Liposome Drug Product Guidances

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Nano Day (via webex)

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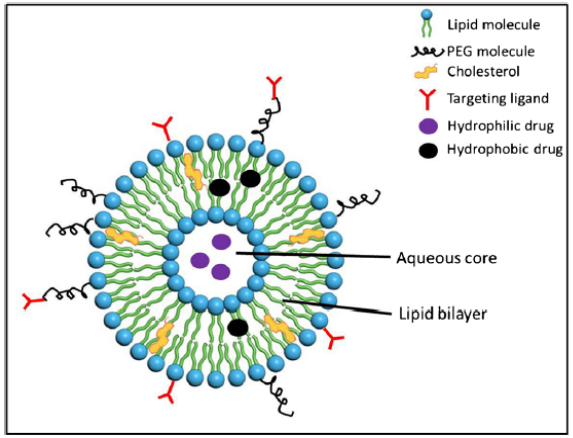
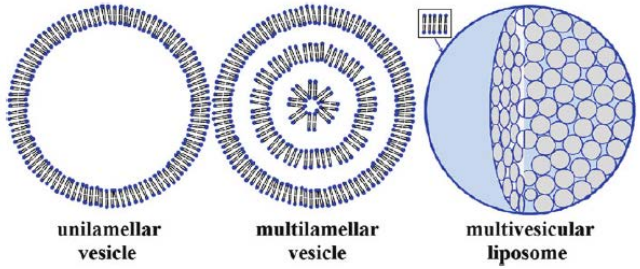
Liposome and Liposome Drug Products





Liposome

- vesicles composed of a bilayer (uni-lamellar) and/or a concentric series of multiple bilayers (multi-lamellar) separated by aqueous compartments formed by amphipathic molecules such as phospholipids that enclose a central aqueous compartment

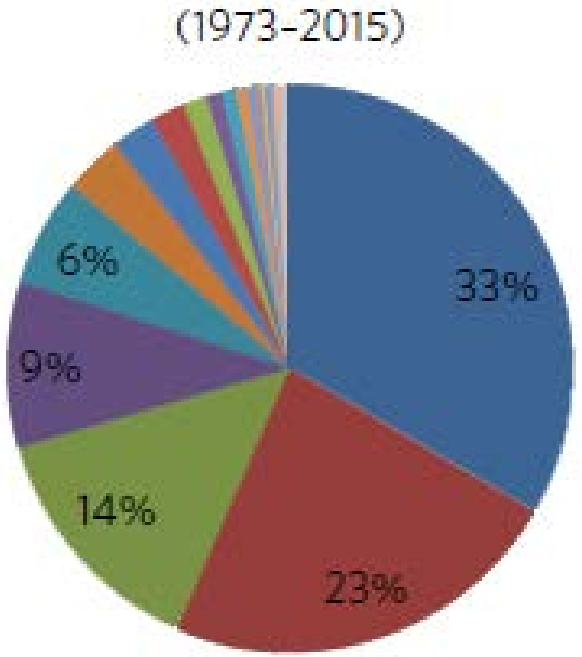
Liposome Drug Product

- A drug product in which the drug substance is contained in liposomes

Guidance for Industry. Liposome drug products, chemistry, manufacturing, and controls; human pharmacokinetics and bioavailability; and labeling documentation. U.S. Food and Drug Administration. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070570.pdf (2018)

Submissions to the U.S. FDA of Drug Products Containing Nanomaterials

- Liposome
- Nanocrystal
- Emulsion
- Iron-polymer complex
- Micelle
- Drug-protein complex
- Drug-polymer complex
- Dendrimer
- Polymeric NP
- Nanobubble
- Silica NP
- Drug-lipid complex
- Drug-metal complex
- Protein NP
- Drug NP
- Solid lipid NP
- Nanotube
- Metal-protein complex
- Metal-nonmetal complex
- Metal-polymer complex



D'Mello S. et al. Nature Nanotechnology DOI: 10.1038/NNANO.2017.67

FDA Approved Liposome New Drug Applications (NDAs)

