Japanese perspectives on complexity of complex generics

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Outline

- Evaluation for complex generics
- Consensus-based standard test methods produced by Japanese Pharmacopoeia

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Complex Generics

- There is no specific regulatory definition of “complex generics” in Japan
- Some examples of generic drugs generally considered as “complex”
  - Complex active substances:

    Approved generic drugs : Low-molecular heparin
  - Complex formulations:

    Approved generic drugs: microcapsule and lipid microspheres
  - Complex route of administration :

    Approved generic drugs: topical dermatological drug products
  - Complex combination with devices :

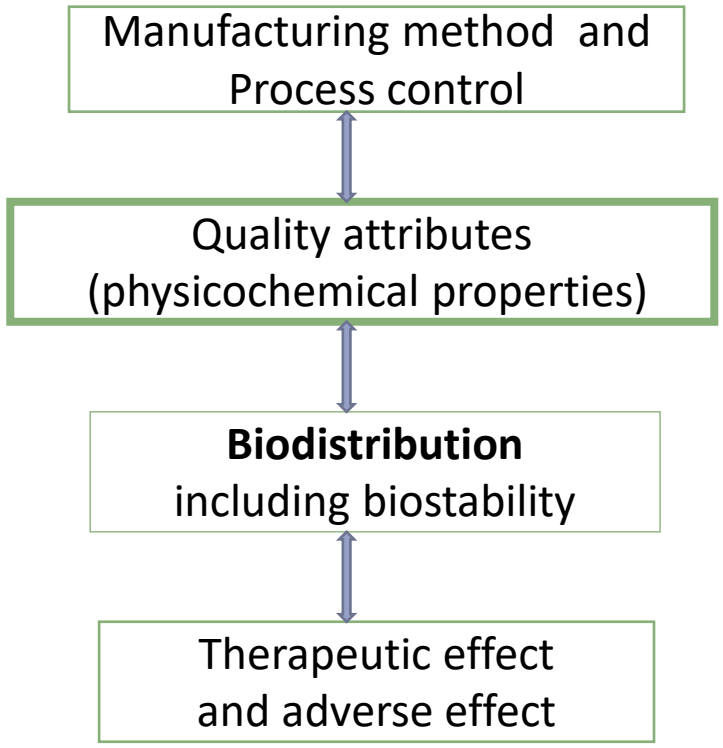
    Approved generic drugs: dry powder inhalers

Nanotechnology-based drug product (Nanomedicines) approved in Japan

Formulation technology	Approved drugs (Brand name)	
Liposome	DOXIL® Injection AmBisome® For I.V. Infusion Visudyne® Onivyde® I.V. Infusion ARIKAYCE®	
Lipid nanoparticle	Onpattro® infusion COMIRNATY® Intramuscular Injection Spikevax® Intramuscular Injection DAICHIRONA® FOR INTRAMUSCULAR INJECTION KOSTAIVE® intramuscular injection	COVID-19 Vaccine
Polymeric nanoparticle (Protein nanoparticle)	Abraxane® I.V.Infusion	
Nanosphere	FESIN® Intravenous Injection	
Nanoemulsion	Palux® injection Liple® INJECTION	
Nanocrystal	EMEND® Capsules	

Complexity of nanomedicines

- Nanomedicines are formulated by use of innovative materials and nanotechnology
- Nanomedicines are mainly developed for control of biodistribution of active substance



Knowledge about the relationship between each element is important for ensuring efficacy and safety as medicines.

Identification of critical quality attribute
Method development of the quality attribute

Current regulation for nanomedicines

- Nanomedicines have been regulated within a general framework of the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices on a product-by-product basis.

- At present, there is no specially designed regulatory framework for nanomedicines. However, Product-specific guideline and reflection papers have been issued from MHLW.

