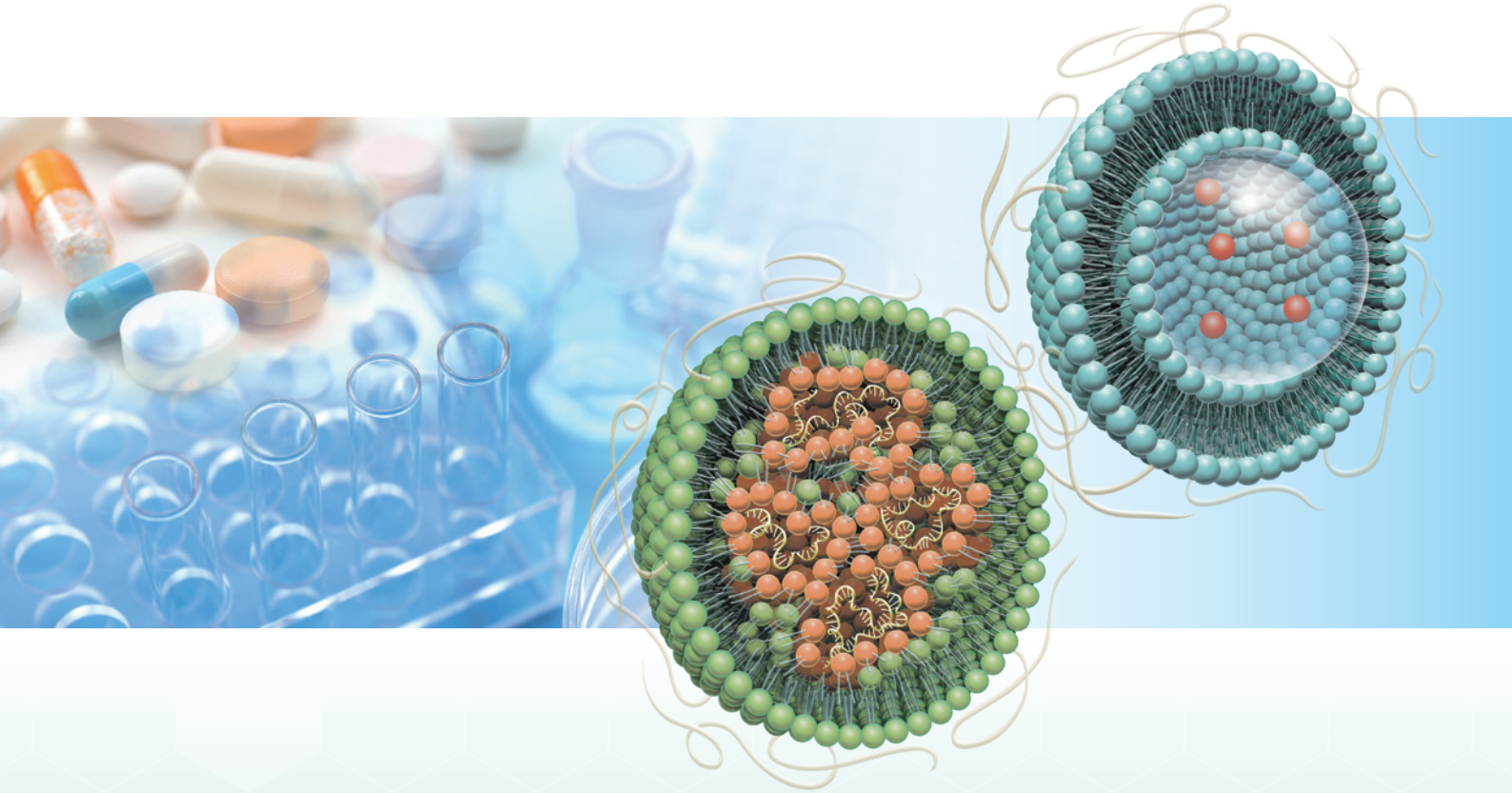
FUJIFILM
Value from Innovation

LNP/Liposome CDMO Services and Technology



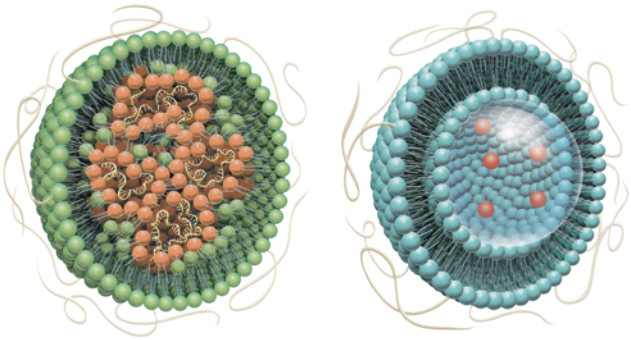
Background

Fujifilm DDS technology and CDMO* services for lipid nanoparticles and liposomes

*CDMO: contract development and manufacturing organization

Nanoparticle carriers are a type of DDS (drug delivery system) and include lipid nanoparticles (LNP) as carriers of nucleic acids (mRNA, etc.) and liposomes as carriers for anticancer drugs.