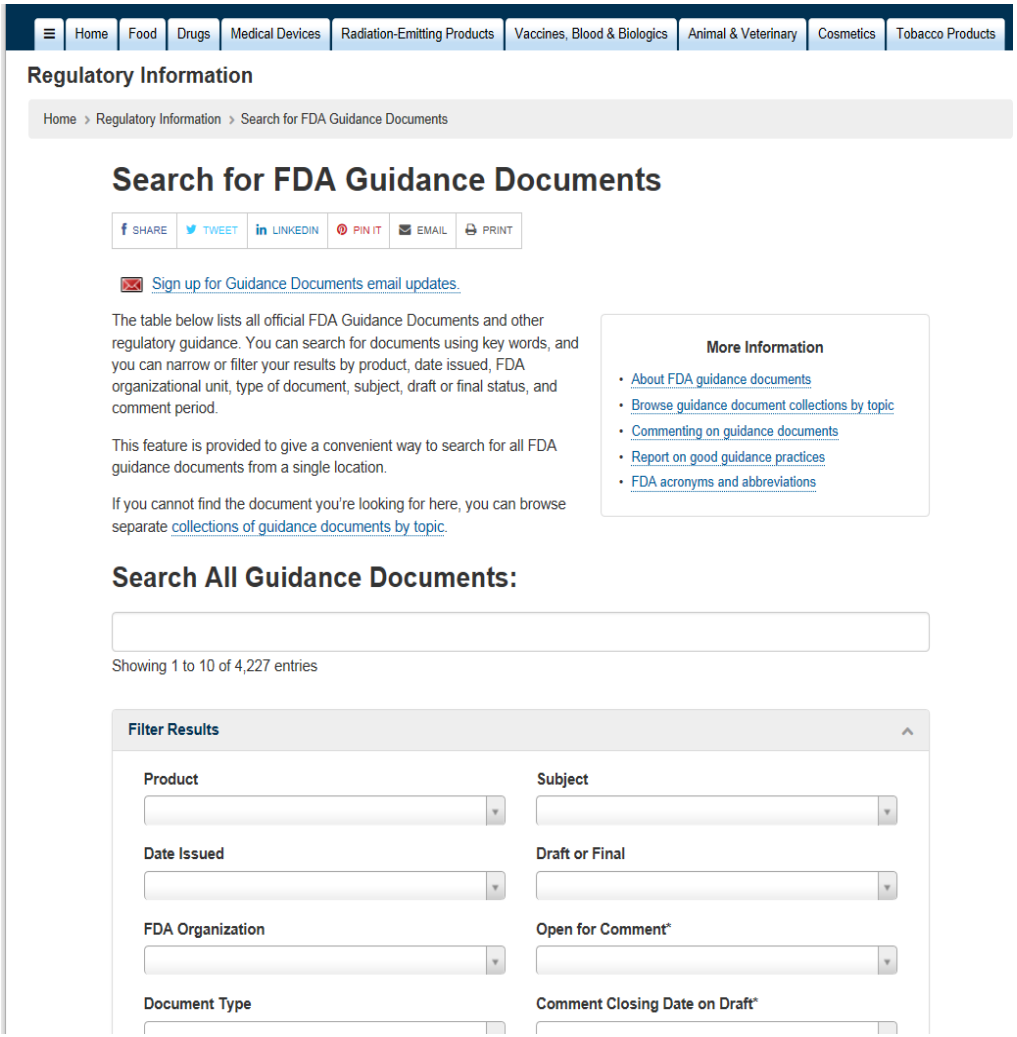
Trade name	Active Ingredient	Indication and Usage	Route	Initial Approval Date	Market Status Available
DOXIL	Doxorubicin HCl	Ovarian cancer, AIDS-related Kaposi's sarcoma, multiple myeloma	Intravenous	11/17/1995	Yes
DAUNOXOME	Daunorubicin Citrate	Advanced HIV-related Kaposi's sarcoma (relapse)	Intravenous	4/8/1996	Discontinued
AMBISOME	Amphotericin B	Certain fungal infections	Intravenous	08/11/1997	Yes
DEPOCYT	Cytarabine	Lymphomatous meningitis	Intrathecal	04/01/1999	Discontinued
VISUDYNE	Verteporfin	Photosensitizer for treatment of certain patients	Intravenous	04/12/2000	Yes
DEPODUR	Morphine Sulfate	Opioid local analgesic	Epidural	05/18/2004	Discontinued
EXPAREL	Bupivacaine	Postsurgical analgesia	infiltration into the surgical site	10/28/2011	Yes
MARQIBO	Vincristine Sulfate	Acute lymphoblastic leukemia	Intravenous	08/09/2012	Yes
ONIVYDE	Irinotecan HCl	Metastatic pancreatic cancer	Intravenous	10/22/2015	Yes
VYXEOS	Daunorubicin and Cytarabine	Therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)	Intravenous	08/03/2017	Yes
ARIKAYCE KIT	Amikacin sulfate	Mycobacterium avium complex (MAC) lung disease	Oral inhalation	09/28/2018	Yes