Guidelines specific to nanomedicines in Japan

1. Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products

   (January 10, 2014, PFSB/ELS Notification No.011-1)

2. MHLW Guideline for the Development of Liposome Drug Products

   (March 28, 2016, PSEHB/ELD Notification No. 0328-19)

3. MHLW Reflection paper on nucleic acids (siRNA)-loaded nanotechnology-based drug products

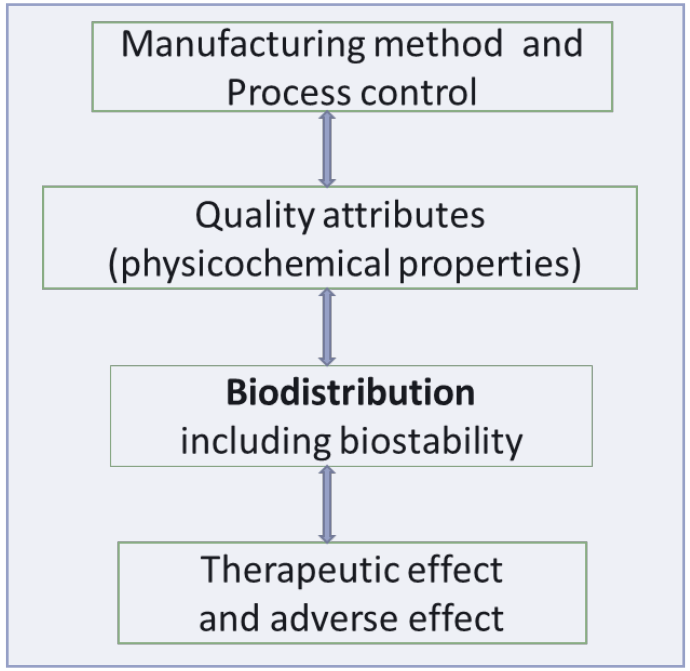
   (March 28, 2016, PSEHB/ELD Administrative Notice)

Note: MHLW communicated with foreign regulators in the process of drafting the above GL/RPs

MHLW Guideline for the Development of Liposome Drug Products

Table of Contents

1. Introduction
2. Scope
3. Chemistry, manufacturing and controls
4. Nonclinical studies
5. Considerations for first-in-human studies
6. Glossary

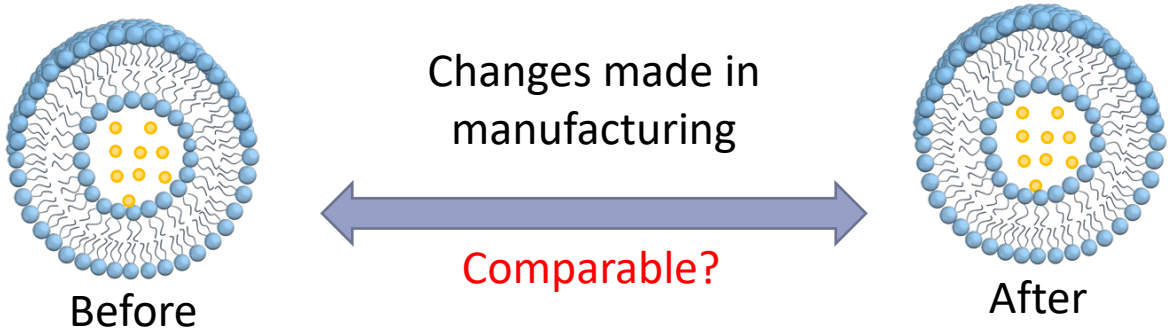


- Appendix: Comparability assessment of liposome drug products subject to change in manufacturing

Physicochemical properties and their analytical techniques for liposomal drug products

Physicochemical properties	Examples of analytical techniques
Particle size distribution	dynamic light scattering, laser diffraction, nanotracking analysis
Morphology and/or structure	transmission electron microscopy, cryoelectron microscopy, atomic force microscopy, and small-angle X-ray scattering measurement
Surface charge (zeta potential)	electrophoretic light scattering (laser Doppler electrophoresis)
Thermodynamic properties of the liposome membrane	differential scanning calorimetry the temperature dependence of a fluorescence spectrum measured using a fluorescent probe
In vitro release	a test solution that appropriately reflects physiological conditions
Osmolality	the reconstituted drug solution should preferably be isotonic (approximately 280 mOsm/kg)
pH	the pH of the dispersion fluid (external liquid phase)
Aggregation	turbidity measurement
Loading efficiency of the active substances	the amount of the active encapsulated in the liposome and unencapsulated in liposome quantitatively measured
Impurities	material-related impurities, process-related impurities, product-related impurities (such as liposome aggregates and variants), and time-related degradation products

