Regulatory Considerations for Nanotechnology-Related Drug Products in Taiwan

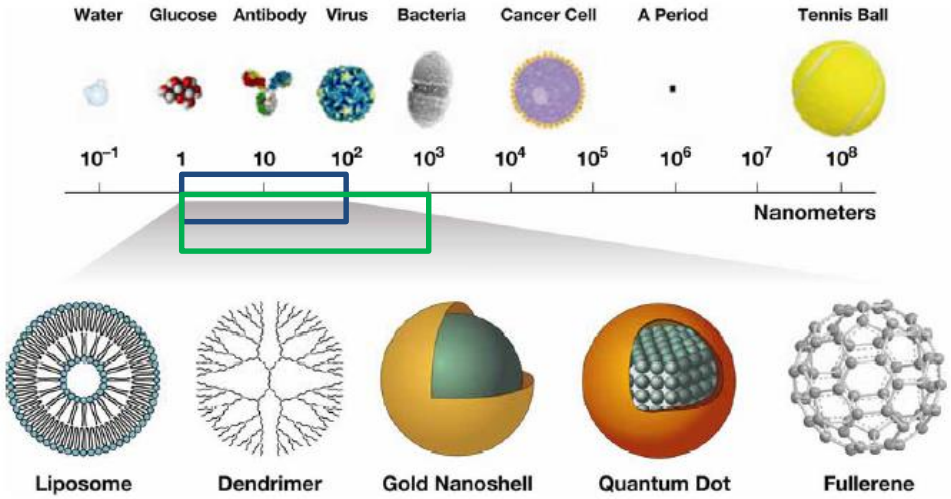
張琳巧 博士/小組長
Chang, Lin-Chau
Ph.D., team leader
Division of Pharmaceutical Science

財團法人醫藥品查驗中心
Center for Drug Evaluation, Taiwan

This presentation was not officially cleared, and the views offered here do not necessarily represent the official positions at MOHW, including TFDA.

Scope

Nanoscale range?



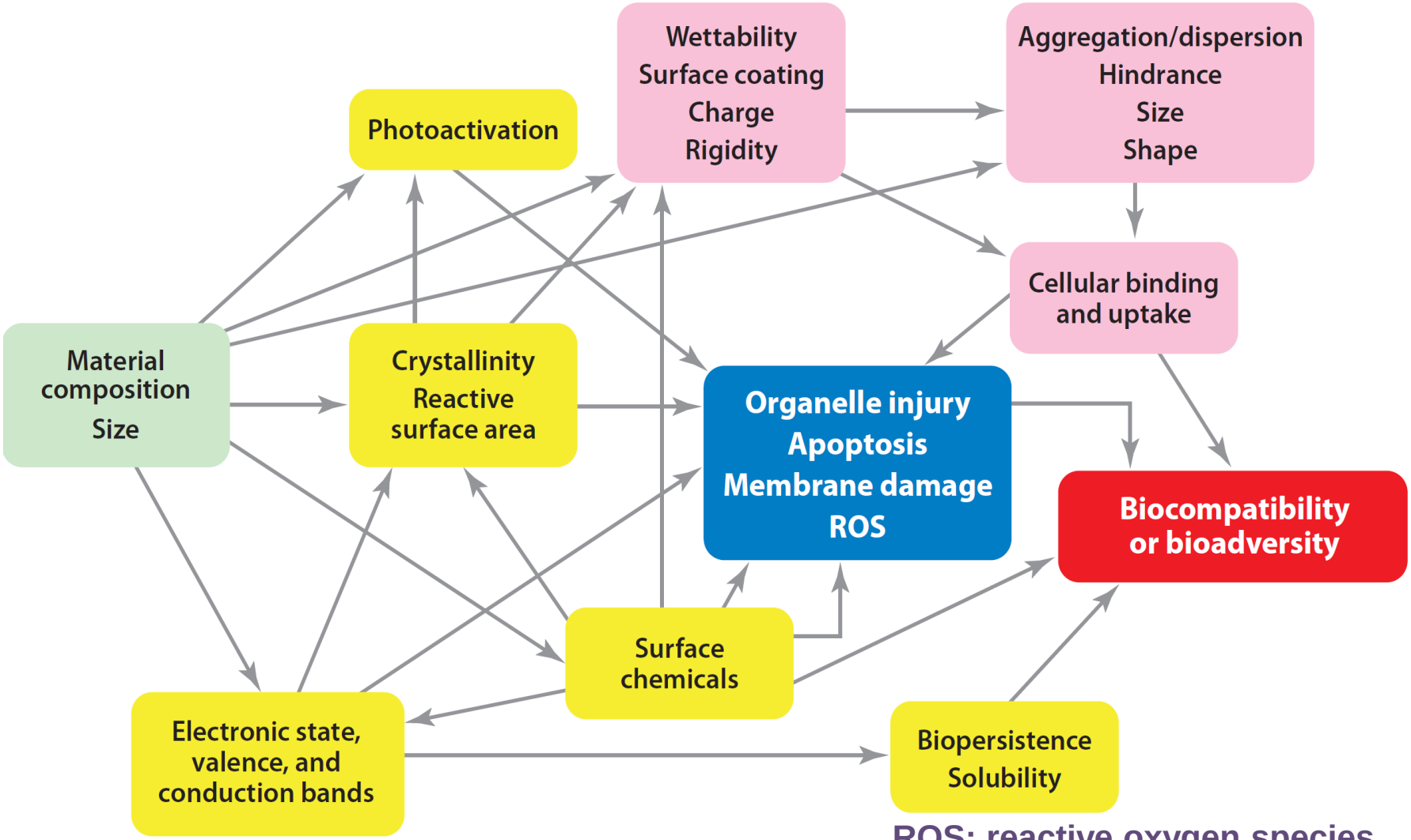
Properties or phenomena attributable to its dimension(s)?

