Guidance for Industry

Liposome Drug Products

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

DRAFT GUIDANCE

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

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GUIDANCE FOR INDUSTRY[1]

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- *Clearly explain each issue and/or concern and, when appropriate, include a proposed revision and the rationale or justification for the proposed change.*
- *Identify specific comments by line number or numbers; use the pdf version of the document, whenever possible.*
- *If possible, send an electronic copy (Word or WordPerfect) of the comments you have submitted to the docket by e-mail to* coryj@cder.fda.gov.

I. INTRODUCTION

This guidance provides recommendations to applicants on the chemistry, manufacturing, and controls (CMC); human pharmacokinetics and bioavailability; and labeling documentation for liposome drug products submitted in new drug applications (NDAs).[2] The recommendations in this guidance focus on the unique technical aspects of liposome drug products. Applicants should

[1] This guidance was prepared by the Liposome Working Group of the Complex Drug Substances Coordinating Committee (CDSCC) in the Center for Drug Evaluation and Research (CDER) at the FDA.

[2] A liposomal formulation of an active moiety that has already been approved or marketed in the United States is not classified as a new molecular entity (Type 1 NDA). When submitted in an NDA, the drug is classified as a Type 3 NDA unless it is a new ester, new salt, or other noncovalent derivative of the approved drug substance. In that case, the NDA would be classified as a Type 2,3.

refer to the forthcoming drug product guidance[3] for other recommendations on the CMC documentation that should be submitted in original NDAs. Applicants can contact the appropriate review division if they have questions on demonstrating bioequivalence and sameness of liposome drug products. The recommendations in this guidance should be considered, to the extent applicable, when a sponsor is submitting an investigational new drug application (IND).

Liposome drug products are defined as drug products containing drug substances (active pharmaceutical ingredients) encapsulated in liposomes. A liposome is a microvesicle composed of a bilayer of lipid amphipathic molecules enclosing an aqueous compartment. Liposome drug products are formed when a liposome is used to encapsulate a drug substance within the lipid bilayer or in the interior aqueous space of the liposome. A drug substance in a liposome formulation is intended to exhibit a different pharmacokinetic and/or tissue distribution (PK/TD) profile from the same drug substance (or active moiety) in a nonliposomal formulation given by the same route of administration. The complete characterization of the PK/TD profile of a new liposome drug product is essential to establish the safe and effective dosing regimen of the product.

The guidance does not provide recommendations on:

- clinical efficacy and safety studies
- nonclinical pharmacology and/or toxicology studies
- bioequivalence studies or those to document sameness
- liposomal formulations of vaccine adjuvants or biologics
- drug-lipid complexes[4]

II. CHEMISTRY, MANUFACTURING, AND CONTROLS

The recommendations provided on CMC documentation focus on the information specific to liposome drug products that should be submitted to CDER. An applicant should consult all relevant regulations and guidances for information on the type of documentation that should be submitted for drug substances and other aspects of documenting the identity, strength, quality, purity, and potency of the drug product.

A. Description and Composition

[3] This guidance is under development and, when finalized, will replace the guidance for industry *Submitting Documentation for the Manufacturing of and Controls for Drug Products*. CDER guidance documents can be found on the Internet at http://www.fda.gov/cder/guidance/index.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web site.

[4] Drug-lipid complexes are formed by mixing a drug with lipids in such a way that true liposomes are not created. The CMC, pharmacokinetics, and bioavailability recommendations for drug-lipid complexes and liposomes can be similar. Applicants intending to submit an NDA for a drug-lipid complex can consult the appropriate review division in CDER for additional guidance if necessary.

The components of liposome drug products are the drug substance, the lipids, and other inactive ingredients. The quantity of lipid in the formulation should be expressed as the molar ratio and percentage by weight of the lipid to the drug substance as well as on the milligram (mg) per milliliter (mL) and per vial basis**.** The pharmacological and toxicological properties and the quality of these drug products can vary significantly with changes in the formulation, including the lipid composition. Therefore, any ranges in the formulation components should be specified and be as narrow as feasible. The drug product composition and any specified ranges for components should be justified.