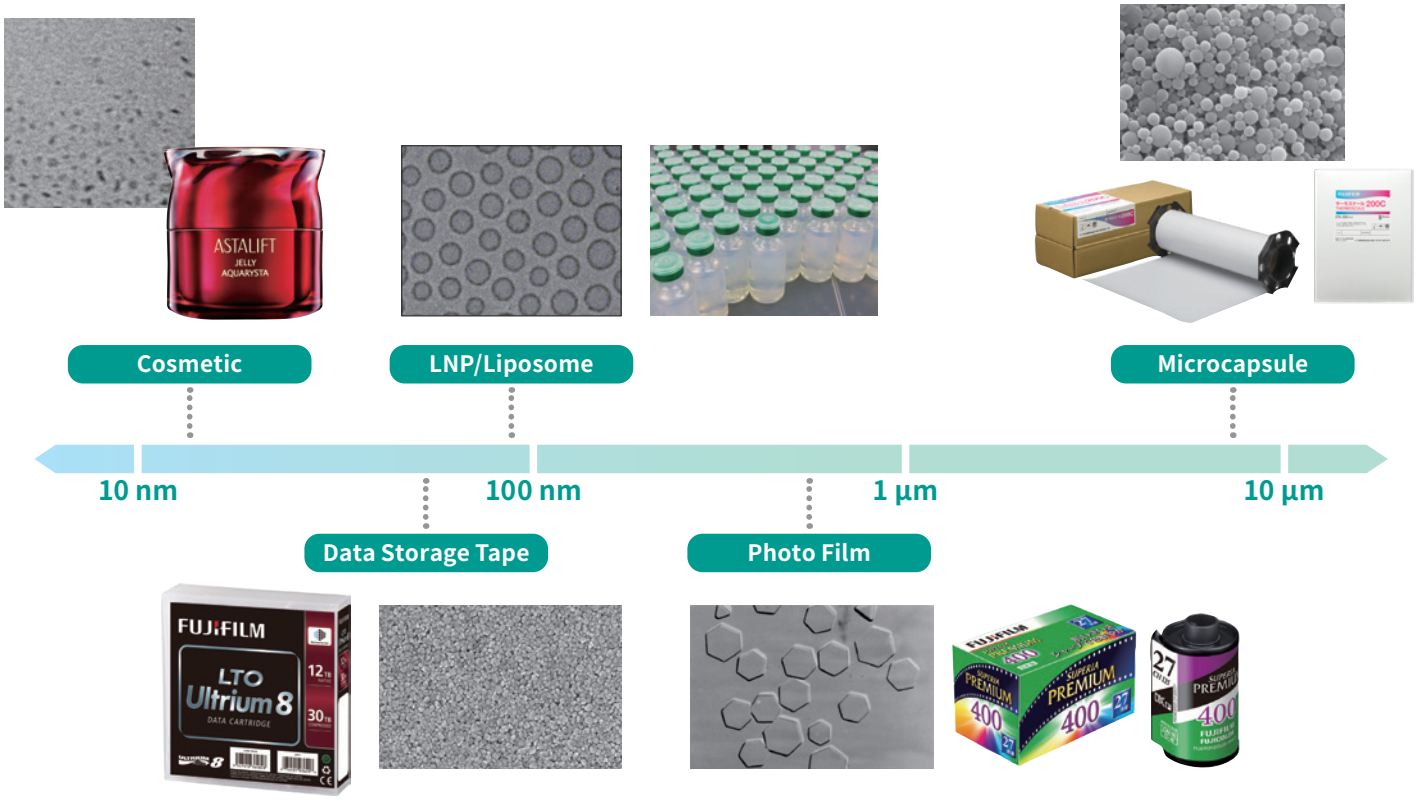
The manufacturing and handling of pharmaceuticals using nanoparticle carriers require precision chemistry and processing technologies, in addition to general injectable formulation technologies, such as aseptic manipulation. Fujifilm's CDMO services leverage the technology and know-how that Fujifilm has cultivated since its foundation to assist customers that develop nanoparticle-based pharmaceuticals.



