US FDA Perspectives for Bioequivalence (BE) Evaluation of Liposome Drug Products

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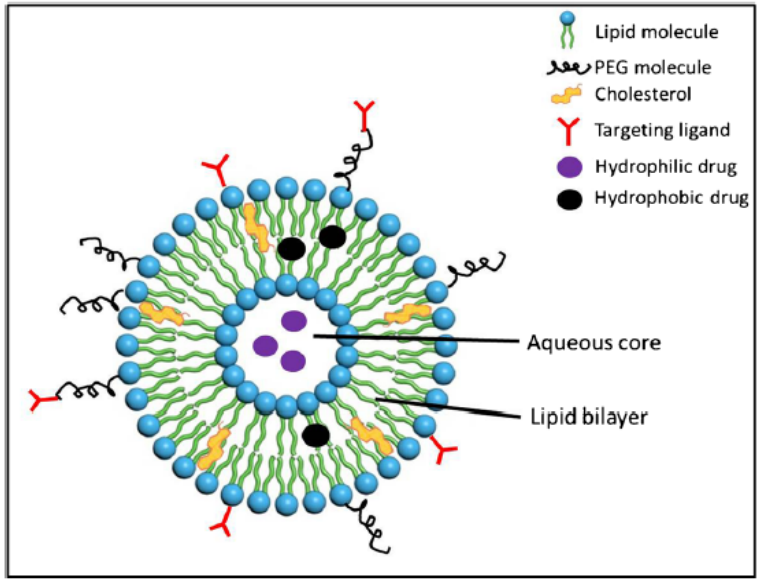
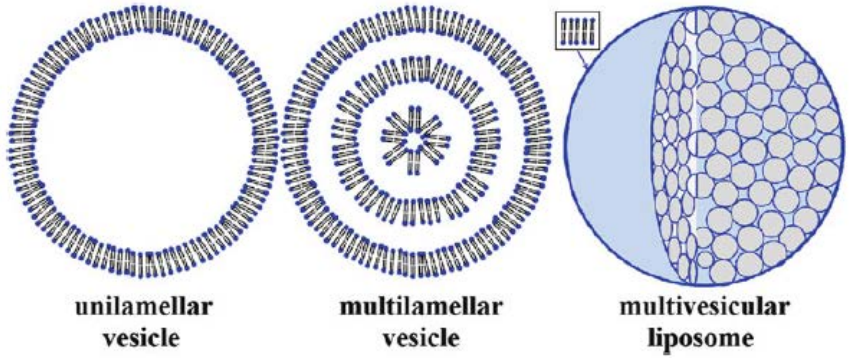
Liposome and Liposome Drug Products





Liposome

- Microvesicle composed of a bilayer and/or a concentric series of multiple bilayers 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 active pharmaceutical ingredient (API) 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)

FDA Approved Liposome Drug Products

Trade name	Active Ingredient	Indication	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	Yes
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

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

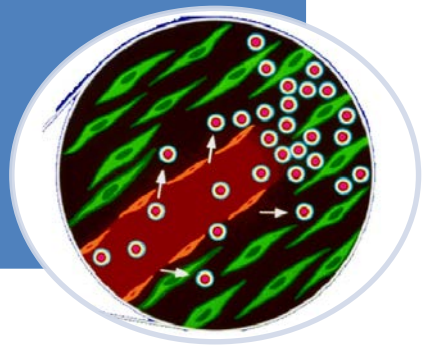
Versatile Nature of Liposome Drug Products

Sizes	• Nanometer to Micrometer
Administration routes	• Intravenous, intrathecal, and epidural
Indications	• Cancer, certain fungal infections, age-related macular degeneration, and pain
Delivery modes	• Immediate, sustained, and/or targeted delivery
Active pharmaceutical ingredients (APIs)	• Hydrophilic and hydrophobic • Single or multiple

Complexity of Liposome Drug Product and Class-specific Guidance

- Tissue uptake of the liposome drug product
- API release/leakage from the liposomes
- Clearance of released and unbound API
- Clearance of the liposome drug product
- Clearance of the liposome carrier

