# 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**

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

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**U.S. Department of Health and Human Services**
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*Contains Nonbinding Recommendations*

# Liposome Drug Products Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or 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 FDA office responsible for this guidance as listed on the title page.

## I. INTRODUCTION

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). The discussion addresses the following topics for liposome drug products: (A) chemistry, manufacturing, and controls (CMC); (B) human pharmacokinetics and bioavailability or, in the case of an ANDA, bioequivalence; and (C) labeling in NDAs and ANDAs. It finalizes the revised draft guidance for industry *Liposome Drug Products, Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation* that published in October 2015.[2] The recommendations in this guidance focus on the unique technical aspects of liposome drug products. This guidance does not provide recommendations on clinical efficacy and safety studies; nonclinical pharmacology/toxicology studies; or drug-lipid complexes.[3]

Although this guidance does not provide recommendations specific to liposome drug products to be marketed under biologics license applications (BLAs), many scientific principles described in this guidance may also apply to these products.

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[1] This guidance has been prepared by the Liposome Working Group in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[3] Drug-lipid complexes are chemically and physically defined nonvesicular associations of drugs with certain lipids. Drug-lipid complexes are formed by mixing a drug with lipids in such a way that liposomes are not created. The CMC, pharmacokinetics, and bioavailability recommendations for drug-lipid complexes and liposomes can be similar. When the submission is for an NDA, contact the specific drug product's review division with questions. When the submission is for an ANDA, submit a Controlled Correspondence via email to GenericDrugs@fda.hhs.gov. For the definition of a *controlled correspondence* as well as the process to submit a *controlled correspondence*, see the final guidance for industry *Controlled Correspondence Related to Generic Drug Development (September 2015)* and the proposed revisions in the draft guidance issued in November 2017.

In addition, you should consider recommendations in this guidance during drug development that may lead to the submission of an investigational new drug application (IND) for a liposome drug product. In connection with ANDA submissions, you should consider recommendations in any product-specific guidances, including bioequivalence and information necessary to demonstrate pharmaceutical equivalence to the reference listed drug (RLD).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## II. BACKGROUND

Liposomes are 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. In a liposome drug product, the drug substance is generally contained in liposomes.[4] Typically, water soluble drugs are contained in the aqueous compartment(s) and hydrophobic drugs are contained in the lipid bilayer(s) of the liposomes. Release of drugs from liposome formulations, among other characteristics such as liposomal clearance and circulation half-life, can be modified by the presence of polyethylene glycol and/or cholesterol or other potential additives in the liposome.

A liposome drug formulation is different from (1) an emulsion, which is a dispersed system of oil in water, or water in oil phases containing one or more surfactants, (2) a microemulsion, which is a thermodynamically stable two phase system containing oil or lipid, water and surfactants, and (3) a drug-lipid complex.

## III. DISCUSSION

### A. Chemistry, Manufacturing, and Controls

*1. Description and Composition*

You should include the following information in your application:

a. The drug product components listed by their established names, as follows:

i. Drug substance
ii. Lipids
iii. Nonlipid components of the liposome

[4] The word *contained* includes both *encapsulated* and *intercalated* drug substance. Encapsulated refers to drug substance within an aqueous space and intercalated refers to incorporation of the drug substance within a bilayer.

iv. Nonliposome inactive ingredients (e.g., buffer components)

b. An expression of the amount of each lipid component used in the formulation based on the final form of the product:

- For liquid – mg/ml and mg/vial
- For dry powder for reconstitution – mg/ml after reconstitution and mg/vial
- For semisolid – w/w (g/g)

An expression of the molar ratio of each individual lipid to the drug substance is also recommended for each individual lipid in the finished formulation.

c. An expression of the amount of drug substance in the formulation.

We recommend expressing the composition of the drug product as milligram of drug substance per milliliter of drug product and also milligram of drug substance per vial for liquid drug products. For dry powders, only the total amount of the drug should be listed.

d. Ranges in the composition and/or attributes of components.

Because the pharmacological and toxicological properties and the quality of a liposome product can vary significantly with changes in the formulation, including the lipid composition, the ranges should be specified based on the following:

i. Product development studies
ii. How the ranges were selected
iii. If and how the source of key excipients affects finished product quality

These ranges should be linked to the factors that were analyzed during drug product development and supported by data.