LNP　　Liposome

Applying Fujifilm's strengths to nanoparticle carriers

Through years of experience in photographic film development, Fujifilm has accumulated expertise in precision chemistry and process technology for controlling the characteristics of chemical materials on a nanoscale. In order to create beautiful photographs, it was necessary to have a technique that allows the precise arrangement of photosensitive particles and dye particles within the thin layers of photographic film. Fujifilm has expanded the application of this technique to various products, such as data storage tapes and pressure-sensitive films using microcapsules. Nanoparticle carriers are one of the fields suitable for applying Fujifilm's technology and know-how.



Fujifilm has performed in-house formulation design, evaluation, scale-up, and GMP manufacturing for its own investigational drugs. This is another reason our CDMO services will be delivered to you by a team of engineers with knowledge and operational experience in the development and manufacturing of specifically designed liposomes.

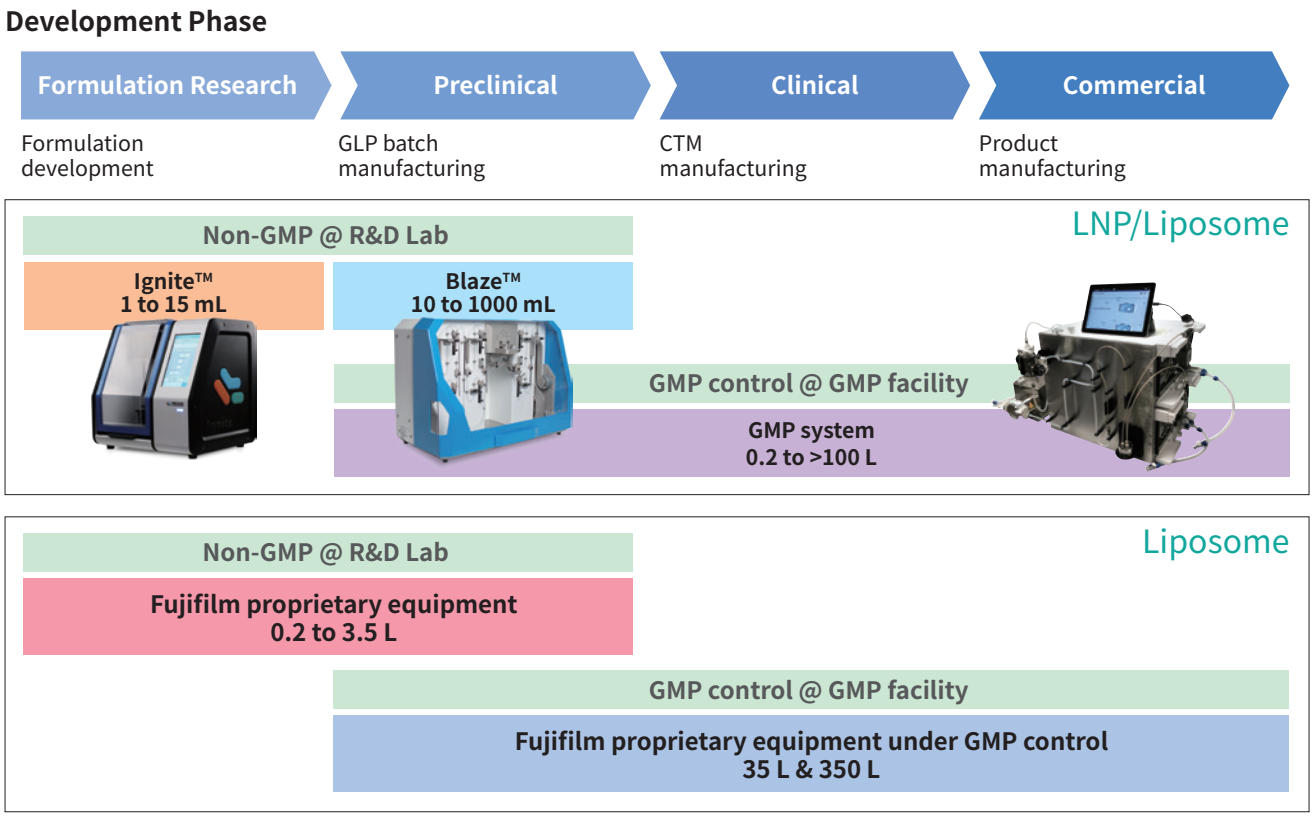
Overview

Nanoparticle CDMO service

Fujifilm's drug delivery technology employs two platforms: the NanoAsssemblr™ LNP/liposome manufacturing equipment by Precision Nanosystems Inc., and Fujifilm's proprietary liposome manufacturing equipment using a dispersion method. Using both platforms, we can provide CDMO services tailored to the customer's development phase, from small-scale formulation development at our research laboratory, to commercial-scale manufacturing at our GMP facility (PIC/S, cGMP).