B. Physicochemical Properties

The physicochemical properties of the liposome drug product are critical to ensuring drug product quality. Therefore, a detailed evaluation of these properties should be provided. Rigorous characterization of the physicochemical properties can also be beneficial in evaluating subsequent changes in manufacturing (see section II.G. on Changes in Manufacturing). The physicochemical characterization tests, which are critical to ensuring product quality of each batch of liposome drug product, should be identified. However, all the characterization tests need not be included in the specifications. Properties specific to liposome drug products that may be useful to assess include:

- morphology of the liposome, including lamellarity determination, if applicable
- net charge
- volume of entrapment in liposomal vesicles
- particle size (mean and distribution profile)
- phase transition temperature
- spectroscopic data, as applicable
- in vitro release of the drug substance from the liposome drug product
- osmotic properties
- light scattering index

C. Description of Manufacturing Process and Process Controls

Liposome drug products are sensitive to changes in the manufacturing conditions, including changes in scale. This should be considered during the development process, and critical manufacturing parameters (e.g., scale, shear force, temperature) should be identified and evaluated. If there are changes in critical manufacturing parameters, complete characterization of the liposome drug product is recommended and in vivo studies may be warranted (see section II.G. on Changes in Manufacturing).

The chemical and physical complexity of liposome drug products can provide unique challenges to the sterilizing filtration process. For example, constituents of the liposome may block adsorptive interactions of organisms with the filter matrix, effectively allowing organisms to pass through the sterilizing filter. Therefore, product-specific validation studies should demonstrate the microbial retentivity of the intended sterilizing filters.

D. Control of Excipients: Lipid Components

The quality and purity of the lipid components can affect the quality of the liposome drug product. Information concerning the CMC of the lipid components should be provided at the same level of detail expected for a drug substance. For further information, refer to the guidance for industry *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (the drug substance guidance). This information can be provided in a Type IV Drug Master File (DMF). (See guidance for industry *Guideline for Drug Master Files*).

In addition to the information recommended by the drug substance guidance, recommendations specific to lipid components are provided below.

1. Description and Characterization

If the lipid is a well-defined synthetic or semisynthetic lipid, such as dimyristoylphosphatidylcholine (DMPC), a structure proof based upon standard spectroscopic techniques is usually sufficient. In the case of natural lipid mixtures (e.g., egg lecithin), the lipid composition (i.e., percentage of each lipid) and the fatty acid composition (i.e., the percentage of each fatty acid) should be provided.

2. Manufacture

For synthetic lipids, the source (e.g., manufacturer) and specifications for any starting materials should be provided. For natural lipid mixtures and natural-sourced materials that start the synthetic segment of a semisynthetic process, the biological source (e.g., eggs), country of origin of the source material, supplier, and specifications should be provided.

A complete description of the synthetic process, extraction, and purification procedures should be provided, as applicable. Specifications should be provided for starting materials, raw materials, solvents, and reagents. The controls for critical steps and intermediates should be provided. Chromatographic purification procedures should be described, including the collection of desired fractions, and a sample chromatogram should be provided. For synthetic and semisynthetic lipids, the manufacturing controls that ensure positional specificity of acyl side chains should be provided, if applicable. (See the drug substance guidance for additional information on the manufacturing information that should be provided.)

Procedures to ensure the removal of animal proteins and viruses should be described, where applicable. Bovine-derived materials should not be imported from countries that are defined as bovine spongiform encephalopathy countries by the U.S. Department of Agriculture (see 9 CFR 94.11).

3. Specifications

A full description of the tests, procedures, and acceptance criteria for the lipid components should be provided. Reference standards should be established and their preparation, qualifications, and storage conditions should be described. In general, the analytical procedures should be validated and the specifications should include a stability-indicating assay. Impurities, including possible synthetic by-products, should be evaluated. The level that would warrant identification and qualification will be determined on a case-by-case basis**.**

For synthetic lipids such as DMPC and semisynthetic lipids, the assay and impurity tests can be done by comparison with the reference standard (e.g., thin-layer chromatography (TLC)) when the analytical procedure can distinguish the desired lipids from possible impurities. If the analytical procedure cannot distinguish the desired lipids from impurities, then assays capable of confirming the fatty acid composition and positional specificity should be used.

For natural lipid mixtures such as egg lecithin, the specifications should be sufficient to ensure that the lipid can perform adequately in the liposome drug product and conform to impurity limits. Based on the nature of lipid or lipid mixtures, the lipid composition (e.g., percentage of each lipid and fatty acid, positional specificity of acyl side chains, degree of fatty acid unsaturation) should be specified in some circumstances. For instance, if the degree of unsaturation of the fatty acid side chains is too high, stable liposomes might not be formed. If the data indicate that this is a critical factor, acceptance criteria for the degree of fatty acid unsaturation should be included in the specifications. Other examples of parameters that can be critical to the performance of the lipid are the amount of phosphatidylglycerol or phosphatidylserine in a *lecithin* preparation.