Comparability assessment



The concepts outlined in the ICH Q5E guideline

Details specific to liposome drug product are described in Appendix

Additional evidence from nonclinical or clinical studies is required when quality data are insufficient to establish comparability.

A1. Nonclinical studies
- A1.1 Nonclinical pharmacokinetics
- A1.2 Nonclinical pharmacodynamics
- A1.3 Nonclinical toxicity

A2. Clinical studies
- A2.1 Clinical pharmacokinetic studies
- A2.2 Other clinical studies
- A2.3 Safety issues

Outline

- Evaluation for complex generics
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Standardization of test method for drug evaluation

Quality assurance of complex generics

Standardization of test method

Validation of the method

Listing them in Japanese pharmacopoeia,

an official document that defines the specifications, criteria and standard test methods necessary to properly assure the quality of medicines in Japan.

Measure for quality assurance of liposomal drug products

Issue of “MHLW Guideline for the Development of Liposome Drug Products”

↓

The following paragraphs were newly added to the General Rules for Preparations

3-1-4. Liposome Injections

↓

Listing the standard test methods for the preparation characteristics

3-1-4. Liposome Injections

(1) Liposome Injections are injections to be used for intravenous administration, which are intended for improvement of in vivo stability, delivery to a target region and control of release, of active substance(s).

(2) Liposome Injections are usually prepared by using amphipathic lipid, etc. to make aqueous injections or freeze-dried injections in which closed microvesicles composed of a lipid bilayer membrane are dispersed.

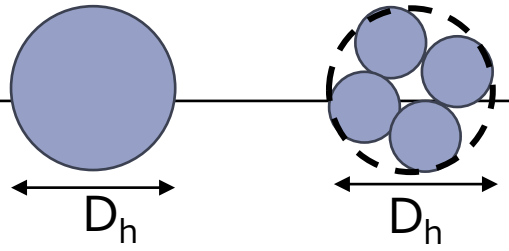
(3) Liposome Injections have an appropriate function of controlled release.

(4) Liposome Injections have an appropriate particle size

Preparation characteristics are specified for the dosage forms. The preparation characteristics are confirmed by appropriate tests.

Analytical methods for size and morphology measurement of nanomedicines

Method	Major purpose	Listing in JP
Dynamic light scattering (DLS)	Particle size measurement	JP18-2 ＜3.07＞
Laser diffraction(LD)	Particle size measurement	JP 17-1＜3.06＞
Nanoparticle tracking analysis (NTA)	Particle size and number measurement	
Centrifugal sedimentation method	Size separation and fractionation	
Size exclusion chromatography (SEC)	Size separation and fractionation	JP18＜2.05＞
Field flow fractionation (FFF)	Size separation and fractionation	
Electron microscopy (EM)	Morphology measurement	
Atomic force microscopy (AFM)	Morphology measurement	JP18-2<*G1-9-182*>
Small angle X-ray scattering (SAXS)	Morphology measurement	