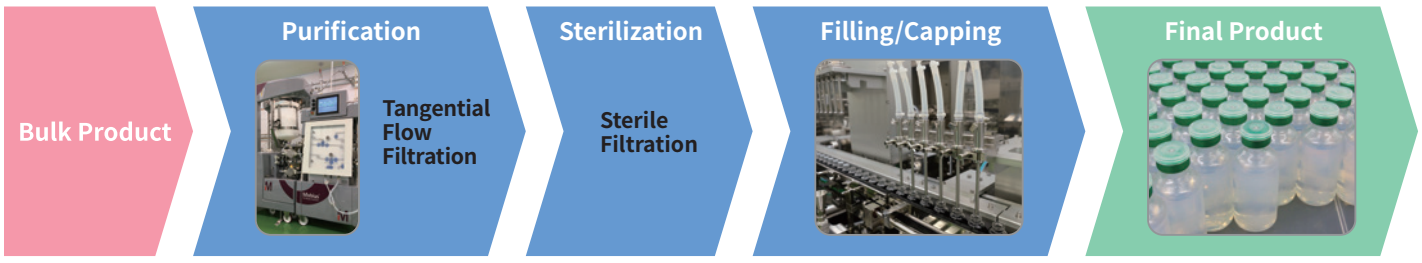
For example, if you are in the initial stage of studying nanoparticle carriers, we can support you with designing a new LNP/liposome formulation and preparing non-GMP samples encapsulating your active pharmaceutical ingredient (API). If you have completed the nanoparticle carrier design and expect to move to the next steps (GLP preclinical, clinical trial, and commercial production), we can perform scale-up studies and contract manufacturing based on the manufacturing method of your choice.

We also offer services for the development of test methods and standards, which are required for issuing a certificate of analysis (CoA).



THE REFERENCED EQUIPMENT IS ANALYTICAL INSTRUMENTS FOR PRODUCTION AND MANUFACTURING. THEY ARE NOT MEDICAL DEVICES.

Injectable preparations of nanoparticle-based pharmaceuticals generally require three critical processes after particle formation: purification (buffer exchange), sterilization, and filling/capping. For these downstream processes, we can also meet your needs through contract process development and manufacturing services at our research laboratory and GMP facility located in Japan.



Our facility can handle a wide range of APIs, such as nucleic acids (mRNA, siRNA, DNA aptamers, etc.) and highly potent compounds (anticancer agents). Please contact us for details.

Process Development

Fujifilm provides LNP/liposome CDMO services using NanoAssemblr™

Fujifilm has introduced the NanoAssemblr™ Platform under a partnership agreement with Precision NanoSystems Inc. Fujifilm's CDMO service provides customers with the NanoAssemblr™ Platform as an LNP/liposome manufacturing device.

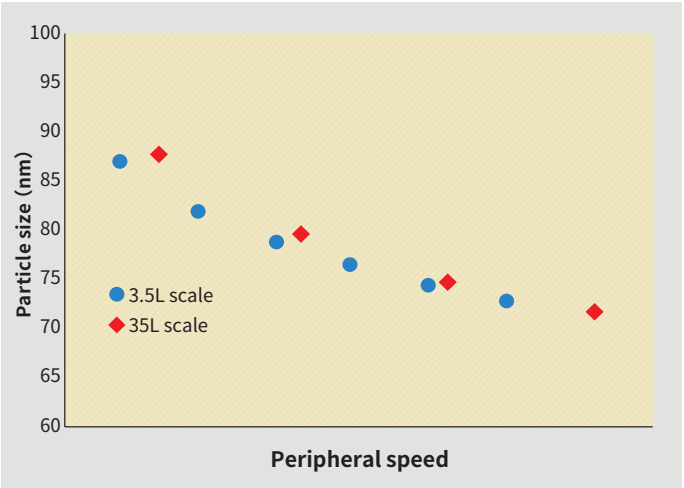
The NanoAssemblr™ Platform has been introduced to universities, research institutes, and pharmaceutical companies around the world, and is used for research and development of LNP for nucleic acid pharmaceuticals such as mRNA. Fujifilm's CDMO service can quickly and seamlessly scale up LNP formulations developed by customers using the NanoAssemblr™ Platform.