4. Stability

Lipids used to manufacture liposomes should undergo stability studies to establish the storage conditions and retest date or shelf life. Stress testing (i.e., high temperature, light, pH, and oxygen), should be performed to determine the degradation profile. The container and closure system for storage and shipment of the lipids should be described, and relevant stability data should be provided.

E. Control of Drug Product: Specifications

For recommendations on specifications, applicants should consult the International Conference on Harmonisation (ICH) guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, where appropriate. Additional testing specific to liposome drug products is recommended over that which is typical of the nonliposomal dosage form. Additional tests may include, for example:

- physicochemical parameters of the liposome determined to be critical to product quality for each batch (see section II. B. on Physicochemical Characterization)

- 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 (see section III.D on In Vitro Stability)

F. Stability

The concepts in the CDER guidance for industry *Submitting Documentation for the Stability of Human Drugs and Biologics* [5] and the ICH guidance *Q1AR Stability Testing of New Drug Substances and Products* apply to the design of stability studies for liposome drug products. In general, stability studies should address both physical and chemical stability of the liposome drug product, including the liposome itself. Stability testing of unloaded liposomes (i.e., liposomes to be combined with a drug substance before use) should also be performed. Stress testing of liposome drug products and unloaded liposomes may be warranted to demonstrate possible degradation or other reaction processes unique to the liposomes.

The physical stability of liposome drug products is a function of the integrity and the size distribution of the lipid vesicles. Liposomes are susceptible to fusion, aggregation, and leakage of the encapsulated drug substance during storage. For instance, small unilamellar vesicles are more susceptible to size changes than are multilamellar vesicles. Also, the type of lipids in the bilayer or the encapsulated drug substance may affect fusion of the liposomes or leakage of drug substance from the liposome. Therefore, tests for physical parameters should be developed to assess the integrity and size of the liposomes.

Liposome drug products should be evaluated for stability of the encapsulated drug substance as well as stability of the lipids that compose the liposomal bilayer. 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. Therefore, tests should be developed to evaluate the chemical stability of the lipids in the liposome drug product.

G. Changes in Manufacturing

Manufacturing changes outside of the variations allowed in the approved application must be reported to FDA, as described in section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 356a). CDER's guidance for industry *Changes to an Approved NDA or ANDA* should be consulted for recommended reporting mechanisms. All changes should be performed in accordance with written change control procedures established by the manufacturer.

[5] The 1987 stability guidance will be superseded by FDA's draft guidance for industry *Stability Testing of Drug Substances and Drug Products* (June 1998) once it is issued in final form.

Because liposome drug products are a relatively new dosage form, it is not possible to provide recommendations on the type of information that should be generated to demonstrate that the change has not adversely affected the quality of the drug product. The extent of the information and documentation to be developed and submitted to support a change should depend on the types of manufacturing changes and the stage of manufacturing at which the changes occur. In general, the information should include testing routinely used for batch release of liposome drug products (see section II.E on Specifications) and depending on the type of change, additional tests specifically directed at evaluating the effect of the change on the liposome drug product (see section II.B. on Physicochemical Properties). In vivo studies may be warranted to demonstrate that the changed product is equivalent to the original product with respect to safety and efficacy.

Before distributing the product made with a change, applicants must assess the effect of each manufacturing change (including site changes, changes to the lipid composition and lipid component specifications) on the identity, strength, quality, purity, and potency of the liposome drug product, as these factors relate to safety and efficacy (section 506A(b) of the Act). The liposome drug product resulting from these changes (i.e., postchange product) should usually be compared to the liposome drug product manufactured as approved in the application (i.e., prechange product). Comparison testing of prechange and postchange drug products should be performed to initially characterize the changed product but is not necessary for routine testing after the change is implemented. An applicant can contact the appropriate review division if it has questions on the type of information to generate or the appropriate reporting mechanism for a postapproval change.

III. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

When an NDA is submitted for a liposome drug product, the requirements to provide human pharmacokinetics and bioavailability data apply (see 21 CFR 314.50, 320.21, and 320.29). This guidance does not provide information on clinical pharmacology and/or clinical efficacy and safety studies that would be submitted in an NDA. Applicants should consult relevant guidance documents for recommendations on the information to be provided for these topics, or they can consult the appropriate CDER review division.