Even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm)…

http://epa.gov/ncer/nano/lectures/mcneil_030706.pdf

U.S. FDA: Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology (2014)

The hypothetical correlations



ROS: reactive oxygen species

Annu. Rev. Pharmacol. Toxicol. 54, 581-598 (2014)

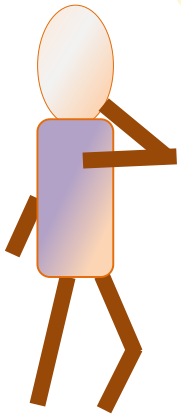
Challenges and points to consider

What's the impact (PK profile, toxicity…)?

Is the characterization enough?

Does size really matter?

Is the method reliable?



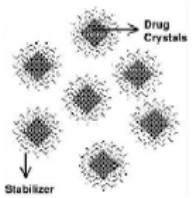
Are there adequate controls to ensure consistency?

How is the stability?

Nanotechnology-related approved drug products in Taiwan

For example

Nanocrystal

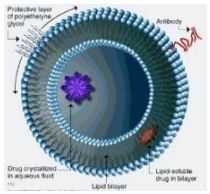


Rapamune Tablets (sirolimus)

Emend Capsules (aprepitant)

Lipanthyl Penta 145 mg film-coated tablet (fenofibrate)

Liposome

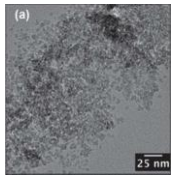


Caelyx Concentrate for Infusion (doxorubicin HCl)

AmBisome for Injection (amphotericin B)

Visudyne Powder for Solution for Infusion (Verteporfin)

Superparamagnetic iron oxide

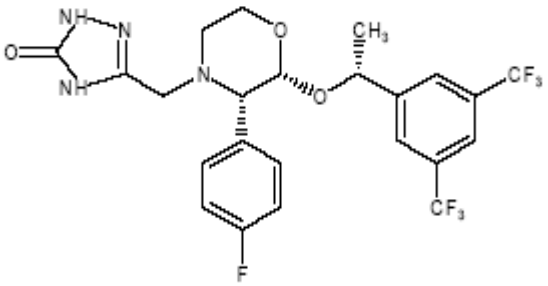


Resovist (ferucarbotran)

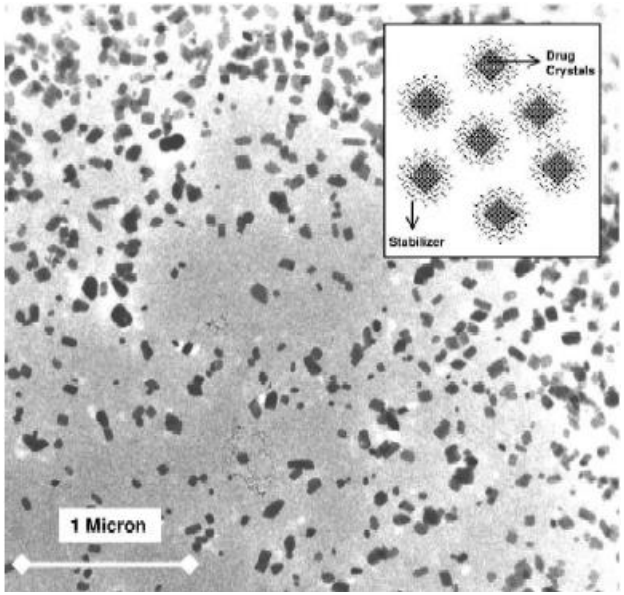
http://www.uic.edu/classes/bios/bios100/lectf03am/liposome.jpg
Eur. J. Pharm. Sci. 18, 113-120 (2003)
Nanoscale 5, 4040-4055 (2013)

Function/benefit-solubility/bioavailability enhancement

Example: Elan NanoCrystal® technology (wet-milling method) for Emend Capsules (aprepitant)



Drug substance: aprepitant
Substance P/neurokinin 1 (NK1) receptor antagonist
Low solubility