https://www.accessdata.fda.gov/scripts/cder/daf/

FDA Guidances

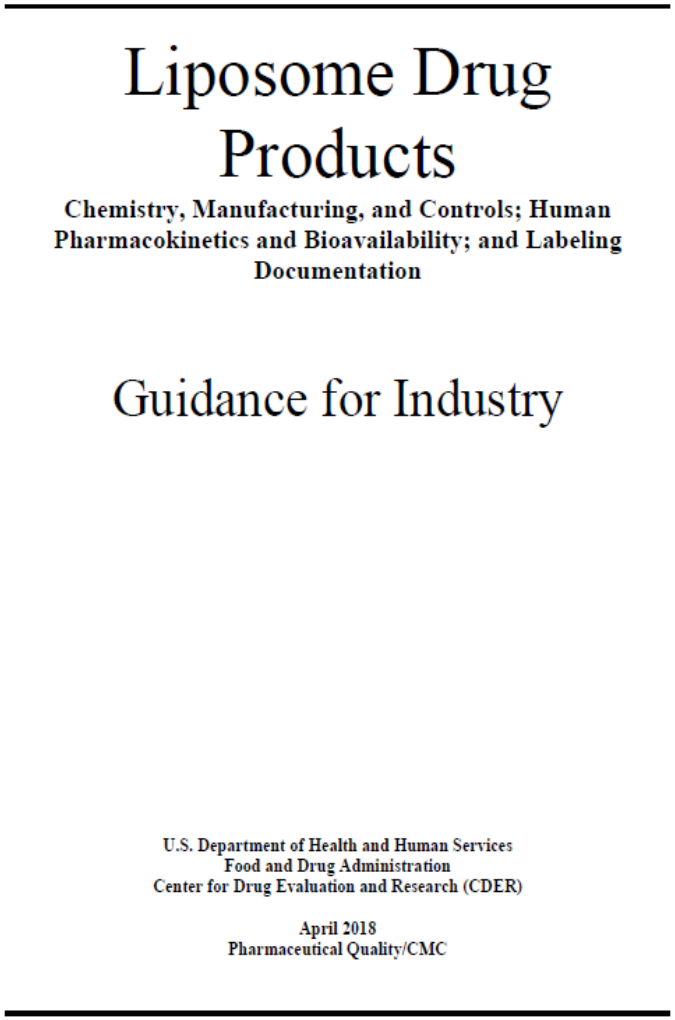
- Guidance documents represent FDA's current thinking on a topic.
  - They do not establish any rights for any person and is not binding to FDA or the public.
  - An alternative approach may be used if the approach satisfies the requirements of the applicable statutes and regulations.

- https://www.fda.gov/RegulatoryInformation/Guidances/default.htm



Nanomaterials in Drug Products: Guidance

- Agency Guidance
  - http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm
- CDER and CBER Guidance
  - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588857.pdf
- Class-specific Guidance
  - Liposome drug product
  - https://www.fda.gov/media/70837/download
- Product-Specific Guidance
  - 20+ guidances
  - Search based on active ingredient
  - https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm



Liposome Drug Products

Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2018
Pharmaceutical Quality/CMC

Guidance for Liposome Drug Products

This guidance discusses what types of information you, the applicant, should submit in your new drug application (NDA) or abbreviated new drug application (ANDA) for a liposome drug product reviewed by the Center for Drug Evaluation and Research (CDER).