*2. Physicochemical Properties*

Liposome structure and integrity are important physicochemical properties and they reflect the ability of the liposome drug formulation to contain the drug substance and to retain the drug substance within the appropriate liposome structure. The following properties are generally useful to characterize a liposome drug formulation. Variability in the following properties may lead to changes in the quality of the liposome drug product, including leakage of the drug from the liposomes. Properties that apply to your liposome drug product may vary from those listed below.

a. Morphology of the liposomes including, if applicable, lamellarity determination.

b. Surface characteristics of the liposomes, as applicable, e.g., pegylation.

c. Net charge, typically measured as zeta potential of the liposomes.

d. Drug product viscosity.

e. Parameters of the contained drug.

For example, drug encapsulation efficiency (the amount of drug contained inside liposomes compared with total amount of drug) and liposome drug loading (the amount of drug contained relative to the amount of the lipid used, which is the drug-to-lipid ratio).[5] This information should be supported by development data, including test results on batches of liposome drug used in pivotal clinical trials or bioequivalence studies.

f. Particle size (i.e., mean and distribution profile), preferably defined on the basis of volume or mass if particle density is known.

g. Liposome phase transition temperature.

h. In vitro release of the drug substance from the liposome drug product under the stated/described experimental conditions with supportive data and information regarding the choice of those conditions.

i. Leakage rate of drug from the liposomes throughout shelf life.

j. Liposome integrity changes (e.g., drug release, drug encapsulation efficiency, liposome drug loading, size) in response to changes in factors such as salt concentration, pH, temperature, or addition of other excipients, as applicable.

k. Liposome structure supported by spectroscopic or other analytical method(s).

[5] Xu, X, Khan, M, and Burgess, D, 2012, A Quality by Design (QbD) Case Study on Liposomes Containing Hydrophilic API: II. Screening of Critical Variables, and Establishment of Design Space at Laboratory Scale, International Journal of Pharmaceutics, 423: 543-553; and Liposomes as Carriers for Controlled Drug Delivery, Long Acting Injections and Implants, chapter 11, pages 195 to 220, ISBN 978-1-4614-0553-5, Publisher: Springer.

### *3. Critical Quality Attributes*

Critical quality attributes (CQAs) particular to liposome drug products include some of the physicochemical properties described above including vesicle/particle size and size distribution, and morphology. For general information on drug product development, see the International Council for Harmonisation (ICH) guidance for industry, *Q8(R2) Pharmaceutical Development*.

### *4. Description of Manufacturing Process and Process Controls*

We recommend including a detailed process flow diagram and a description of unit operations with ranges for the process parameters and process controls. These ranges should be supported by pharmaceutical development studies. The process and mechanism of liposomal drug loading, as well as the removal of free (un-incorporated) drug from the liposome formulation via purification should be described in detail. The manufacturing process should be validated to demonstrate manufacturing process consistency and reproducibility before commercial distribution.[6]

Liposome drug products are sensitive to changes in the manufacturing conditions, including changes in scale (size of the batches). Appropriate process controls should be established during product development. Prior knowledge can be leveraged and risk assessment techniques can be used to identify manufacturing process parameters that potentially affect finished product quality.

Some examples of manufacturing process parameters that may affect liposome drug performance are shear force, pressure, pH, temperature, batch-size-related hold times, lyophilization parameters, etc. You should provide adequate justification for the selection of the operating ranges for different batch sizes.

The physical and chemical complexity of liposome drug products present unique challenges to the sterilizing filtration process. For example, components of liposomes could interact with the filter matrix and clog it. Therefore, validated product-specific purification and sterilization methods should demonstrate the ability of the microbial sterilizing filters to function correctly, without compromising the integrity and structure of liposomes.

### *5. Control of Lipid Components*

The quality of lipid components, including modified lipids (e.g., polyethylene glycol (PEG) modified lipids), can affect the quality and performance of the liposome drug product. In case of a novel lipid component, i.e., any lipid component not listed in the Inactive Ingredient Database (IID),[7] or a component that exceeds the amount listed in the IID for the intended route of administration, the level of detail provided in the submission should be comparable to that for a

[6] See guidance for industry *Process Validation: General Principles and Practices*.
[7] See http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

drug substance.[8] This information should be provided in the application or in a Type IV Drug Master File (DMF).[9]

In addition, you should provide the following information specific to lipid components:

a. Description and Characterization of Lipid Components

If the lipid is synthetic (e.g., a lipid manufactured by chemical synthesis from specified starting materials) or semi-synthetic (e.g., a lipid manufactured by modification of naturally occurring precursors such as dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), or dimyristoylphosphatidylcholine (DMPC)), you should provide proof of structure, including fatty acid composition and positional specificity. You should specify the lipid composition (e.g., percentage of each lipid and fatty acid, positional specificity of acyl side chains, and degree of fatty acid unsaturation).