In vivo processes



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

Recommendations for Liposome Drug Bioavailability Studies

For new drug application (NDA) of liposome drug products

- 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

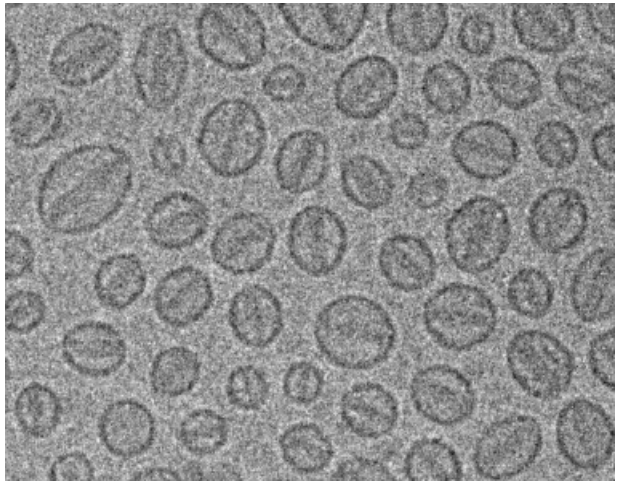
- Compare liposome drug products to the corresponding approved nonliposome formulation to elucidate differences in absorption, distribution, metabolism, and excretion (ADME)

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

Generic Liposome Drug Products

Approved Generic Liposome Drug Products

	ANDA	Manufacturer	Approval Date
Doxorubicin HCl (liposomal)	203263	Sun Pharma Global	Feb 4, 2013
	208657	Dr Reddys Labs LTD	May 15, 2017



