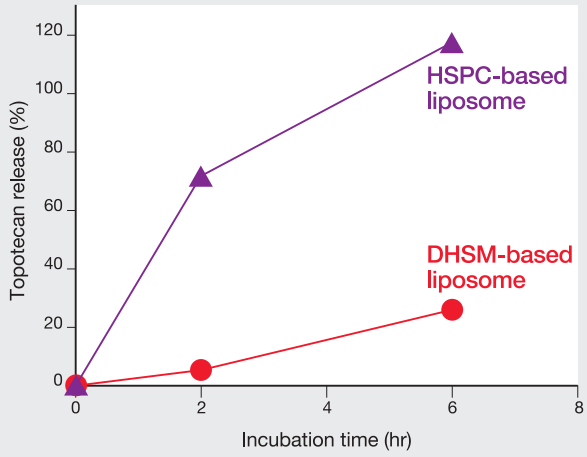
FFTC provides CDMO services with Fujifilm's proprietary liposome platform using the phospholipid, DHSM. The figure on the right shows the estimated structure of the lipid membranes with DHSM. DHSM forms a lipid bilayer with a high free-energy barrier through hydrogen bonds. Thus, DHSM-based liposomes are characterized by their resistance to the release of encapsulated small-molecule compounds in plasma.

Inferred structure of lipid membrane by DHSM



The figure below shows the drug release rate in mouse plasma. DHSM-based liposomes show lower drug release than conventional HSPC (Hydrogenated soybean phosphatidylcholine) based liposomes due to their unique lipid membrane structure.

***In vitro* payload release in mouse plasma**



Process development for liposomes

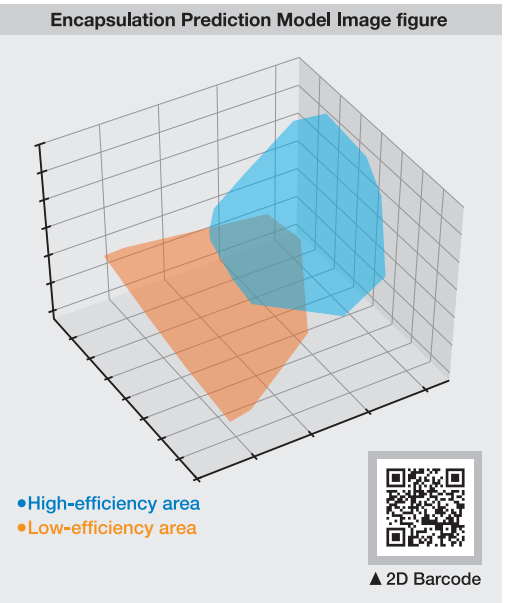
For our liposome-CDMO services, FFTC has a DHSM-based liposome platform, which allows customer to easily and quickly explore the possibility of encapsulation of your compounds as an option for your formulations, minimizing your expenditure of time and resources.

For manufacturing, customers can use the NanoAsssemblr™ series of Precision Nanosystems, or our own original liposome manufacturing equipment. We have small to GMP-scale equipment in operation, allowing for seamless scalinge up. Our GMP facility can handle a wide range of active pharmaceutical ingredients, including highly active compounds like anticancer drugs.

Liposome Encapsulation Prediction App

FFTC has developed a new app that predicts the feasibility of liposome encapsulation of customer's compounds. If you are considering employing liposome formulation to improve the safety, PK and stability of your compounds, please visit the following URL and try the app for yourself (https://liposome-tools.fujifilm.com/). We don't record or retain your compound information.

Encapsulation Prediction Model Image figure



FFTC's quality control and biological evaluation

FFFTC has seasoned analytical experts specialized in nanoparticulate analysis. This allows us to provide seamless support for the analysies of payload, mRNA, LNP and liposome quality. Our analytical laboratory also possesses the necessary analytical equipment to evaluate nanoparticle formulations. We can thus provide seamless services from the development of test methods in the lab, through product shipping testing, to stability testing.