In the case of naturally-sourced lipid mixtures, (e.g., egg lecithin), you should provide the lipid composition as a range of percentages for each stated lipid present in the mixture and its fatty acid composition.

b. Manufacture of Lipid Components

The information provided on the manufacture of lipid components depends on whether the lipid is synthetic, semi-synthetic, or naturally sourced.

For synthetic and semi-synthetic lipids, we recommend you provide the following information:

i. A complete description of the synthetic process and purification procedures, as applicable
ii. Specifications for starting materials,[10] raw materials, solvents, and reagents
iii. Controls for critical steps and intermediates, including the manufacturing controls that ensure positional specificity of acyl side chains, if applicable

For naturally-sourced lipid mixtures, and any naturally-sourced materials that start the synthetic segment of a semi-synthetic process, you should provide the following information:

i. Biological source (e.g., eggs)
ii. Country of origin for animal-sourced material
iii. Supplier
iv. A description of extraction and purification procedures, as applicable[11]

[8] For further information, see ICH *Q11 Development and Manufacture of Drug Substances* (ICH Q11).
[9] See guidance for industry *Drug Master Files: Guidelines.*
[10] See ICH Q11 for recommendations about the selection of starting materials.
[11] Ibid.

Procedures to ensure the avoidance, removal, and/or inactivation of animal proteins and viruses and any other infectious agents should be described, where applicable.

You should address the avoidance and/or removal of pyrogenic material and bacterial endotoxins by establishing appropriate controls during the manufacturing process, and include this information in the application.

c. Specifications for Lipid Components

You should provide the following specification information for each lipid component used to manufacture the drug product.

i. The identity test capable of distinguishing the intended lipid component from lipids with similar structures.
ii. The assay based on a stability-indicating analytical procedure.
iii. The validated analytical procedures accompanied by the validation data.
iv. Impurity testing:
    1. Trans-fatty acid
    2. Free-fatty acid
    3. Peroxides (associated with unsaturated fatty acids)
    4. Lysophospholipids
    5. Solvents and catalysts used in the synthesis or purification processes
v. Other testing:
    1. Counterion content and limits on divalent cations, when appropriate
    2. The degree of unsaturation of the fatty acid side chains (for lipid mixtures)

Information about impurities, including synthetic by-products, where applicable, should be provided. Impurities may warrant identification and qualification, depending on the following:

i. The amount of the impurity in the final liposome drug product
ii. Known toxicities of the impurity
iii. Structural alerts[12]

For synthetic lipids and semi-synthetic lipids, compare the lipid under test with the reference standard or material using an analytical procedure that is capable of distinguishing the desired lipids from their impurities (e.g., HPLC, TLC).

[12] Ashby, J, Paton, D, March 1993, The Influence of Chemical-Structure on the Extent and Sites of Carcinogenesis for 522 Rodent Carcinogens and 55 Different Human Carcinogen Exposures, Mutation Research, Volume 286, Issue 1, Pages 3-74; and guidance to industry *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*. When final, this guidance will represent the FDA's current thinking on this topic.

Information about the preparation, qualification, and storage conditions for each reference standard or material used in testing lipid components should be provided.

d. Stability of Lipid Components

For each lipid used to manufacture the liposome, you should provide results from stability studies and stress testing (e.g., after exposure to high (e.g., 50 ºC) and low (e.g., -20 ºC) temperatures, light, pH, and oxygen) that were used to determine the degradation profile, to develop an appropriate stability-indicating analytical procedure, and to establish appropriate storage conditions and retest period(s). Reference to a DMF is acceptable when the stability studies referenced in the DMF used the same lipids (source, grade, supplier) as proposed to be used in the drug product. Stability studies and validation of analytical procedures should be conducted according to ICH guidelines.[13]

You should retest the lipid component after its storage beyond the lipid manufacturer's stated "retest period" or when the lipid component is exposed to temperatures other than its labeled storage temperature to ensure conformance to its specification prior to use in a drug product. For example, if unusual conditions occur during shipping or transit leading to exposure of the lipid component to elevated temperatures for a significant time period, you should retest the lipid component to ensure conformity with specification.