Topics covered:

- Chemistry, manufacturing, and controls (CMC)
- Human pharmacokinetics and bioavailability or, in the case of an ANDA, bioequivalence
- Labeling in NDAs and ANDAs

Topics not covered:

- Clinical efficacy and safety studies
- Nonclinical pharmacology/toxicology studies
- Drug-lipid complexes

Chemistry, Manufacturing, and Control

1. Description and Composition

2. Physicochemical Properties

a. Morphology, e.g., lamellarity
b. Surface characteristics, e.g., pegylation
c. Net charge
d. Drug product viscosity
e. Parameters of the contained drug
f. Particle size (i.e., mean and distribution profile)
g. Liposome phase transition temperature.
h. In vitro release
i. Leakage rate of drug from the liposomes throughout shelf life
j. Liposome integrity changes
k. Liposome structure

3. Critical Quality Attributes

Chemistry, Manufacturing, and Control

4. Description of Manufacturing Process and Process Controls Description and Composition

5. Control of Lipid Components

a. Description and Characterization of Lipid Components
b. Manufacture of Lipid Components
c. Specifications for Lipid Components
d. Stability of Lipid Components

6. Drug Product Specification

7. Stability

8. Post-approval Changes in Manufacturing

Human Pharmacokinetics: Bioavailability and Bioequivalence

1. Clinical Pharmacology Studies

a. Pharmacokinetic and Mass Balance Studies for Liposome Drug Products

- Multiple-dose study evaluating the drug pharmacokinetics after administration of the liposome drug product.
- Dose-proportionality study over the expected therapeutic dose range of the liposome drug product.
- Exposure-response studies if available.

b. Comparison Clinical Pharmacology Studies with Nonliposome Drug Product

2. Biopharmaceutics

a. Drug Release Characteristics

b. In Vitro/In Vivo Correlation (IVIVC)

Labeling

1. Nonproprietary name

- [DRUG] Liposome Type X [DOSAGE FORM]
- [DRUG] Pegylated Liposome Type X [DOSAGE FORM]

2. Description

- A cautionary note should be included emphasizing that liposome drug products may behave differently from nonliposome drug products or other liposome products even though the active ingredient is the same. The applicant should specifically describe such differences. Note: this is not necessary for liposome drug products determined by FDA to be therapeutically equivalent.

3. Dosage and Administration

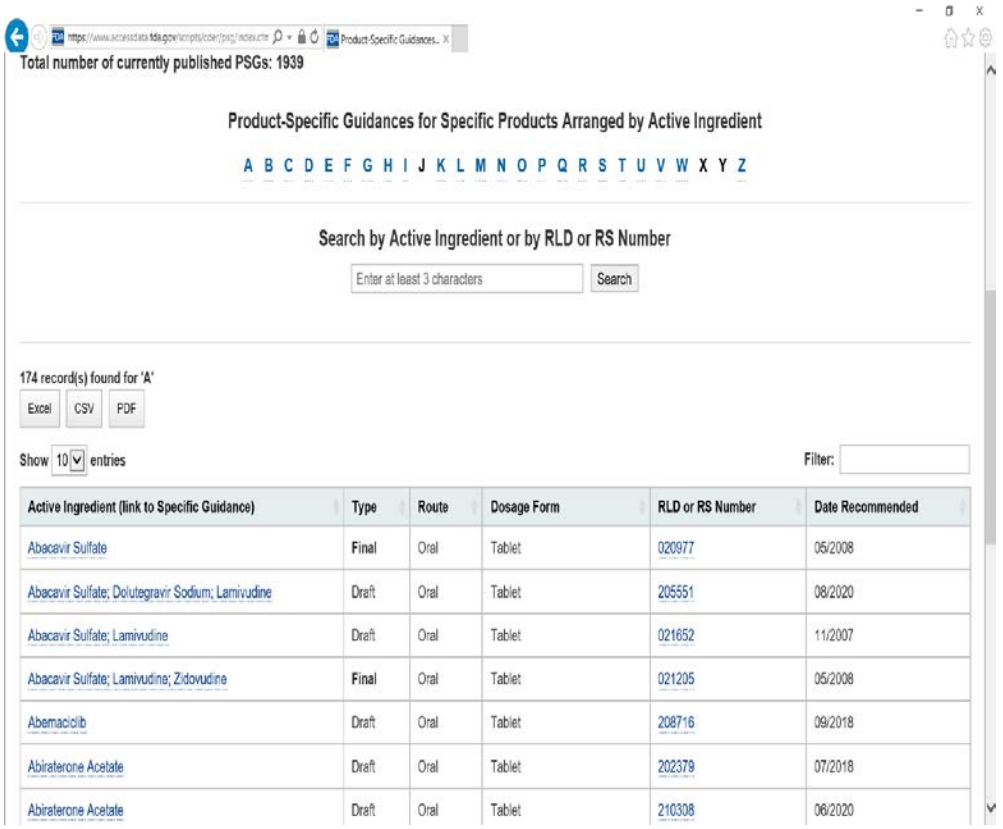
- Reconstitution instructions and a statement regarding the appropriate in-use period
- Storage conditions for the reconstituted drug, robustness of the liposome drug product under varied reconstitution conditions (e.g., degree of shaking), and use of in-line filters.