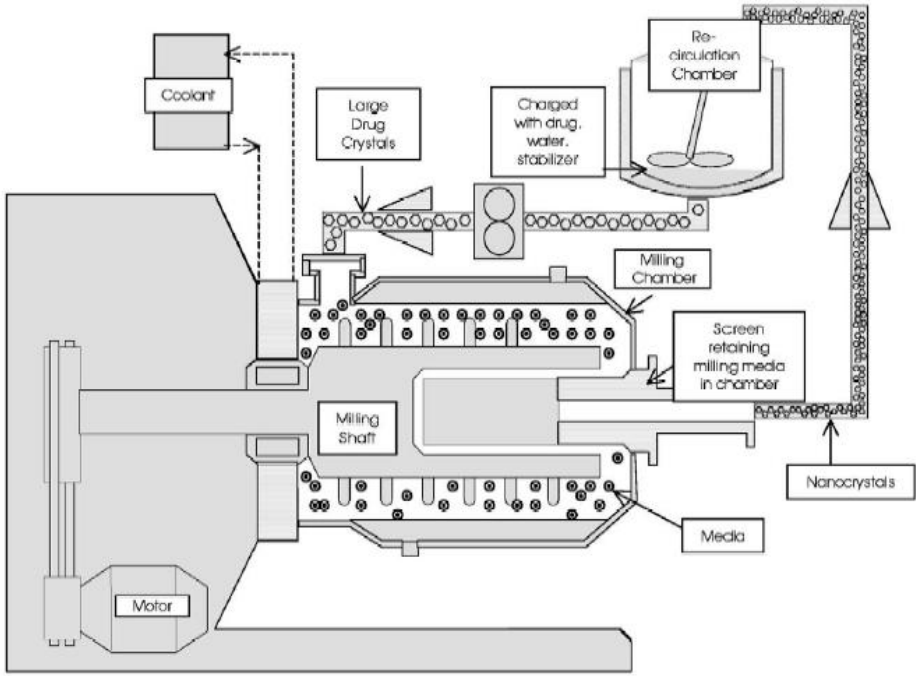


<The transmission electron micrograph of a NanoCrystal® colloidal dispersion>

Decreasing **particle size** of the active substance to **nanoscale** in order to **enhance the bioavailability**

EMA EPAR
Eur. J. Pharm. Sci. 18, 113-120 (2003)

Regulatory considerations



Milling media: a proprietary highly cross-linked polystyrene resin

Particle size!
Dissolution!

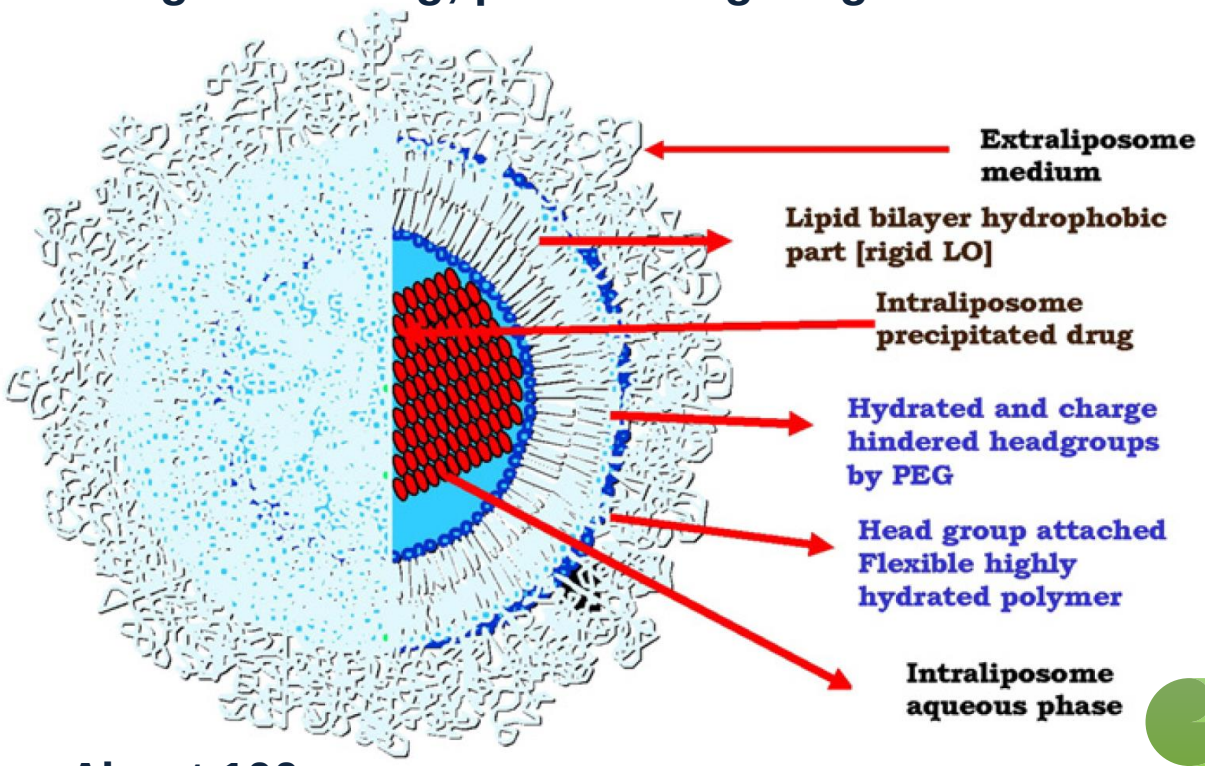
(1) Production of a slurry of water, hydroxypropyl cellulose, and aprepitant
(2) Pre-milling
(3) Addition of an aqueous sodium lauryl sulphate dispersion
(4) Media-milling to form a colloidal dispersion
(5) Addition of an aqueous sucrose dispersion
(6) Spray-coating of microcrystalline cellulose beads with the colloidal dispersion
(7) Sieving of the coated beads
(8) Blending of coated beads with micronised sodium lauryl sulphate
(9) Encapsulation of the blended beads

EMA EPAR
Eur. J. Pharm. Sci. 18, 113-120 (2003)

Function/benefit-reducing unacceptable toxicity

Example: Doxil® (doxorubicin HCl liposome injection) for Intravenous Infusion (Caelyx® Concentrate for Infusion)