A. Bioanalytical Methods

Validated bioanalytical methods should be used when evaluating the pharmacokinetics and bioavailablity of a drug substance.[6] For liposome drug products the bioanalytical method should also be capable of measuring encapsulated and unencapsulated drug substance. If a method that distinguishes between encapsulated and unencapsulated drug substance cannot be developed, a justification as to why it is not feasible to develop such a method should be provided.

[6] While the term *drug substance* is used throughout section III, it is recognized that the drug substance may exist as the active moiety in vivo.

Additional information on validation of methods can be found in CDER's guidance for industry *Bioanalytical Method Validation*.

B. In Vivo Integrity (Stability) Considerations

In addition to the general stability considerations of the drug substance in a biological fluid, the stability of the liposome in vivo should be considered.

If the bioanalytical method can distinguish between encapsulated and unencapsulated drug substance, the in vivo stability of the liposome should be determined. A single-dose study is recommended to assess the in vivo stability of the liposome. The concentration-time profile should be evaluated at multiple time points over an adequate period of time. The concentration of encapsulated and unencapsulated drug substance should be determined at each sampling time point.

The liposome is considered stable in vivo if, over the time course of the single-dose study, the:

- drug substance, when in circulation, remains substantially in the encapsulated form
- ratio of unencapsulated to encapsulated drug substance remains constant

When the liposome is stable in vivo, the total drug substance concentration can be measured to determine the pharmacokinetics and bioavailability. However, for an unstable liposome drug product, the concentration of both encapsulated and unencapsulated drug substance should be measured.

If an applicant uses a bioanalytical method that does not distinguish encapsulated and unencapsulated drug substance, this method should be justified (see section III.A on Bioanalytical Methods). When the applicant justifies the use of such a method, the total drug substance concentration can be measured to determine pharmacokinetics and bioavailability.

C. Protein Binding

The stability of liposomes in vivo can be affected by interactions with lipoproteins and other proteins in the blood. Such interactions can have safety implications if dose dumping occurs as a result of premature release of the drug substance from the liposomes. Interactions of liposomes with serum proteins and lipoproteins can be dependent on the type of lipids used in formulating the liposomes. The protein (including lipoprotein) binding of the drug substance and liposome drug product should be determined over the expected therapeutic concentration range. The major binding proteins should be identified.

D. In Vitro Stability

A validated in vitro test method should be established that uses an appropriate simulated physiological medium and/or human plasma and acceptance criteria for the in vitro release

of the drug substance from the liposome. An in vitro test that measures the release of the drug substance from the liposome can be important for assessing the (1) quality of a liposome drug product, (2) adequacy of the process controls, (3) release characteristics of the product over time, and (4) the effect of CMC changes (e.g., minor manufacturing process changes or change in site of manufacture). As experience is gained in the manufacturing of a liposome drug product, an in vitro test, rather than an in vivo test, may be useful in characterizing the liposome drug product when manufacturing changes are made.

E. Pharmacokinetics and Bioavailability

To adequately characterize the pharmacokinetics and bioavailability of a drug substance after administration of liposome drug product, the following studies should be performed:

1. *Mass Balance Study*

The Agency recommends a comparative mass-balance study be performed to define and assess the differences in systemic exposure and pharmacokinetic measures or parameters between liposome and nonliposome drug products when (1) the two products have the same active moiety, (2) the two products are given by the same route of administration, and (3) one of the products is already approved for marketing. The disposition and pathways of elimination (including metabolism and excretion) and several important pharmacokinetic measures (Cmax, AUC) and parameters (clearance, volume, half-life) of a liposomal formulation administered intravenously can be different from that of a nonliposomal formulation given by the same route of administration. Although no examples currently exist, absorption could also be altered for liposome drug product when given via non-intravenous routes. For these reasons, if satisfactory[7] mass balance information is already available for the approved drug product, a limited mass balance study can be undertaken for the proposed drug product. In such a study, the quantity of the drug substance excreted via the major route should be compared in sufficient subjects by giving the liposomal and the nonliposomal formulations, using a crossover or a parallel study design.