Product-Specific Guidances

- FDA publishes product-specific guidances describing the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference listed drugs

- FDA publishes these product-specific guidances to foster drug product development, and ANDA submission and approval, ultimately providing increased access to safe, affordable generic drugs

- https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm



Total number of currently published PSGs: 1939

Product-Specific Guidances for Specific Products Arranged by Active Ingredient

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Search by Active Ingredient or by RLD or RS Number

Enter at least 3 characters Search

174 record(s) found for 'A'

Excel CSV PDF

Show 10 entries Filter:

Active Ingredient (link to Specific Guidance)	Type	Route	Dosage Form	RLD or RS Number	Date Recommended
Abacavir Sulfate	Final	Oral	Tablet	020977	05/2008
Abacavir Sulfate; Dolutegravir Sodium; Lamivudine	Draft	Oral	Tablet	205551	08/2020
Abacavir Sulfate; Lamivudine	Draft	Oral	Tablet	021652	11/2007
Abacavir Sulfate; Lamivudine; Zidovudine	Final	Oral	Tablet	021205	05/2008
Abemaciclib	Draft	Oral	Tablet	208716	09/2018
Abiraterone Acetate	Draft	Oral	Tablet	202379	07/2018
Abiraterone Acetate	Draft	Oral	Tablet	210308	06/2020

Product-Specific Guidance for Doxorubicin HCl liposome Injection

Contains Nonbinding Recommendations

Draft Guidance on Doxorubicin Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Doxorubicin hydrochloride

Dosage Form; Route: Injectable, liposomal

Recommended Studies: Two studies: in vivo and in vitro

To be eligible for the bioequivalence studies recommended in this guidance, the Test product should meet the following criteria:

- Qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD)
- Manufactured by an active liposome loading process with an ammonium sulfate gradient
- At least one batch of the Test product should be produced by the commercial scale process and be used in the in vivo bioequivalence study
- Equivalent liposome characteristics including liposome composition, state of encapsulated drug, internal environment of liposome, liposome size distribution, number of lamellar, grafted PEG at the liposome surface, electrical surface potential or charge, and in vitro leakage rates comparable to the Reference Standard (RS).

In Vivo Study:

Type of study: Fasting*
Design: Single-dose, two-way crossover in vivo
Strength: 50 mg/vial or 20 mg/vial
Dose: 50 mg/m2
Subjects: Ovarian cancer patients whose disease has progressed or recurred after platinum-based chemotherapy and who are already receiving or scheduled to start therapy on doxorubicin hydrochloride (liposomal).
Additional comments:

- The pivotal bioequivalence study should be conducted using test product produced by the proposed commercial scale manufacturing process
- Doxorubicin is a cytotoxic drug. Therefore, a Bio-IND is required for bioequivalence studies of a doxorubicin HCl liposomal injection to ensure the safety of human test subjects

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

Recommended Feb 2010; Revised Nov 2013, Dec 2014, Apr 2017, Sept 2018

Analytes to measure (in appropriate biological fluid): Free doxorubicin and liposome encapsulated doxorubicin.

Bioequivalence based on (90% CI): AUC and Cmax for free doxorubicin and liposome encapsulated doxorubicin.