Long circulating; passive targeting to tumors



About 100 nm

LO: liquid ordered (phase)

PEG: polyethylene glycol

Incidence of cardiotoxicity (compared with conventional doxorubicin) ↓

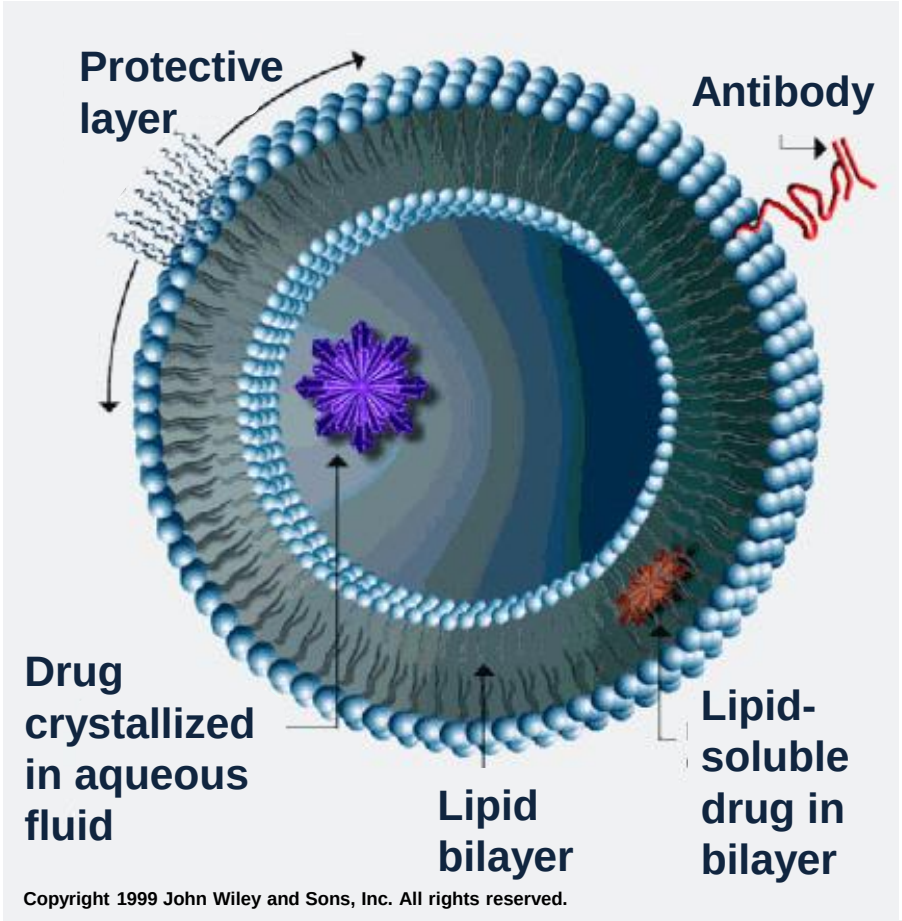
Incidence of palmar-plantar erythrodysesthesia (PPE)(hand-foot syndrome or hand-to-foot syndrome) ↑

U.S. FDA label

J. Control. Release 160, 117-134 (2012)

Ann. Oncol. 18, 1159-1164 (2007)