Comparison of the absorption, distribution, metabolism, and excretion (ADME) of the liposome and nonliposome drug product form should be made, using a crossover or noncrossover study design that employs an appropriate number of subjects. Depending on the drug substance under investigation, the dose of the liposome and nonliposome drug product may be different. The mass balance study should be based on drug substance tagged with a radioactive label (e.g., ^{14}C, ^{3}H) before its incorporation into liposomes to allow for sensitive monitoring of

[7] Rarely, historical pharmacokinetic data for comparative purposes can be considered on a case-by-case basis in lieu of formal comparative mass balance and/or pharmacokinetic study, taking into account the following factors: (1) when and how the historical data was obtained, (2) similarities of study populations (e.g., disease condition), (3) analytical procedures, and (4) data analysis. The appropriate CDER review division should be consulted to determine whether historical data can be relied upon.

radioactive label after administration. Blood (plasma or serum as appropriate), urine, and fecal samples should be collected and assayed for radioactive label. Other routes of elimination should be monitored as appropriate. Both parent drug substances and any metabolites present should be quantitated. If feasible, mass balance studies can use nonlabeled drug moieties and ingredients. However, CDER recommends that a applicant contact the appropriate review division before conducting studies using nonlabeled drug substance.

2 Pharmacokinetic Studies

When given by the same route of administration, the pharmacokinetics of a drug substance in a liposomal formulation are expected to be different from the same drug substance in a nonliposomal formulation. For this reason, the pharmacokinetic studies should include a study to compare the ADME of a liposome and nonliposome drug product when (1) the two products have the same active moiety, (2) the two products are given by the same route of administration, and (3) one of the products is already approved for marketing. This information can be useful in establishing dosing regimens and in developing dose-concentration-response relationships. The detailed design of the study should be based on the anticipated dosing regimen in the intended patient population. These measures or parameters should include area under the plasma concentration versus time curve, peak plasma concentration, time to peak plasma concentration, elimination half-life, volume of distribution, total clearance, renal clearance, and accumulation, as appropriate. (See section III.B on In Vivo Integrity Considerations for recommendations on whether the pharmacokinetic measures or parameters should be based on total drug substance or both encapsulated and unencapsulated drug substance.) Major metabolites associated with the therapeutic or toxic effects of the drug substance should be determined. The following pharmacokinetic studies should be conducted:

- a single-dose pharmacokinetic study; this should be a comparative study between the liposome and nonliposome drug product, when appropriate (see above)
- a multiple-dose study evaluating the pharmacokinetics of the drug substance after administration of the liposome drug product
- a dose-proportionality study over the expected therapeutic dose range after administration of the liposome drug product

A population-pharmacokinetics approach can be used where appropriate. See CDER's guidance for industry *Population Pharmacokinetics*.

3. Additional Pharmacokinetic Studies

The following pharmacokinetic studies should be considered:

a. Food-Effect Studies

Food intake can affect the lipid composition of plasma, which may affect the disposition of liposome drug products. The applicant should consult with the Agency if there are questions regarding the conduct and design of food studies.

b. Drug Interactions and/or Special Populations

Depending on the results of the mass balance and the pharmacokinetic studies, investigation of drug-drug interactions and/or pharmacokinetics in special populations may be warranted. The applicant should consult with the Agency if there are questions regarding the conduct and design of these studies.

c. Exposure-Response Studies

Exposure-response studies should be provided when available.

IV. LABELING

Information on labeling requirements can be found in sections 502(e)(3) and 508(a) of the Act (21 U.S.C. 352(e)(3) and 358(a)) and in parts 201 and 299 (21 CFR parts 201 and 299). Guidance specific to liposome drug products is provided below

A. Product Name

The product name should include the established name, dosage form, terminology to describe that it is a liposome drug product, and, if desired, a proprietary (i.e., brand) name. The descriptive terminology should include the term *liposome* and, when appropriate, such terms as *Type A, Type B, and Type C,* to distinguish one liposome product from other liposomal formulations of the same drug substance that are not therapeutically equivalent. For example:

BrandX (Acetaminophen) Liposome-Type A For Injection

B. Cautionary Notes and Warnings

Liposome encapsulation can substantially affect a drug product's functional properties relative to those of the unencapsulated or nonlipid-associated drug substance. In addition, different liposome products with a common drug substance can vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect the functional properties of these drug products. CDER recommends that when warranted:

- A cautionary note should be included in the description section of the labeling

regarding the fact that liposome drug products may behave differently from nonliposome drug products.

- A warning should be included in the labeling that the liposome drug product is not equivalent to or cannot be substituted for other drug products containing the same drug substance.

C. Dosage and Administration

Under § 201.57(j), reconstitution instructions with supporting data are required for lyophilized liposome drug products (21 CFR 201.57(j)). This information should be provided for both unloaded lyophilized liposomes that are reconstituted with a drug substance-containing solution at the time of use, as well as products in which the drug substance is loaded into the liposome by the manufacturer and then lyophilized. Other issues that should be addressed, 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 appropriateness of using in-line filters.