*6. Drug Product Specification*

You should provide a drug product specification that accounts for specific attributes for your liposome products. The following are examples of characteristics or attributes specific to the liposome formulation that should be included in the specification:

a. Physicochemical parameters of the liposome determined to be the CQAs of the product (e.g., mean particle size and size distribution of liposomes, osmolality, zeta-potential and physical stability)

b. Liposome contained and free drug substance

c. Total drug substance content, as labeled

d. Degradation products related to the lipids (e.g., lysolipids) or drug substance

e. Lipid content (to demonstrate consistency with the intended formulation)

f. Residual solvent(s), if any organic solvent(s) are used in the manufacture of the liposome product

[13] See guidances for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*; *Q2(R1) Validation of Analytical Procedures: Text and Methodolology.*

The residual solvents acceptance criteria should be based on the performance of the liposome drug product as well as safety concerns.

g. In vitro release of drug substance from the liposome drug products

A validated analytical procedure for in vitro release should be established, preferably using an appropriate physiological medium (e.g., simulated physiological medium or human plasma) with suitable agitation. When a liposome drug product is extremely stable under physiological conditions, an in vitro quality control (QC) release test can be performed under nonphysiological conditions to accelerate the release of drug substance from the liposomes. For all drug products, information about any relationship or correlation between the in vitro quality control release test and the in vivo pharmacokinetic profile should be provided to justify the use of such a QC test, as established through analytical method development studies. In some cases, a test using cell culture or animal models may be appropriate.

h. For injectable liposome drug products, sterility and the absence of pyrogens or bacterial endotoxins

*7. Stability*

Stability studies should address the microbiological, physical, and chemical stability of the liposome drug product, including the integrity of the liposomes in the drug product.[14]

The physical stability of liposome drug products can be affected by a number of factors (e.g., the liposome integrity,[15] the size distribution of the lipid vesicles, unsaturation of the fatty acid groups). Some liposomes are susceptible to fusion (i.e., irreversible coalition of smaller liposomes to form larger liposomes), aggregation (i.e., reversible conglomeration or pooling of two or more liposomes without fusion), and leakage of the contained drug substance during storage. Fusion, aggregation, or leakage can be affected by the lipid components in the liposome or by the contained drug substance. Stability testing should include tests to assess liposome size distribution and integrity.

You should evaluate the chemical stability of the lipid components in the liposome as well as the chemical stability of the contained drug substance. Lipids with unsaturated fatty acids are subject to oxidative degradation, while both saturated and unsaturated lipids are subject to hydrolysis to form lysolipids and free fatty acids. It may be appropriate to conduct stress testing of unloaded liposomes to assess possible degradation or other reaction processes unique to the liposomes.

When designing stress and accelerated stability testing studies, you should recognize that liposome drug products behave differently near or above the phase transition temperature(s).

[14] See ICH *Q1A(R2) Stability Testing of New Drug Substances and Products.*
[15] See section III.A.2.

If the liposome drug product is marketed as an approved kit containing unloaded liposomes and drug substance in separate containers, your stability program should include testing of the unloaded liposomes and the drug substance in their commercial container-closure systems.

If the liposome product is labeled for use after reconstitution with a co-packaged or other specified diluent, or is labeled for use after mixing it with other approved drug products (e.g., large volume injectable solutions), supporting stability data on the product under the in-use conditions of its storage and use should be submitted in the application. This should include physical, chemical, and microbiological studies to support the in-use period. A specified in-use or storage interval, after which an admixed and/or unused liposome product must be discarded, should be determined through an in-use stability study. A statement regarding the appropriate in-use period(s) for the reconstituted/admixed drug product should be included in the labeling, together with instructions for reconstitution or mixing.