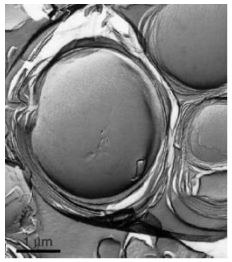
Regulatory considerations



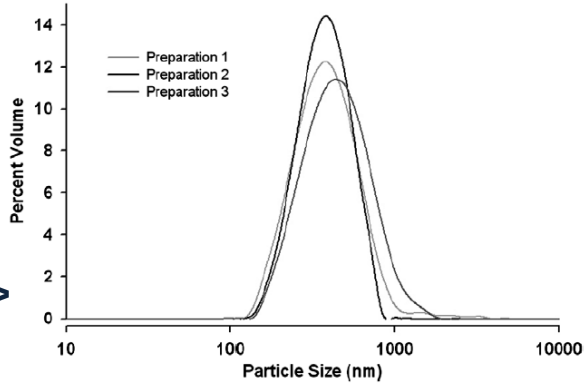
Extensive characterization

Critical

Specification



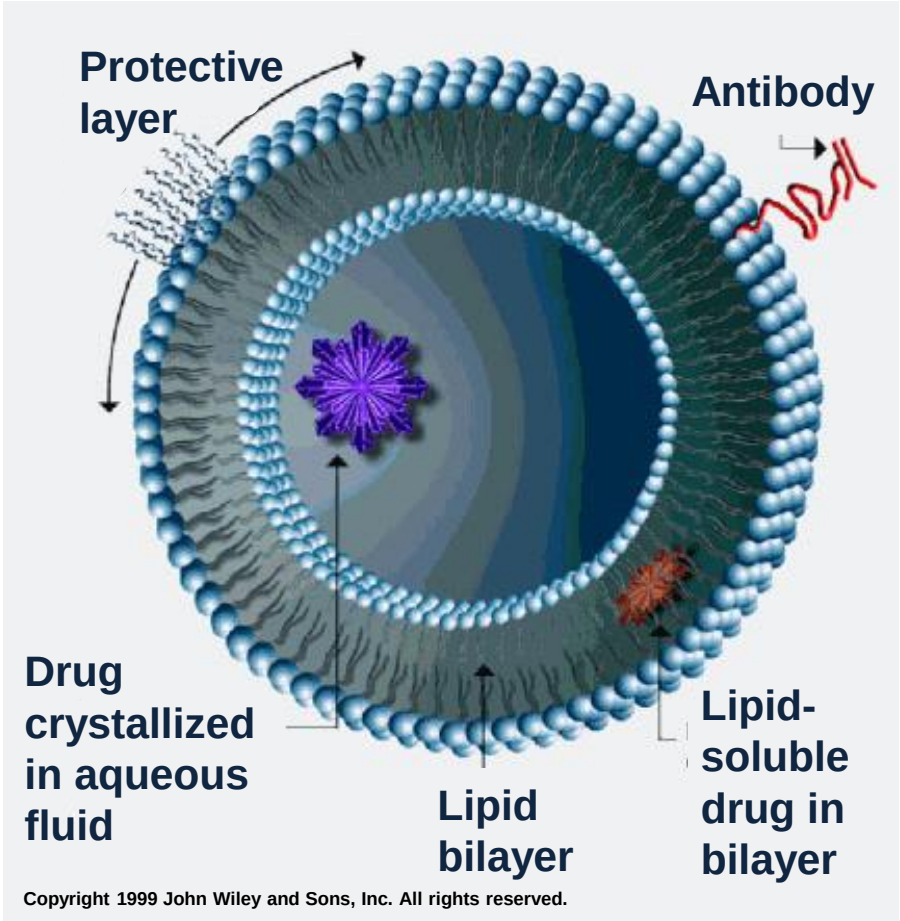
<Freeze-fracture electron microscopy>



<Light scattering>

Nat. Protoc. 2, 547-576 (2007)
Cryobiology 55, 98-107 (2007)
U.S. FDA: Guidance for Industry-Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation (2002)(draft)
Modified from http://www.uic.edu/classes/bios/bios100/lectf03am/liposome.jpg

Regulatory considerations

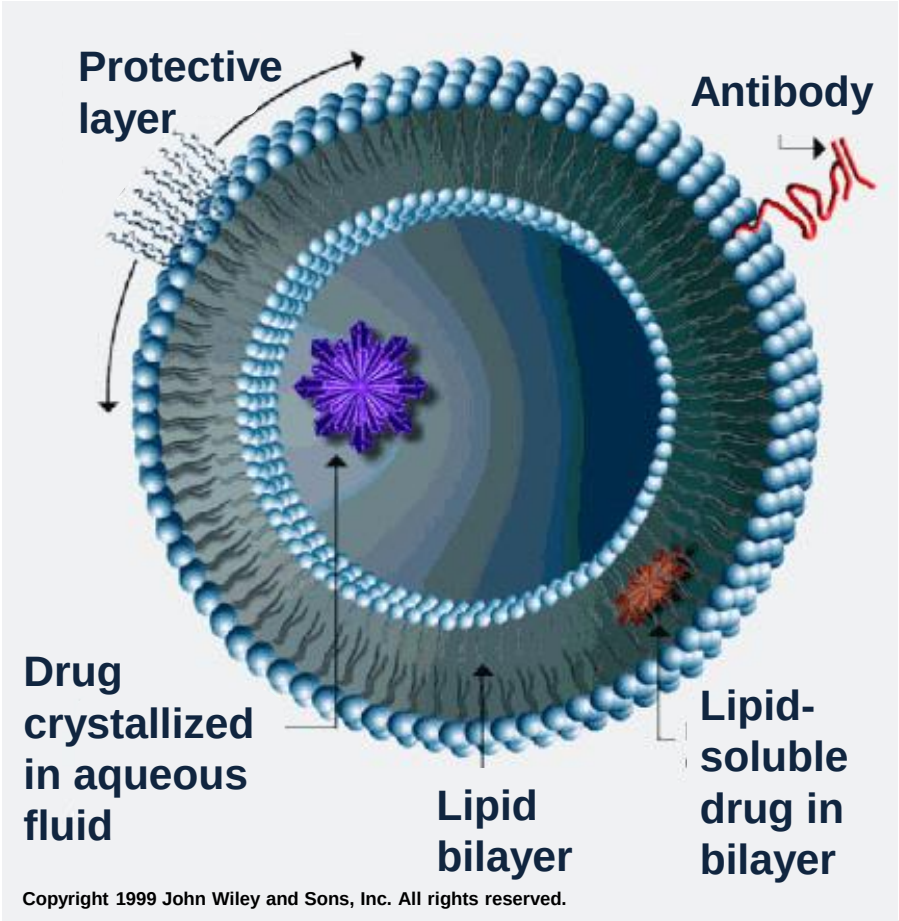


Control of drug product: specifications

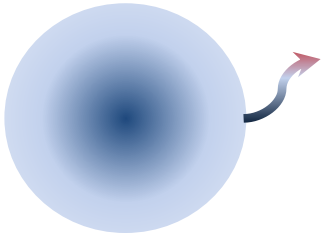
- Physicochemical parameters
- Assay for encapsulated and unencapsulated (i.e., free) drug substance
- Degradation products related to the lipids
- Assay of lipid components
- *In vitro* test for release of drug substance from the liposome…

U.S. FDA: Guidance for Industry-Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation (2002)(draft)
Modified from http://www.uic.edu/classes/bios/bios100/lectf03am/liposome.jpg