Doxorubincin HCl liposomes

Product Specific Guidance Development

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

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

* Product discontinued

Challenges in Demonstrating Therapeutic Equivalence of Liposome Drug Products

Pharmaceutical Equivalence + Bioequivalence

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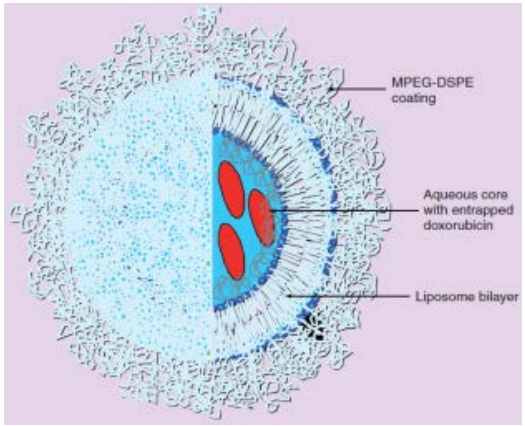
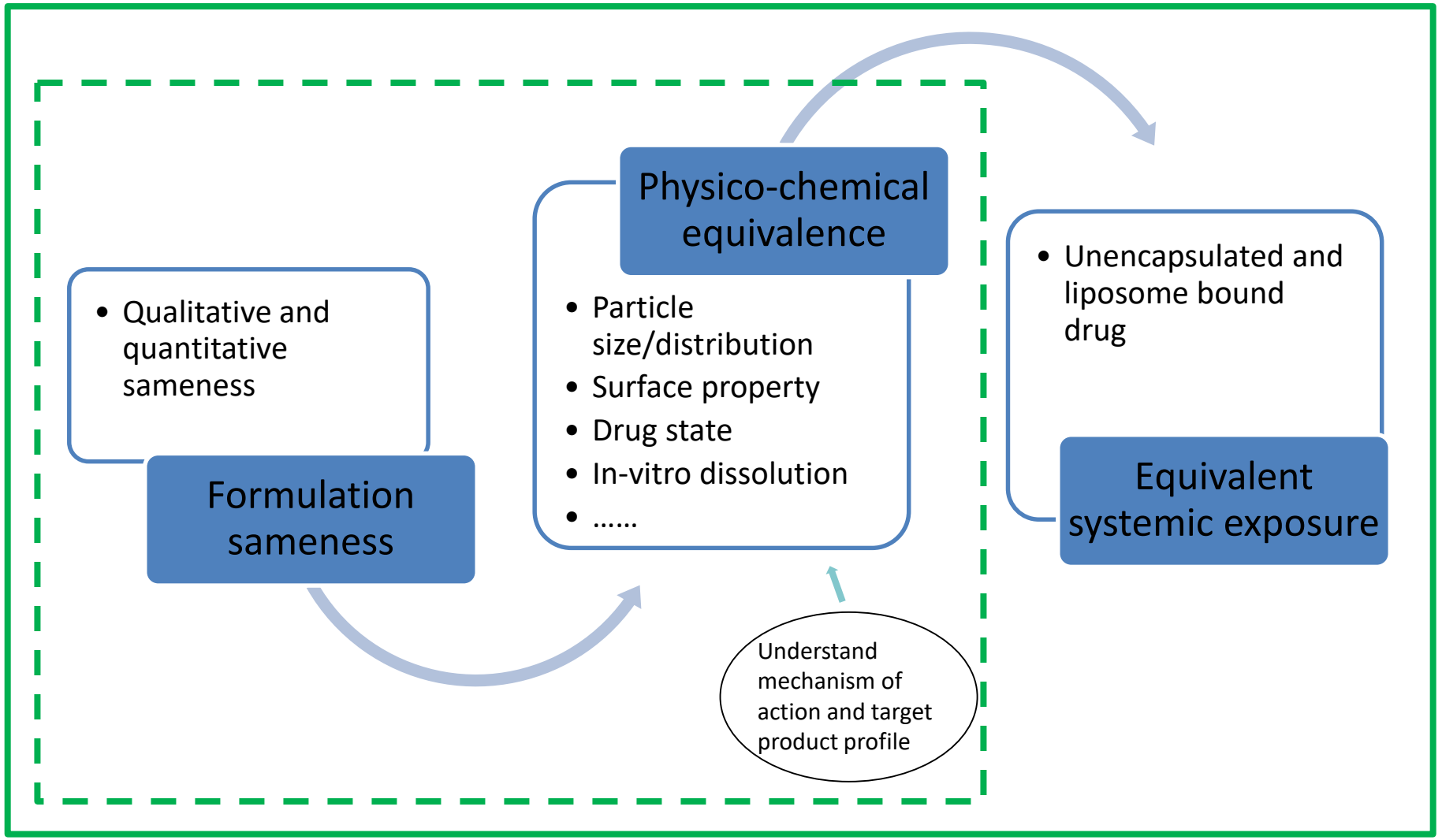
Therapeutic Equivalence



- Qualitative (Q1)/Quantitative (Q2) sameness cannot ensure supramolecular structure sameness
- Conventional plasma pharmacokinetics may not fully reflect rate and extent of drug available at target sites
- Total drug alone insufficient to demonstrate bioequivalence

- Difficulty in determining the amount of various forms of API
- Limited number of patients for BE study
- Intensive sampling not feasible for certain sites
- Versatile properties

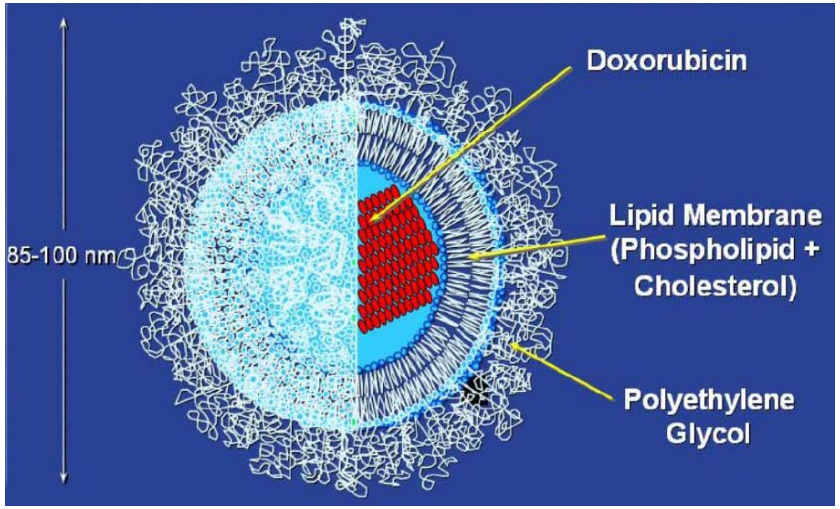
General Paradigm for Equivalence Recommendation of Liposome Drug Products