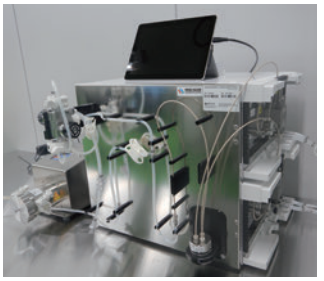
These operations related to quality control can be performed under GMP control, if required. In addition, we can also perform data acquisition required for IND/NDA upon the customer's request.
Furthermore, if you require biological evaluations, we can provide CRO services in cooperation with Fujifilm group companies. Our integrated contract services, from manufacturing to evaluation, can significantly minimize your expenditure of time and resources.

FFTC's manufacturing facilities for mRNA, LNP and Liposome

FFTC has a GMP plant dedicated to mRNA, LNPs and liposomes in Toyama Prefecture, Japan.
The facility is equipped with isolators for the manufacture of aseptic formulations. Single-use system has been introduced for the purification and sterilization/filtration processes, in order to achieve efficient and flexible manufacturing.
FFTC has installed a single-use bioreactor (up to 25 L) as mRNA manufacturing equipment, And we have installed a NanoAssemblr™ (up to 200 ml/min), and our own liposome production machines (35 L and 350 L).

We have also installed various scales of TFF equipment that enables purification and concentration according to scale.
At this GMP facility, we have experience of contract manufacturing of clinical-stage mRNA-LNP vaccines and liposome formulations of anti-cancer drugs.
In addition, our facility can also provide filling-only contract services upon the customer's request. The current filling capacity is 50 vial/min, but will be expanded to 300 vial/min in the future to meet a wide range of customer needs.

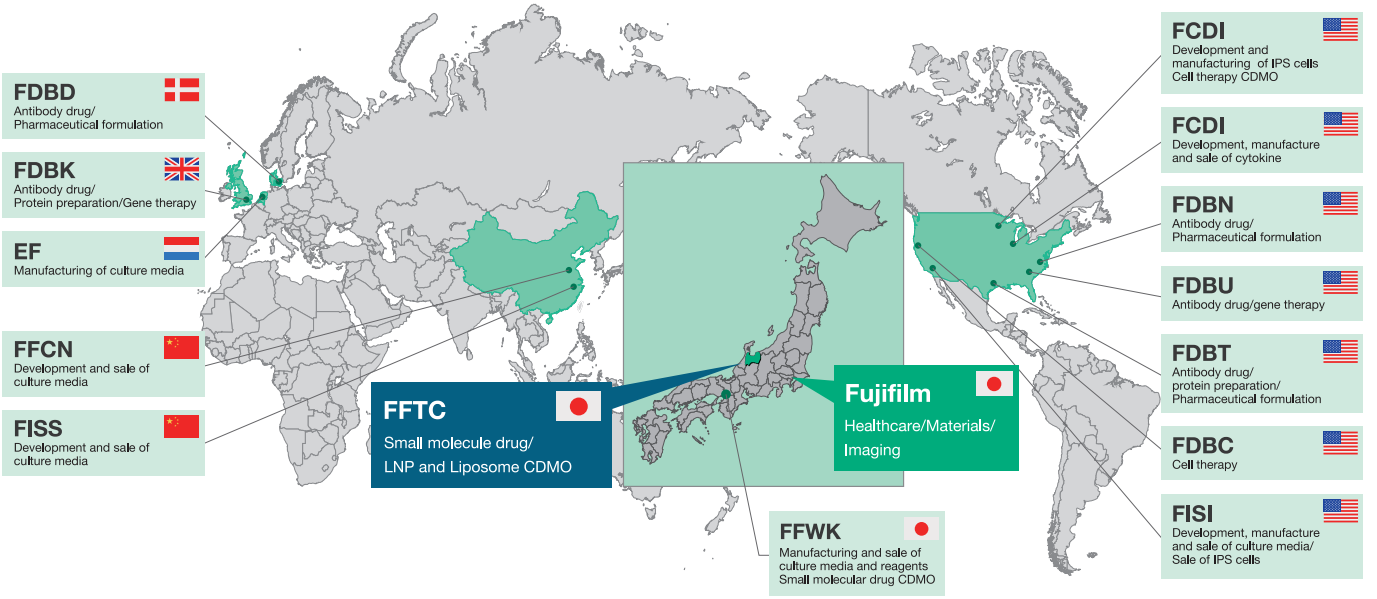
Currently, we only handle liquid formulations. We are planning to handle lyophilized preparations in the near future.