#### *8. Postapproval Changes in Manufacturing*

Liposome drug products are complex and sensitive formulations and response to CMC changes is less predictable than with more conventional formulations. Therefore, changes to the formulation, container closure, site of manufacture, or manufacturing process (including substantive equipment and scale changes) will usually require a prior approval supplement. In vivo studies may be needed to assess changes that can affect the performance of the drug product. You can contact the appropriate review division[16] associated with your application if you have questions regarding the type of information to generate or the appropriate reporting mechanism for a postapproval change.[17]

### B. Human Pharmacokinetics: Bioavailability and Bioequivalence

For ANDA submissions for liposome drug products, please refer to applicable product-specific FDA guidance documents[18] that outline recommendations regarding human pharmacokinetic and other bioequivalence studies for generic liposome drug products. These guidance documents also discuss additional characterization studies and information (e.g., drug product composition and active ingredient loading) necessary to demonstrate pharmaceutical equivalence to the RLD. When no product-specific guidance exists for a generic product, this guidance applies. If you are contemplating submitting an ANDA, you should consider contacting OGD[19] to request a pre-ANDA meeting.

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[16] When the submission is for an NDA, contact the specific drug product's review division with questions. When the submission is for an ANDA, submit a Controlled Correspondence via email to GenericDrugs@fda.hhs.gov. For the definition of a *controlled correspondence* as well as the process to submit a *controlled correspondence*, see the final guidance for industry *Controlled Correspondence Related to Generic Drug Development (September 2015)* and the proposed revisions in the draft guidance issued in November 2017.

[17] See 21 CFR 314.70 and FDA guidances related to submission of postapproval changes to the chemistry, manufacturing, and controls section of drug applications.

[18] See http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[19] See draft guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.

Because of the complex interaction between drug release from the liposome drug product and the tissue and/or cellular uptake of the drug substance and/or the liposome, a simple measurement of total drug substance concentration in plasma[20] may not be reflective of bioavailability of the drug at the intended target organ (i.e., site of action).[21] Therefore, for NDA submissions, you should consult the appropriate CDER review division[22] for advice concerning the determination of bioavailability of liposome drug products.

*1. Clinical Pharmacology Studies*

a. Pharmacokinetic and Mass Balance Studies for Liposome Drug Products

Information from pharmacokinetic studies is useful for establishing dosing regimens and developing dose-concentration-response relationships. The study design should be based on the anticipated dosing regimen in the intended patient population. We recommend using a population pharmacokinetics approach, where appropriate.[23]

The pharmacokinetic measures or parameters should include area under the plasma concentration versus time curve (AUC), peak plasma concentration, time to peak plasma concentration, elimination half-life, volume of distribution, total clearance, renal clearance, and accumulation for both free and total drug, as appropriate. For mass balance studies, you should collect and assay blood (i.e., plasma or serum, as appropriate), urine, and fecal samples for the radiolabeled moiety. For these studies, you should monitor and quantify both parent drug and any metabolites present, as appropriate.

You should determine major metabolites associated with the therapeutic and toxic effects of the drug substance. We also recommend conducting the following in vivo studies:

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

Depending on the target patient population and the proposed therapeutic indication for the drug, you should consider conducting drug interactions studies in specific populations.

You should consult the appropriate CDER review division[24] regarding the conduct and design of these studies if you have questions.

[20] See 21 CFR 320.24(b)(1)(i).
[21] See 21 CFR 320.21.
[22] See footnote 16.
[23] See guidance for industry *Population Pharmacokinetics.*
[24] See footnote 16.

b. Comparison Clinical Pharmacology Studies with Nonliposome Drug Product

The drug disposition and pathways of elimination (including distribution, metabolism and excretion) as well as several important pharmacokinetic measures (Cmax, AUC) and parameters (e.g., clearance, volume of distribution, half-life) of a liposome formulation are likely to be different than those of a nonliposome formulation given by the same route of administration. For example, a liposome drug formulation may exhibit extended-release characteristics in comparison to a non-liposome formulation with the same active pharmaceutical ingredient.

If nonliposome formulations have been approved, we recommend comparing the proposed liposome to the corresponding approved nonliposome formulation to elucidate differences in absorption, distribution, metabolism, and excretion (ADME). Conducting a mass balance study of a drug substance labeled with a radioactive isotope (e.g., $^{14}C$, $^{3}H$) in a liposome formulation and in a nonliposome formulation can be helpful in comparing drug distribution in organs of interest.

You should conduct comparative studies to define and assess differences in ADME of the active ingredient between liposome and nonliposome drug products when the following apply:

i. Two products have the same active ingredient.
ii. Two products are given by the same route of administration.
iii. The nonliposome drug product is approved and available for comparison.

In a single dose pharmacokinetic study, you should compare the liposome and nonliposome drug products using either a crossover or parallel study design that employs an appropriate number of subjects considering the study drug, disease for which it is used, use in specific populations, and other factors that apply. Depending on the drug substance under investigation, different doses of liposome and nonliposome drug products may be appropriate.