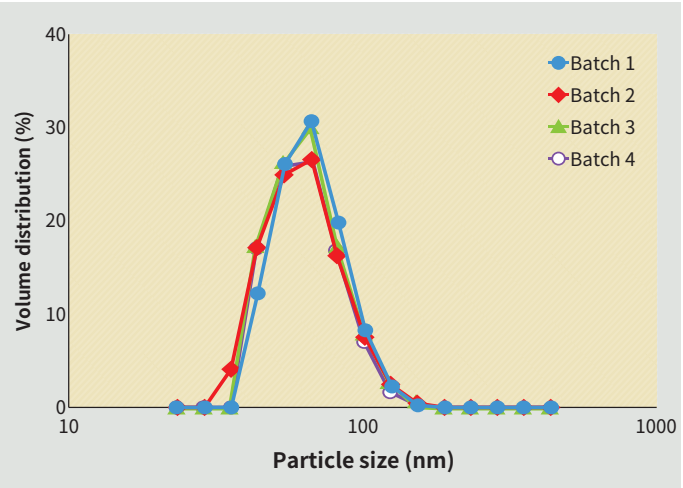
ANALYTICAL INSTRUMENT FOR PRODUCTION AND MANUFACTURING - NOT A MEDICAL DEVICE.

Fujifilm's proprietary liposome manufacturing technology

Extrusion using membrane filters is a common method for producing liposomes of defined size ranges. However, process control in this method is notoriously difficult, as the membranes used for sizing can get easily clogged. Fujifilm has employed a dispersion method to develop equipment and manufacturing processes that allow fine control of liposome particle size without using the membranes. This method can be used to replace our customers' extrusion manufacturing processes to improve the manufacturability of their final products.

The graph on the left shows the particle size of liposomes manufactured at 3.5 L and 35 L scales with Fujifilm's dispersion technology. The mixer speed allows precise control of the particle size of the liposomes produced. In addition, the mean liposomal particle diameter can be matched between batches, even though liposomes were produced at scales with a tenfold difference. The graph on the right shows the particle size distribution of four batches of liposomes manufactured with Fujifilm's dispersion technology. Our manufacturing method has resulted in a tight particle size distribution that is highly reproducible across batches.





Fujifilm's services can also accommodate manufacturing contracts using the extrusion method.

Formulation Research

Fujifilm's highly active pH-responsive lipids

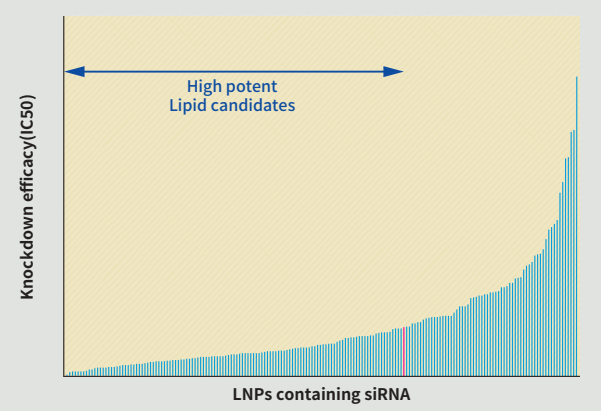
pH-responsive lipids are an important consideration for obtaining LNPs that meet the desired performance. With that in mind, Fujifilm has searched for and synthesized new pH-responsive lipid compounds.

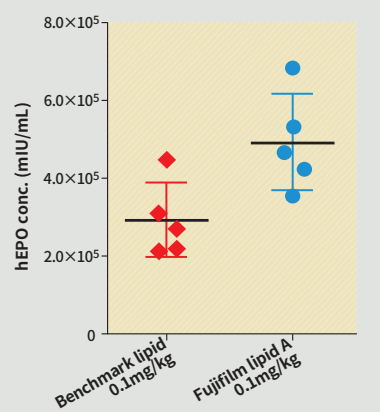
The graph on the left shows the results of an *in vivo* test using LNPs composed of different lipid compounds developed by Fujifilm. The vertical axis shows efficacy of protein expression knockdown induced by LNP containing siRNA. We have found multiple compounds that show higher activity compared to the benchmark lipid (red). The graph in the middle shows the expression of Human Erythropoietin (hEPO) induced in an animal model (n=5) by LNP containing mRNA. The LNP composed of Fujifilm Lipid A shows higher protein expression compared to the LNP composed of benchmark lipid.