Zheng N, Sun DD, Zou P, Jiang W. Scientific and Regulatory Considerations for Generic Complex Drug Products Containing Nanomaterials. AAPS J. 2017 May;19(3):619-631.

Doxorubicin HCl Liposomes

Proprietary Name: DOXIL®
Generic Name:
Doxorubicin HCl liposome injection
Indication and Regimen:
Aids-related Kaposi's Sarcoma
Ovarian cancer
Multiple myeloma with bortezomib

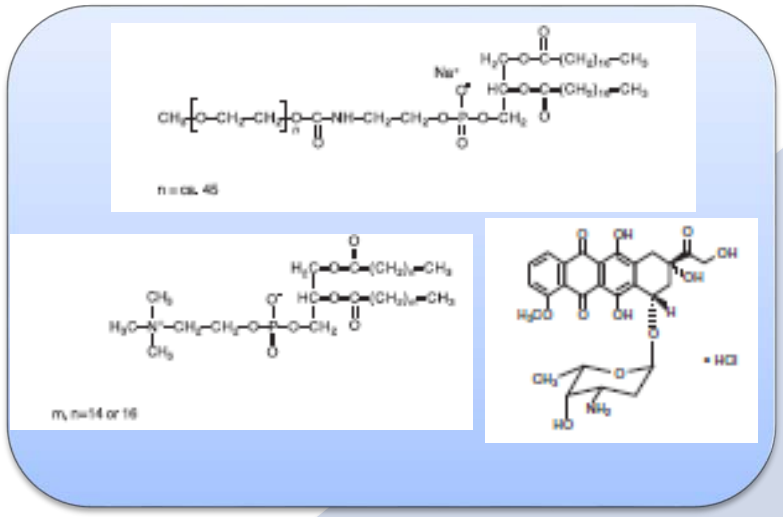


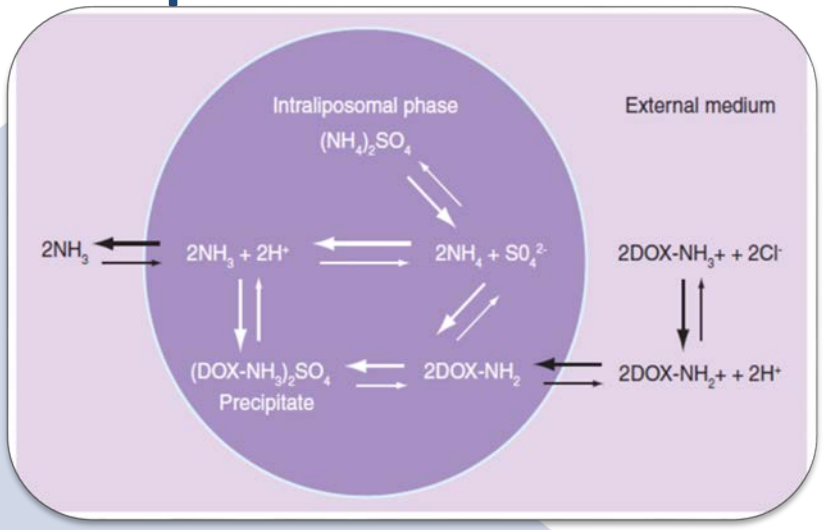
Mechanism of Action

- Passively targets tumor sites due to its small size and persistence in the circulation (Enhanced Permeation and Retention (EPR) effect)
- Free doxorubicin HCl becomes available at the tumor cell. The exact mechanism of release is not understood.
- Doxorubicin HCl binds DNA and inhibits nucleic acid synthesis.