Equivalent liposome characteristics

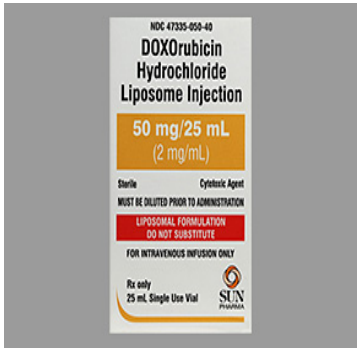
Comparative physicochemical characterization studies should be performed on at least three batches of both the Test and RS products, at least one Test batch should be produced by the commercial scale process and be used in the in vivo bioequivalence study, and should include:

- Liposome composition: Liposome composition including lipid content, free and encapsulated drug, internal and total sulfate and ammonium concentration, histidine concentration, and sucrose concentration should be measured. The drug-to-lipid ratio and the percentage of drug encapsulation can be calculated from liposome composition values.
- State of encapsulated drug: Doxorubicin is largely in the form of a doxorubicin sulfate crystal inside the liposome. The proposed Test product must contain a comparable doxorubicin sulfate crystal inside the liposome, as the RS product.
- Internal environment (volume, pH, sulfate, and ammonium ion concentration): The internal environment of the liposome Test product should be comparable to the RS, including its volume, pH, sulfate, and ammonium concentration maintains the doxorubicin sulfate crystal.
- Liposome morphology and number of lamellae: Liposome morphology and lamellarity should be comparable to the RS as drug loading, drug retention, and the rate of drug release from the liposomes are likely influenced by the degree of lamellarity.
- Lipid bilayer phase transitions: Equivalence in lipid bilayer phase transitions will contribute to demonstrating equivalence in bilayer fluidity and uniformity. The phase transition profile of the liposomal Test product should be comparable to the RS product.
- Liposome size distribution: The ANDA sponsor should select the most appropriate particle size analysis method to determine the particle size distributions of both Test and RS products. The number of liposome product vials to be studied should not be fewer than 30 for each of the Test and RS products (i.e., no fewer than 10 from each of three batches). See recommended study 2 (above) for details of the recommended statistical equivalence tests.
- Grafted PEG at the liposome surface: The surface-bound methoxypolyethylene glycol (MPEG) polymer coating protects liposomes from clearance by the mononuclear phagocyte system (MPS) and increases blood circulation time. The PEG layer thickness is known to be thermodynamically limited and estimated to be in the order of several nanometers. The PEG layer thickness should be comparable to the RS.

Generic Liposome Drug Products

Approved Generic Liposome Drug Products

Doxorubicin HCl (liposomal)	ANDA	Manufacturer	Approval Date
	203263	Sun Pharma Global	Feb 4, 2013
	208657	Dr Reddy's Labs LTD	May 15, 2017
	212299	Zydus	Sept 10, 2020



Approved Liposome Drug Products and Product-Specific Guidance Available

Trade name	Initial Approval Date	Product-Specific Guidance Available
DOXIL	11/17/1995	Yes
DAUNOXOME*	4/8/1996	Yes
AMBISOME	08/11/1997	Yes
DEPOCYT*	04/01/1999	No
VISUDYNE	04/12/2000	Yes
DEPODUR*	05/18/2004	No
EXPAREL	10/28/2011	Yes
MARQIBO	08/09/2012	No
ONIVYDE	10/22/2015	No
VYXEOS	08/03/2017	No
ARIKAYCE KIT	09/28/2018	No

https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

* Product discontinued

Guidelines for Liposome Drug Products from Other Regulatory Agencies

- Guideline for the Development of Liposome Drug Products (Japan MHLW)

- Data requirements for intravenous liposomal products developed with reference to an innovator liposomal product (EMA)

MHLW: Ministry of Health, Labour and Welfare

EMA: European Medicines Agency

IPRP Nanomedicine Working Group Liposome Survey

- Survey Objectives
  - Capture the regulatory progress for liposome products from the expanded International Pharmaceutical Regulator Programme (IPRP) members
  - Identify the needs of both research and standard development
  - Enhance the potential for harmonization of regulatory requirements
- Survey for both regulatory agencies and non-regulatory stakeholders
- Survey out on 07/02/20 and response due 09/01/20
- Analysis ongoing

http://www.iprp.global/working-group/nanomedicines

Summary

- FDA published a general guidance for liposome drug products in 2018
  - CMC
  - Clinical Pharmacology
  - Labeling

- FDA publishes product-specific guidances for generic product referencing innovator liposome drug products

- More research, standard development, and guideline harmonization are needed for liposome drug products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