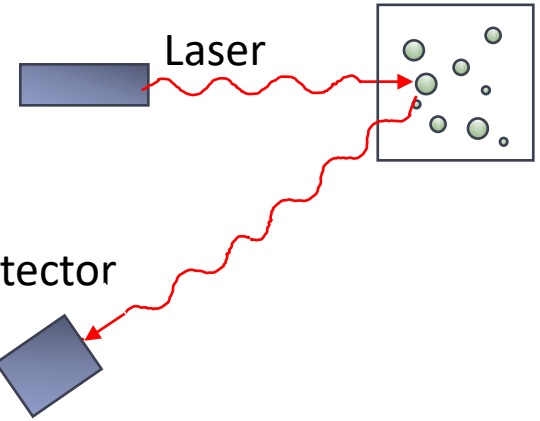


Standard method for particle size in Japanese pharmacopoeia

Dynamic light scattering
Size analysis of nanomedicines

Pharmacopoeial Discussion Group Meeting

G-21 Dynamic Light Scattering



Harmonized
March 14,2023

JP18-2 ＜3.07＞ Particle Size Analysis by Dynamic Light Scattering

Analytical methods for size and morphology measurement of nanomedicines

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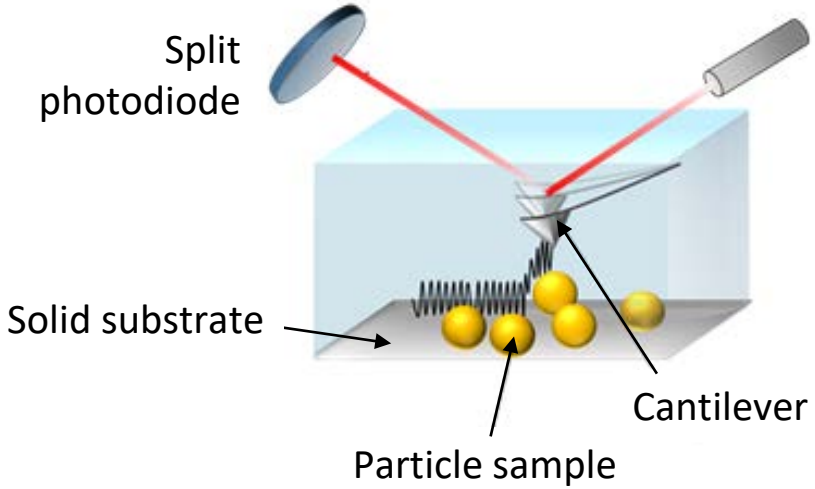
Standard method development by AMED research
AMED: Japan Agency for Medical Research and Development

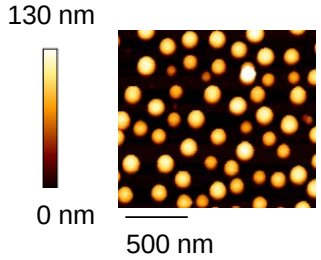
Standard method development for particle size of nanomedicines

Atomic force microscopy

Size and morphology analysis of nanomedicines



AFM image of polystyrene nanoparticles



- Effect of cantilever
- Effect of analysis method on measured size of polystyrene nanoparticles
- Effect of particle sample size
- Effect of solid substrate and solvation
- Differences between instruments and reproducibility

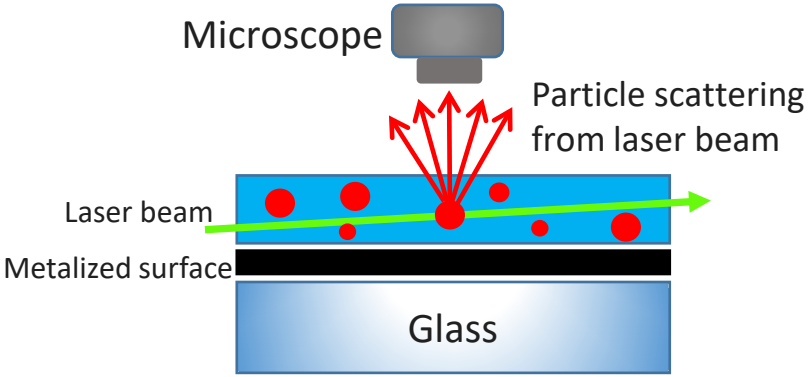
Chem. Pharm. Bull. 68, 1-7, 2020

Robust analytical conditions

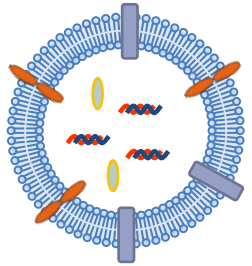
Standard method development for particle size of nanomedicines