Equivalence Recommendation for Doxorubincin HCl Liposomes

Qualitative (Q1) and Quantitative (Q2) sameness

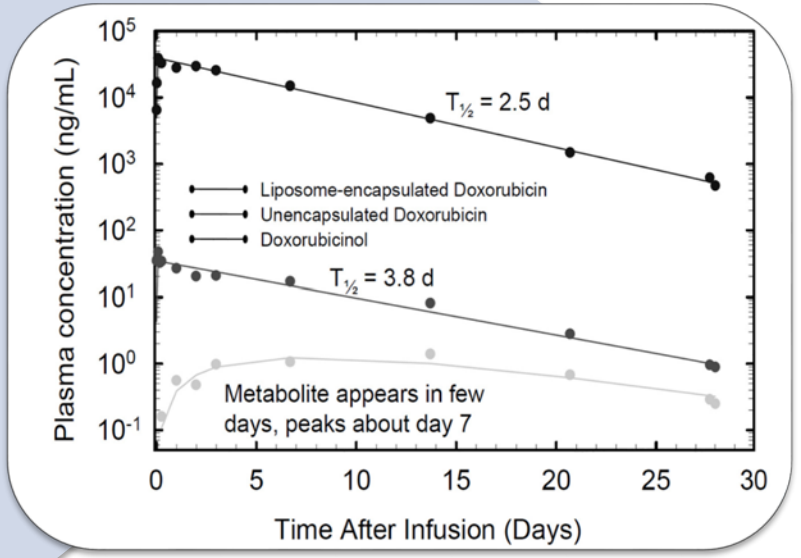




Same remote loading manufacturing process

Equivalent physico-chemical characteristics

Characteristics	Analytical methods
Lipid composition (e.g., lipid quantities, free and encapsulated drug, internal and total sulfate conc., histidine and sucrose conc., drug to lipid ratio)	HPLC
State of encapsulated drug	Cryo TEM, XRD
Internal environment (e.g., pH, volume)	NMR, ESR, and others
Liposome morphology & number of lamella	TEM, Cryo-TEM, AFM
Lipid bilayer phase transition	DSC
Liposome size distribution	DLS, EM
Grafted PEG at the liposome surface	NMR
Surface charge	Zeta potential measurement
In vitro drug leakage	Multiple release conditions



Equivalent free and liposome associated drug exposure

Metabolite measurement not recommended

Jiang W, Lionberger R, Yu L, In vitro and in vivo characterizations of PEGlyated liposome doxorubicin. Bioanalysis. 2011 Feb;3(3):333-44

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf

Recommended In Vivo Pharmacokinetic Studies for Doxorubincin HCl Liposomes

In Vivo Bioequivalence Study:

1. Type of study: Fasting*
   Design: Single-dose, two-way crossover in vivo
   Strength: 50 mg/vial or 20 mg/vial
   Dose: 50 mg/m^2
   Subjects: Ovarian cancer patients whose disease has progressed or recurred after platinum-based chemotherapy and who are already receiving or scheduled to start therapy with the reference listed drug (RLD) or the reference standard product.
   Additional comments:
   - Doxorubicin is a cytotoxic drug. Therefore, a Bio-IND is required for bioequivalence studies of a doxorubicin liposome injection to ensure the safety of human test subjects.
   - The two arms of the crossover study are to be conducted on two of the days when the patients are scheduled to receive their usual therapy so that the treatment regimen is not altered or delayed.
   - The standard of care treatment regimen should not be altered except to randomize the patients to the test or reference therapy on the specified dosing days.
   - Given that the dosage is every 4 weeks, two consecutive treatment cycles should be used for the two treatment periods.
   - Any concomitant medications must be exactly the same in both periods of the study.
   - Due to concerns about cardiac toxicity, cardiac status should be documented at baseline.
   - Any patient whose weight changes during the study requiring a ±5% dose adjustment must be discontinued from the study and excluded from the analysis.