Regulatory considerations



Surface coatings



Non-covalent or covalently bound coating

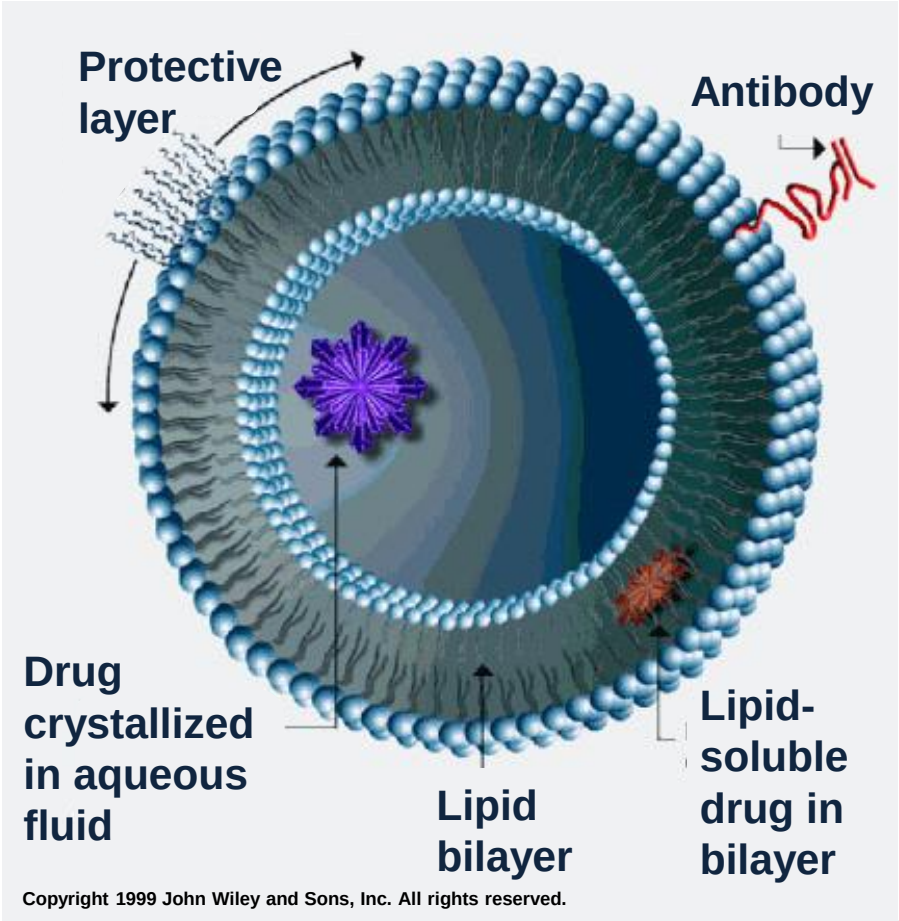
Possible benefits

- Minimize aggregation
- Improve stability
- Minimize reticuloendothelial system clearance after intravenous administration
- Targeting…

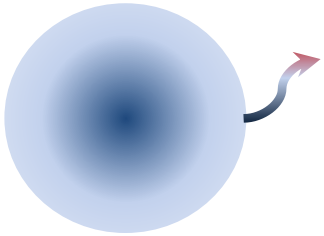
EMA: Reflection Paper on Surface Coatings: General Issues for Consideration Regarding Parenteral Administration of Coated Nanomedicine Products (2013)