Nanoparticle tracking analysis

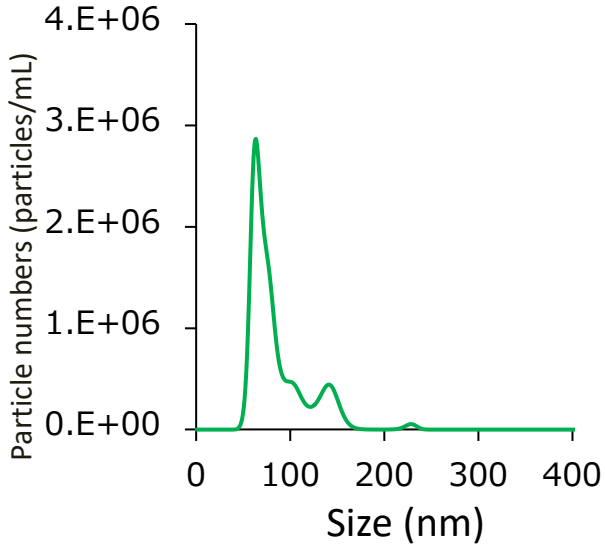
Size and particle numbers analysis of nanomedicines and exosome



Exosome



Exosome



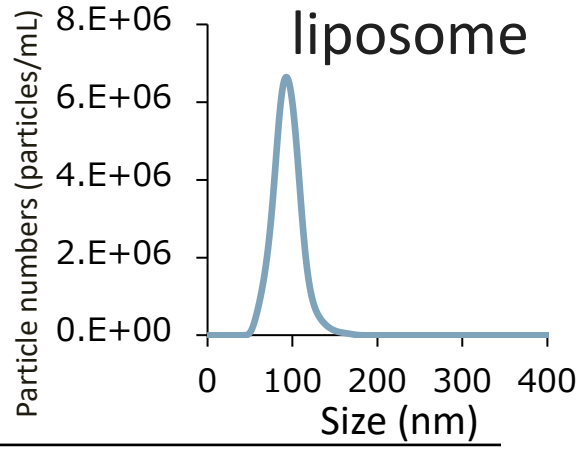
Sample

- Polystyrene nanoparticles certified reference standard
- liposome
- exosome (small extracellular vesicles)

Study points

- Effect of data acquisition time
- Effect of sample concentration
- Repeatability
- Differences between Instruments

liposome



Points to consider in quality evaluation

PHARM TECH JAPAN 38, 213-218, 2022

Chem. Pharm. Bull. 69, 1045–1053, 2021

Analyses of Size and Morphology of Nano particles by Atomic Force Microscope <*G1-9-182*>

1. Equipment and operating principle
    - 1.1. AFM system
    - 1.2. AFM operating principle
    - 1.3. Other equipment
2. Measurement
    - 2.1. Preparation of samples
    - 2.2. Preparation of substrate for fixing nanoparticles
    - 2.3. Nanoparticle fixation on a solid substrate
    - 2.4. Acquisition of AFM images
3. Image analysis and size (height) measurement of nanoparticles
    - 3.1 Size measurement by cross-sectional shape analysis
    - 3.2. Size measurement by automated particle analysis
    - 3.3. Analysis of nanoparticles having shapes other than true sphere
    - 3.4. Reporting size data
4. Verifying AFM performance

Perspective of quality control of complex generics using nanotechnology

With an increase in development and clinical use of nanomedicines, enhancing the development of the complex generics using nanotechnology is important .

For that purpose, the development of standardized methods for physicochemical properties of nanomedicines is required.

Listing in JP and harmonization of the methods can contribute to the access of those generics and innovative drugs worldwide.

Acknowledgements

JP Secretariat

Division of Pharmacopoeia and Standards for Drugs, Office of Review Management, PMDA

Dr. Hiroyuki Yoshida

Division of Drugs, National Institute of Health Sciences

Thank you for your attention.