Verteporfin Liposome Injection

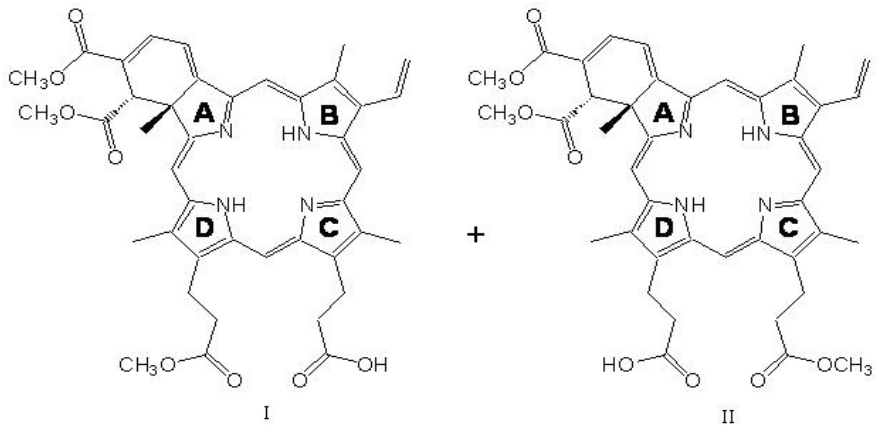
Proprietary Name: VISUDYNE

Generic Name:

Verteporfin liposome injection

Indication and Regimen:

Age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.



Mechanism of Action

- Verteporfin is transported in the plasma primarily by lipoproteins.
- Once verteporfin is activated by light in the presence of oxygen, highly reactive, short-lived singlet oxygen and reactive oxygen radicals are generated.
- Light activation of verteporfin results in local damage to neovascular endothelium, resulting in vessel occlusion

Rationales for In Vitro Option

In vitro release studies	• Immediate and complete transfer of verteporfin from liposomes to plasma proteins and lipid vesicles.
Clinical pharmacokinetic study	• Relatively large volume of distribution of liposomal verteporfin (0.6 L/kg) and a high plasma protein binding (90%), indicating an extensive extravascular distribution of released verteporfin.
Preclinical tissue distribution study	• Liposome formulation of Visudyne did not cause accumulation of verteporfin in mouse liver, lung and spleen • Negligible reticulo-endothelial system (RES) uptake of verteporfin after i.v. administration of Visudyne when compared with DMSO solubilized verteporfin

No drug retention in liposomes after intravenous administration

Chowdhary RK et al. Drug release characteristics of lipid based benzoporphyrin derivative. Journal of Pharm. Pharmaceut. Sci. (2003) 6 (1): 13-19

Equivalence Recommendation for Verteporfin Liposomes

In Vitro Option

- When the test and reference liposome products
  - **have the same drug product composition (qualitatively (Q1) and quantitatively (Q2) the same) and**
  - **have equivalent liposome characteristics** including liposome size, composition, morphology, number of lamellae, electrical surface potential, and in vitro drug leakage under physiologically relevant conditions.
- **In vivo bioequivalence study can be waived**. In vitro characterization should be conducted with at least three lots of both test and reference products.

In Vivo Option

- If a test product is Q1 and Q2 the same as the RLD but has different in vitro liposome characteristics from the RLD, BE should be established by conducting an in vivo study in healthy subjects.

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384173.pdf

Bupivacaine Liposome Injection

Proprietary Name: EXPAREL

Generic Name:

Bupivacaine liposome injection

Indication and Regimen:

Single-dose infiltration into the surgical site to produce postsurgical analgesia

Scanning electron micrograph of a typical DepoFoam particle

Mechanism of Action

- Local anesthetics blocks the generation and the conduction of nerve impulses

- Local infiltration of EXPAREL results in significant systemic plasma levels of bupivacaine which can persist for 96 hours.

However, systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy.

Equivalence Recommendation for Bupivacaine Liposomes

Formulation Q1 and Q2 sameness

Equivalent physico-chemical characteristics

- Internal Liposome Environment
- Liposomal Particle Structure, Morphology, and Surface Potential
- Liposome Particle Size and Size Distribution
- In Vitro Bupivacaine Release Profiles

Equivalent systemic exposure of bupivacaine in plasma in healthy subjects

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM586176.pdf

In Vivo Bioequivalence Study Considerations of Liposome Drug Products

Fasting or Fed

Generally a fasting BE study recommended

If the health conditions of patients prevent fasting,

- A non high-fat diet
- The treatment can be initiated 2 hours after a standard (non high-fat) breakfast.

Healthy Subjects or Patients

Healthy Subjects

Patients (one or multiple indications)

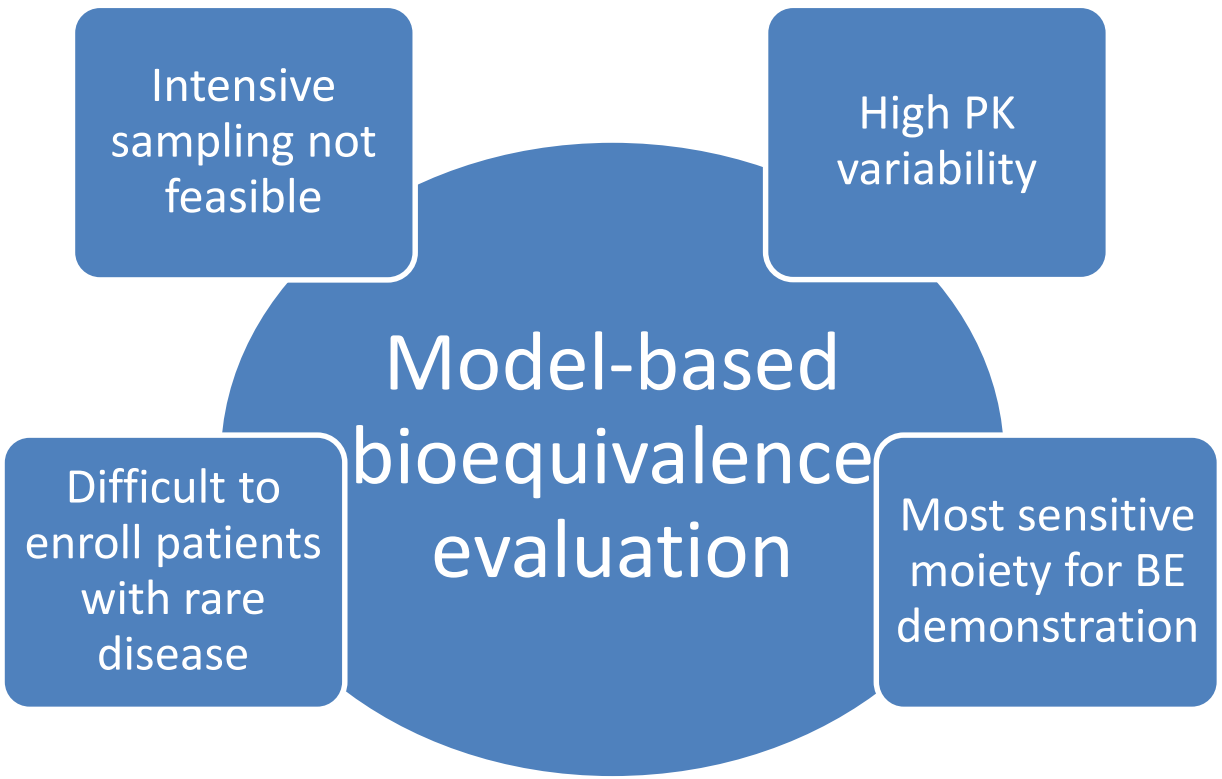
(Bio-Investigational New Drug Application (Bio-IND) may be needed)