Modified from http://www.uic.edu/classes/bios/bios100/lectf03am/liposome.jpg

Regulatory considerations



Surface coatings



Non-covalent or covalently bound coating

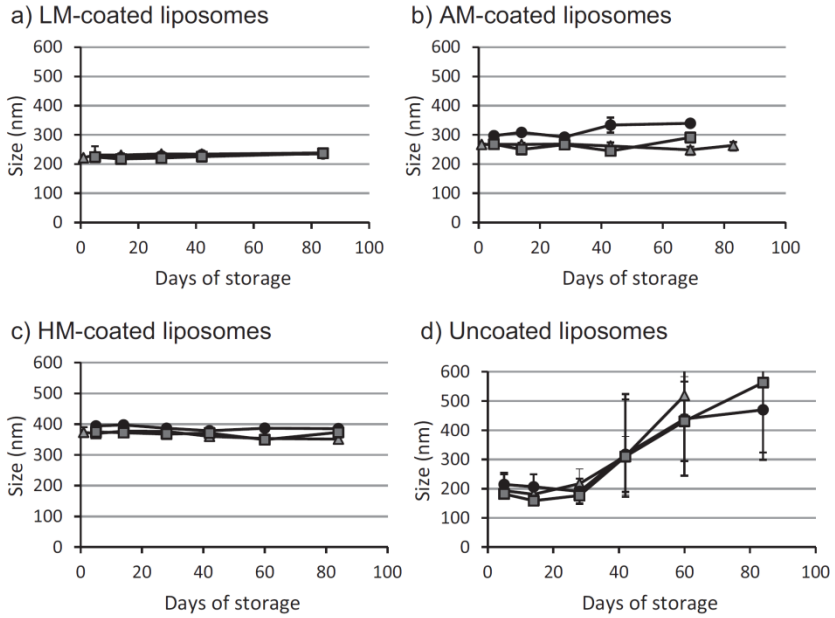
Product characterization

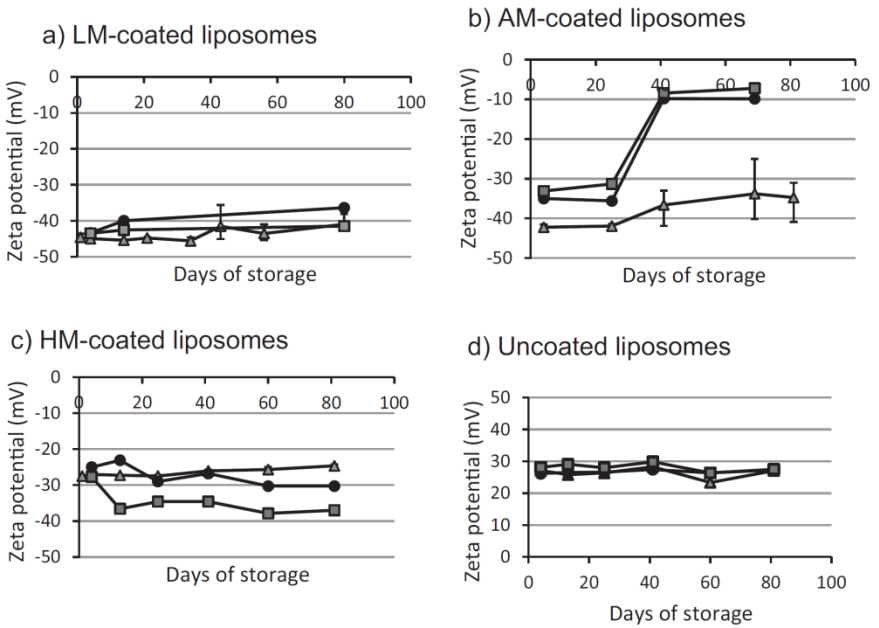
- Composition and control of the coating material
- Complete validation of the coating step
- Potential impact of surface coverage
- Orientation and conformational state of any ligand
- Stability…

EMA: Reflection Paper on Surface Coatings: General Issues for Consideration Regarding Parenteral Administration of Coated Nanomedicine Products (2013)

Modified from http://www.uic.edu/classes/bios/bios100/lectf03am/liposome.jpg

Regulatory considerations





4 °C (▲), room temperature (●) and 35 °C (■)

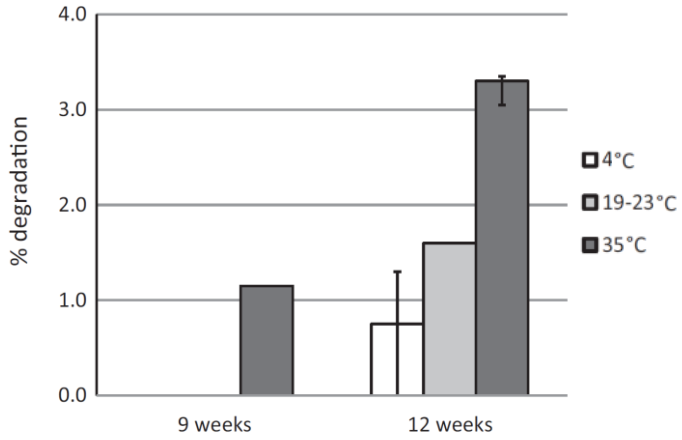
LM: Low-methoxylated pectin
HM: High-methoxylated pectin
AM: Amidated pectin

U.S. FDA: Guidance for Industry-Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation (2002)(draft)

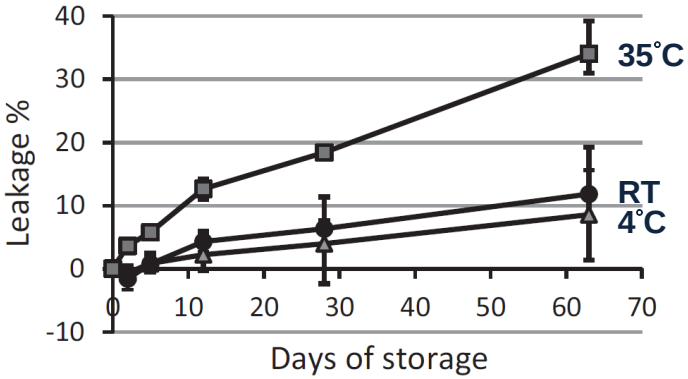
Carbohydr. Polym. 90, 1337-1344 (2012)

Regulatory considerations

Stability



Lipid degradation (calculated from the amount of lyso phosphatidylcholine detected in the samples) of amidated pectin-coated liposomes during storage



Leakage from amidated pectin-coated liposomes during storage at different temperatures

Fusion? Aggregation? Leakage of the encapsulated drug substance?

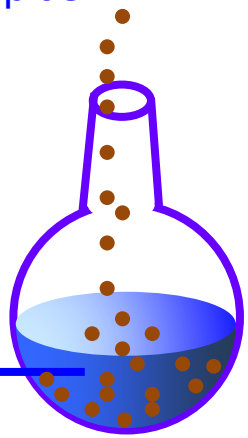
U.S. FDA: Guidance for Industry-Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation (2002)(draft)

Carbohydr. Polym. 90, 1337-1344 (2012)

Regulatory considerations

Description of manufacturing process and process controls

Addition of lipids



Organic solvent

Preparation of liposomes

First described by Dr. Alec Bangham and his colleagues at the Agricultural Research Council Institute of Animal Physiology at Babraham, Cambridge in the mid-1960s:

Bangham method (hand shaken or thin film hydration method)