Advantage of FFTC's bio-CDMO services: Gathering all strength of Fujifilm group

The FUJIFILM group is offering services globally in the field of life sciences, especially focusing on bio-CDMO. FFTC is committed to providing bio-CDMO services through close cooperation with Fujifilm group companies.

Gathering all strengths of Fujifilm group



FFWK: FUJIFILM Wako Pure Chemical Corporation, FCDI: FUJIFILM Cellular Dynamics, Inc., FDBN: FUJIFILM Diosynth Biotechnologies North Carolina, Inc., FDBU: FUJIFILM Diosynth Biotechnologies U.S.A. Inc., FDBT: FUJIFILM Diosynth Biotechnologies Texas, LLC, FDBC: FUJIFILM Diosynth Biotechnologies California, Inc, FISI: FUJIFILM Irvine Scientific, Inc., FDBD: FUJIFILM Diosynth Biotechnologies Denmark ApS, FDBK: FUJIFILM Diosynth Biotechnologies UK Limited, EF: FUJIFILM Manufacturing Europe B.V., FFCN: FUJIFILM (China) Investment Co., Ltd., FISS: FUJIFILM Irvine Scientific (Suzhou) Co., LTD.

R&D laboratory (Toyama and Kanagawa, Japan)

Functions	Formulation, process, and analytical method development LNP/Liposome production & analysis for pre clinical
Manufacturing equipment	NxGen™ NanoAssemblr® (1-1000 mL) Liposome Proprietary equipment (200 mL, 3.5 L, 35 L) Tangential flow filtration Column chromatography Automated formulation screening Liquid filling and stoppering system Freeze dryer
Analytical methods & equipment	Particle size and distribution Zeta potential, pH, osmolality Lipid & API analysis by HPLC (UV, CAD, MS) Flow Nanoanalyzer (NanoFCM™) Field Flow Fractionation (FFF) Residual solvent analysis by GC (FID, MS) Ion analysis (IC) Metal analysis (ICP-MS) Spectroscopy (UV, IR, Fluorescence, NMR) Particulate matter (Accusizer®) Cyro-TEM imaging Thermal analysis (DSC,TG-DTA) Sterility and endotoxin testing Karl Fischer, polarimeter, melting point meter Further analysis is provided upon request
Handling	Highly potent APIs
Regulatory	non-GMP

GMP facility (Toyama, Japan)

Functions	GMP production of mRNA/LNP/Liposome
Manufacturing equipment	NxGen™ NanoAssemblr® (0.2-100 L) Liposome Proprietary equipment (35 L, 350 L) Bioreactor (～25L) Tangential flow filtration Sterile filtration Fill & finish Column chromatography
Analytical methods & equipment	Particle size and distribution (DLS) Zeta potential, pH, osmolality, conductivity Lipid & API analysis by HPLC (UV, CAD, MS) Residual solvent analysis by GC (FID) Ion analysis (IC) Metal analysis (ICP-MS) Particulate matter (Accusizer®) Spectroscopy (UV, IR) Sterility and endotoxin testing Karl Fischer, polarimeter, potentiometric titrator, melting point meter Deep freezer
Handling	Highly potent APIs
Regulatory	Facility designed to comply with cGMP, EU-GMP and JP-GMP

Specifications are subject to change without notice.

FUJIFILM

FUJIFILM Toyama Chemical Co.,Ltd

14-1, Kyobashi 2-Chome, Chuo-ku, Tokyo 104-0031, Japan
Global Website: https://www.fujifilmpharma.com/
JPWebsite: https://www.fujifilm.com/fftc/ja/what-we-do

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