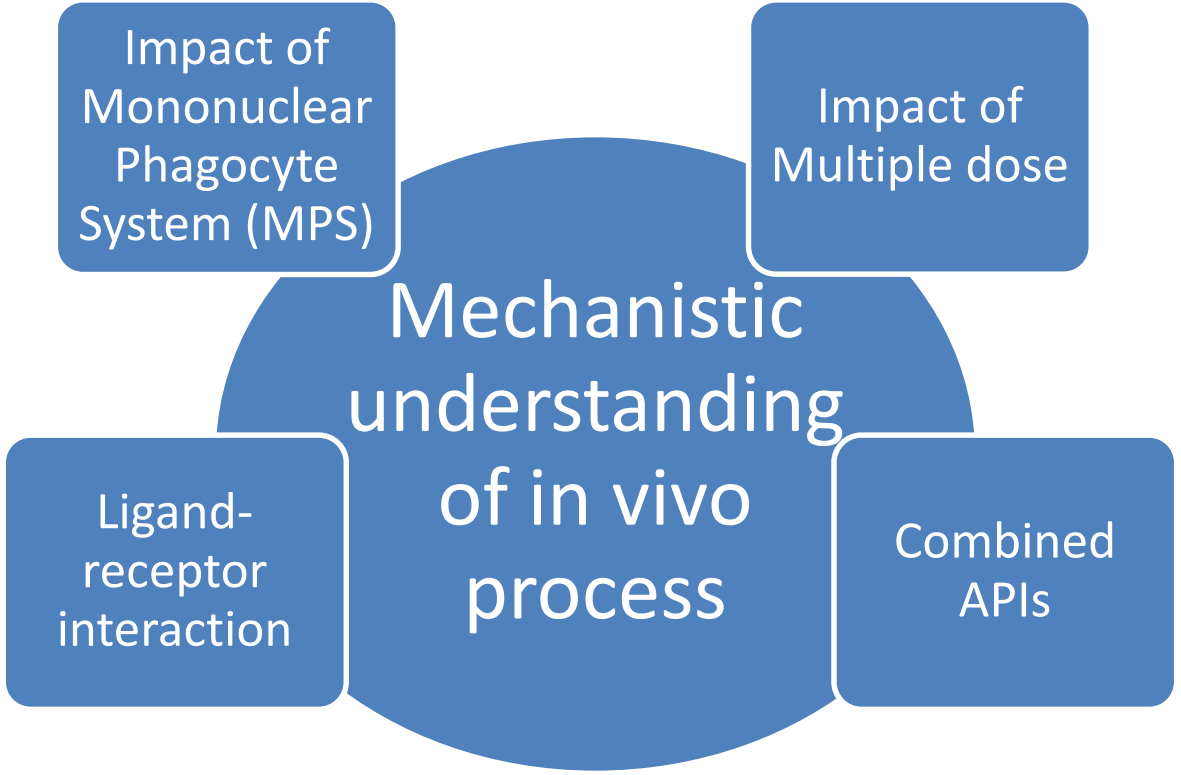
Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs
https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/UCM079593.pdf

In Vivo Bioequivalence Study Considerations of Liposome Drug Products

Parent or Metabolite	Parent drug for bioequivalence assessment
Liposome Associated or free drug	Both liposome associated and free drug Free drug only
Single or Multiple Dose	Either single or multiple dose
Parallel or Crossover	Generally crossover

Future Opportunities for Liposome Drug In Vivo Bioequivalence Evaluation





Summary

- There are unique challenges for therapeutic equivalence demonstration of liposome drug products due to their diverse and complex natures.

- FDA applies a product-specific approach to tailor bioequivalence recommendations for each liposome product.

- More research is needed to develop model-based bioequivalence evaluation and to understand the in vivo process of liposomes with increasing complexity.

Acknowledgement

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U.S. FOOD & DRUG ADMINISTRATION

Thank you for your attention

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