Solvent removal
(several hours under vacuum)

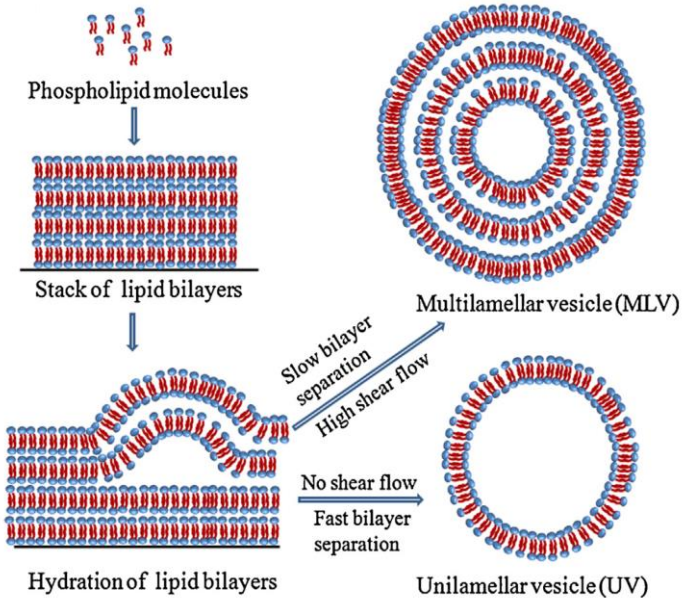
Regulatory considerations

Description of manufacturing process and process controls

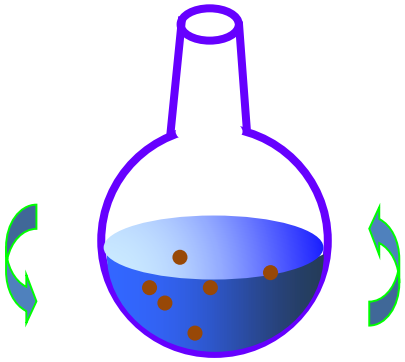
Scale up

Filtration

Dispersion or hydration of the lipid film with an aqueous media



Agitation



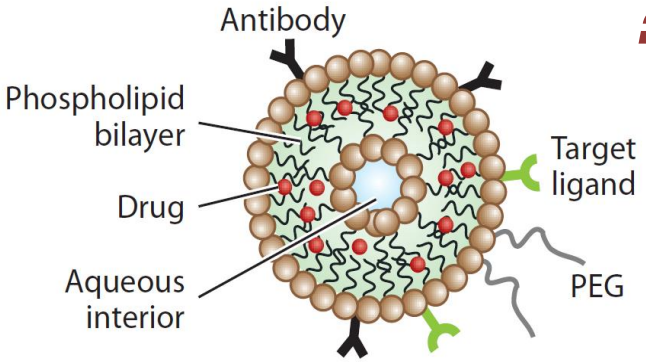
Formation of liposomes

Sonication, extrusion or high pressure homogenization

Chem. Phys. Lipids 177, 8-18 (2014)

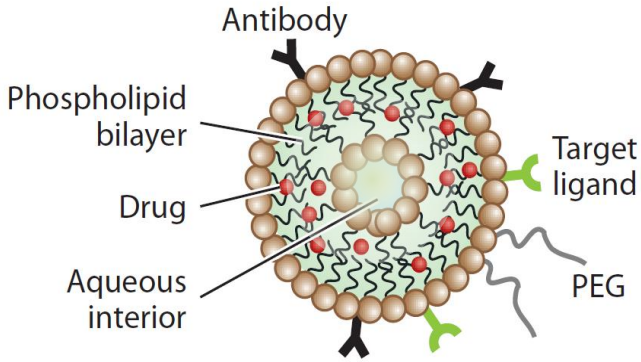
Regulatory considerations- generic drug products/nanosimilars

Reference drug product



?

Generic drug product



For example (doxorubicin HCl liposome injection)

Pharmaceutical comparability

Bioequivalence

Other studies?

Same drug product composition?
Manufactured by an active liposome loading process with an ammonium sulfate gradient?
Equivalent liposome characteristics?

U.S. FDA: Draft Guidance on Doxorubicin Hydrochloride (2013)
EMA: Reflection Paper on the Data Requirements for Intravenous Liposomal Products Developed with Reference to an Innovator Liposomal Product (2013)
Annu. Rev. Pharmacol. Toxicol. 54, 581-598 (2014)

Current thinking and future perspectives

Our regulatory requirements evolve…

Drafting of guidelines for liposome drug products, innovative/generic

Extensive discussion between the authorities, industries, and academia

Cooperation between different organizations; support from the government



Current thinking and future perspectives

Integration of updated information of cutting-edge technology into regulatory considerations

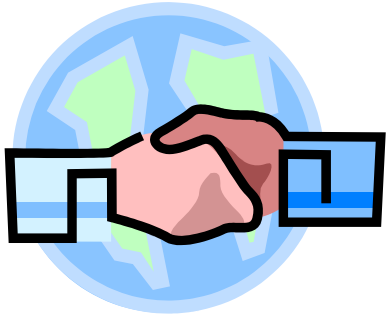
Case-by-case assessment under the existing regulatory framework

Characterization in accordance with special properties, the quality assurance, and safety concern

Cooperation between Japan and Taiwan

Communication

Exchange of information and ideas



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Thank you very much for your attention

どうもありがとうございます