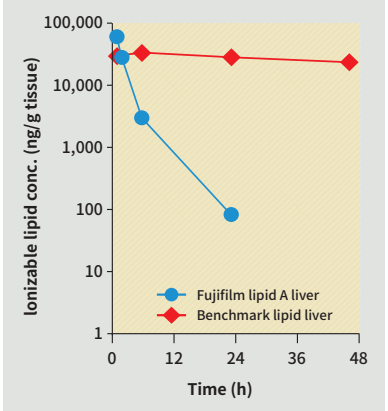
Lipids developed and synthesized by Fujifilm are designed to quickly metabolize and disappear from the body. The graph on the right shows the concentration of ionizable lipids in the liver following intravenous injection. Fujifilm lipid A rapidly disappears, compared to the benchmark lipid.

Under contract, Fujifilm can provide these pH-responsive lipids to partners and collaborators.

[Reference] Makita K., et al., Poster presented at 8th International mRNA Health Conference (2020)



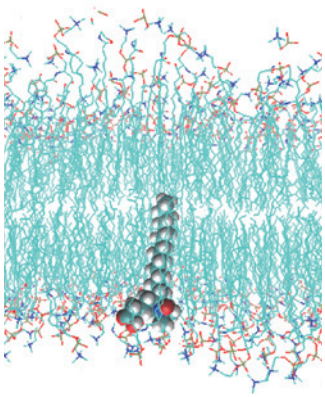


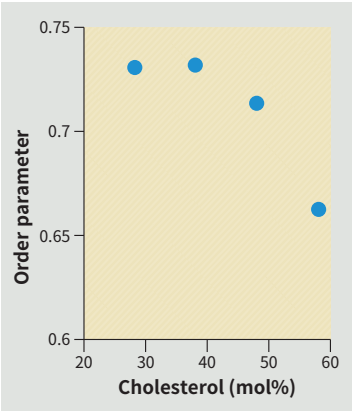


Fujifilm's capabilities for liposome formulation development

Fujifilm takes various approaches to improve the performance of liposomes. For example, liposome design can be optimized based on the results of flow analysis of the lipid bilayer membrane performed computationally or by physicochemical experiments. In the figure on the right, the percentage of cholesterol that minimizes the amount of drug released from liposomes was determined from the results of a flow analysis. In this case, 35-40% cholesterol content is optimal.

We are also searching for new components that can be employed in the makeup of liposomes. One example is a synthetic form of dihydrosphingomyelin (DHSM) as a liposome membrane component. Our animal studies showed higher blood retention of encapsulated API with DHSM-composed liposomes compared to liposomes made of sphingomyelin (SM) or hydrogenated soybean phosphatidylcholine (HSPC), both of which have been used clinically.





[Reference]
Shimoyama S., et al., Poster presented at 30th EORTC-NCI-AACR Symposium (2018)

R&D laboratory (Kanagawa, Japan)

Functions	Formulation, process, and analytical method development LNP production for GLP testing *in vitro* evaluation
Manufacturing methods	LNP/Liposome NxGen™ NanoAssemblr® (1-1000 mL) Liposome Extruder (1 , 10, 100 mL) Liposome Proprietary Method (200 mL, 3.5 L, 35 L)
Analytical methods & equipment	Particle size and distribution Zeta potential, pH, osmolality Lipid & API analysis by HPLC (UV, CAD, MS) Residual solvent analysis by GC (FID, MS) Ion analysis (IC) Metal analysis (ICP-MS) Particulate matter (Accusizer®) Microscopy (TEM, SEM, AFM etc.) Spectroscopy (SAXS, NMR, ESR, etc.) Thermal analysis (DSC,TG-DTA) Sterility and endotoxin testing KF volumetric titrator, 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 LNP/Liposome
Manufacturing methods	LNP/Liposome NxGen™ NanoAssemblr® (0.2-100 L) Liposome Proprietary Method (35 L, 350 L)
Downstream process	Tangential flow filtration Sterile filtration Fill & finish
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 KF volumetric titrator, polarimeter, potentiometric titrator, melting point meter Deep freezer
Handling	Highly potent APIs
Regulatory	US, EU, JP GMP

Specifications are subject to change without notice.

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