*2. Biopharmaceutics*

a. Drug Release Characteristics

You should demonstrate that the release characteristics of the liposome product meet the label claim, and describe any release differences between the liposome product and nonliposome product with the same active ingredient.

b. In Vitro/In Vivo Correlation (IVIVC)

Although it is challenging to establish IVIVC for liposome products, we encourage you to attempt it for your liposome product. Some in vitro/in vivo relationships (IVIVRs) may be established even if a complete IVIVC is not feasible.

c. Bioanalytical Methods

You should use validated bioanalytical methods when evaluating the pharmacokinetics and bioavailability of the liposome-contained and free drug substance (drug released from the liposome).[25]

d. Liposome-Protein Interaction

Depending on the types of lipids used in formulating liposomes, interactions between liposome surface and blood proteins may affect the drug release and pharmacological properties of a liposome drug product in vivo. Such interactions can have safety implications because of "dose dumping." Submission of information from prior studies of protein-liposome interactions may suffice for a new liposome drug product if the following apply:

i. Lipid composition of the formulation ingredients is the same as in the previously studied liposome drug product.
ii. Physicochemical characteristics of the two liposome drug products are similar.

## C. Labeling

Specific recommendations regarding labeling content for liposome drug products are provided below. Additional guidance on current labeling requirements is available on the CDER guidance Web site. In particular, the guidance on *Safety Considerations for Container Labels and Carton Labeling Designs to Minimize Medication Errors* provides general labeling recommendations.

### *1. Nonproprietary Names of Drug Products Approved under the Federal Food, Drug, and Cosmetic Act*

The nonproprietary name of a drug product approved under the Federal Food, Drug, and Cosmetic Act is its established name, which, in most instances, will be the United States Pharmacopeia (USP) drug product monograph title for that product. If there is no USP monograph for the liposome drug product, refer to 21 CFR 299.4, USP General Chapter <1121> *Nomenclature*,[26] and the USP Nomenclature Guidelines.[27] The liposome drug product nonproprietary name should include terminology to express that the product is a liposome or a pegylated liposome.

Examples:

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

[25] See draft guidance for industry *Bioanalytical Method Validation*.
[26] United States Pharmacopeia-National Formulary (USP 40-NF 35, supplement 2 <1121> NOMENCLATURE.
[27] Refer to USP Nomenclature Guidelines on the USP website at http://www.usp.org/health-quality-safety/compendial-nomenclature.

The first liposome product approved for a particular drug and dosage form will be type A, but the type should not be given (i.e., "Type A" should not be included in the labeling). For subsequent drug products of the same drug and dosage form, you should list the type and replace "X" sequentially with B, C, D, . . . Z.[28]

*2. Description Section*

You should include a cautionary note 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*

You should include a statement recommending against substituting the liposome drug product for the nonliposome product or another liposome drug product that contains the same active ingredient unless FDA has determined that the products are therapeutically equivalent.

Where appropriate, reconstitution instructions[29] and a statement regarding the appropriate in-use period should be provided. This information should be provided for both unloaded liposomes that are reconstituted with a drug substance-containing solution at the time of use and for products in which the drug substance is loaded into the liposomes during manufacturing. For liposome drug products that are labeled for use after mixing with other approved drug products (e.g., large volume injectable solutions), admixing instructions and a statement regarding the appropriate in-use period of the admixed product should be included. As warranted, include 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.

[28] Note that with respect to ANDA submissions, the product name is the same as the nonproprietary or established name of the RLD.
[29] See 21 CFR 201.57(c)(3)(i)(J)(iv).

## IV. REFERENCES

Guidance for Industry[30]

*Bioanalytical Method Validation*

*Changes to an Approved NDA or ANDA*

*Controlled Correspondence Related to Generic Drug Development*

*Drug Master Files Guidelines*

*Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*

*Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*

*PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*

*Population Pharmacokinetics*

*Process Validation: General Principles and Practices*

ICH, Q*1A(R2) Stability Testing of New Drug Substances and Products*

ICH, *Q2(R1) Validation of Analytical Procedures: Text and Methodology*

ICH, *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*

ICH, *Q8(R2) Pharmaceutical Development*

ICH, *Q11 Development and Manufacture of Drug Substances*

[30] The guidances listed in the References are available on the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.