Liposome Drug Products

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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Richard Lostritto, 301-796-1697.

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

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Pharmaceutical Quality/CMC
Revision 1

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Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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TABLE OF CONTENTS

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Guidance for Industry[1]

This revised draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create 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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This revised draft guidance discusses what types of information you, the applicant, should submit in your new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA) 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 It replaces the draft guidance for industry on *Liposome Drug Products, Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation* that published in August 2002.[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]

Some of the scientific principles mentioned in this guidance may be applicable to biological liposome products reviewed by CDER's Office of Biotechnology 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. If you intend to submit an NDA/ANDA for a drug-lipid complex, you can consult the appropriate review division in CDER for additional guidance, if necessary.

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 bioequivalence 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 microvesicles 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. In a liposome drug product, the drug substance is contained in liposomes.[4] Typically, water soluble drugs are contained in the aqueous compartment(s) and hydrophobic drugs are contained in the lipid layer(s) of the liposomes. Release of drugs from liposome formulations 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 one 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 lipid(s) used in the formulation, both as a molar ratio and as a weight-by-weight percentage of the lipid compared to the drug substance

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

We recommend expressing the composition of the drug product on a milligram of drug substance per milliliter of drug product basis (and also milligram of drug substance per vial basis), 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 and whether the source of key excipients has an effect on finished product performance (i.e., quality, safety, and efficacy)

These ranges should be supported by data.

2. Physicochemical Properties

The following properties are generally useful to characterize a liposome drug formulation. The properties listed in items below can lead to changes in the behavior 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 liposome, including lamellarity determination, if applicable

b. Surface characteristics, as applicable

c. Liposome structure and integrity, which refers to the ability of the liposome drug formulation to contain the desired drug substance and to retain the drug substance inside the liposome

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

e. Drug product viscosity

f. Parameters of the contained drug

For example, drug encapsulation efficiency (defined as percentage of drug contained inside liposomes compared with total amount of drug) and liposome drug loading (defined as the percentage of drug contained which is then compared with the amount of the lipid used, which is the drug-to-lipid ratio).[5]

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

h. Phase transition temperature

i. 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

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

k. Liposome integrity changes (e.g., release, containment efficiency, size) in response to changes in salt concentration

l. Spectroscopic data to support the proposed liposome structure (e.g., phosphorus nuclear magnetic resonance)

3. Critical Quality Attributes

Critical quality attributes (CQAs) particular to liposome drug products may include some of the physicochemical properties described above including vesicle/particle size and size distribution, and morphology. The International Conference on Harmonisation (ICH) guidance for industry, *Q8(R2) Pharmaceutical Development,* has further information.

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 monitored process parameters and process controls. These ranges should be supported by pharmaceutical development studies.

Liposome drug products are sensitive to changes in the manufacturing conditions, including changes in scale (size of the batches). It is important to establish process controls to ensure

[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.

liposome drug product quality. You should establish appropriate process controls during development of the product, and also consider leveraging prior knowledge and/or risk assessment techniques to identify manufacturing process parameters that have a potential to affect finished product quality.

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

The physical and chemical complexity of liposome drug products can provide unique challenges to the sterilizing filtration process. For example, components of liposomes could interact with the filter matrix and clog it. Therefore, product-specific purification and sterilization methods with corresponding validation studies should demonstrate the ability of the microbial sterilizing filters to function correctly.

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 cases of novel lipid components, the level of detail provided in the submission should be comparable to that for a drug substance.[6]

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

a. Description and Characterization of Lipid Components

If the lipid is a well-defined synthetic or semisynthetic lipid, such as dimyristoylphosphatidyl-choline (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 lipid and its fatty acid composition.

b. Manufacture of Lipid Components

The information that should be provided on the manufacture of lipid components depends on whether the lipid is synthetic, semi-synthetic, or naturally derived.

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

[6] For further information, see ICH *Q11 Development and Manufacture of Drug Substances* (ICH Q11).

i. A complete description of the synthetic process and purification procedures, as applicable
ii. Specifications for starting materials,[7] 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 semisynthetic 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[8]

You should describe procedures to ensure the avoidance, removal, and/or inactivation of animal proteins and viruses and any other infectious agents, where applicable.

You should address the avoidance and/or removal of pyrogenic material and bacterial endotoxins by establishing appropriate controls during the manufacturing process.

c. Specifications for Lipid Components

You should provide the following information in the lipid(s) specification for each lipid component used in the manufacture of the drug product. In the specification:

i. The identity test should be capable of distinguishing the intended lipid component from lipids with similar structures.
ii. The assay should be based on a stability-indicating analytical procedure.
iii. The analytical procedures should be validated (the validation data should be provided).
iv. Impurities testing should be included (see below).
v. For natural lipid mixtures (e.g., egg lecithin), examples of other tests can include the following:
    1. The degree of unsaturation of the fatty acid side chains
    2. Counterion content and limits on divalent cations
vi. For synthetic lipids or lipid mixtures, examples of other tests can include the following:
    1. Trans-fatty acid

[7] See ICH Q11 for recommendations about the selection of starting materials.
[8] Ibid.

2. Free-fatty acid
3. Peroxides
4. Lysophospholipids
5. Counterion content and limits on divalent cations

You should provide information about impurities, including synthetic by-products, where applicable. 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[9]

For synthetic lipids, such as DMPC, and semisynthetic lipids, you should 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).

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 conduct stability studies and perform stress testing (e.g., high (e.g., 50ºC) and low (e.g., freezing) temperatures, light, pH, and oxygen) to establish appropriate storage conditions and retest period(s), determine the degradation profile, and develop an appropriate stability-indicating analytical procedure.

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, and physical stability)

b. Liposome contained and free drug substance

c. Total drug substance content, as labeled

d. Degradation products related to the lipids or drug substance

[9] 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.

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

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. 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 presence of any 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.[10]

The physical stability of liposome drug products can be affected by a number of factors (e.g., the liposome integrity,[11] 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

[10] See ICH *Q1A(R2) Stability Testing of New Drug Substances and Products*.
[11] See section III.A.2.c and k.

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).

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.

8. Postapproval Changes in Manufacturing

Liposome drug products are complex and sensitive formulations that may respond to CMC changes with greater unpredictability than 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. It may be advisable to conduct in vivo studies if the changes can affect the performance of the drug product. You can contact the appropriate review division if you have questions regarding the type of information to generate or the appropriate reporting mechanism for a postapproval change.[12]

B. Human Pharmacokinetics: Bioavailability and Bioequivalence

For ANDA submissions for liposome drug products, please refer to applicable product-specific FDA guidance documents 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.

Because of the complexity of the interaction between drug release from liposome drug product and tissue uptake of the drug substance, a simple measurement of total drug substance

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

concentration in plasma[13] may not be reflective of bioavailability of the drug at the intended target organ (i.e., site of action).[14] Therefore, for NDA submissions, you should consult the appropriate CDER review division 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 design of the study should be based on the anticipated dosing regimen in the intended patient population. We recommend using a population pharmacokinetics approach, where appropriate.[15]

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. You should monitor other routes of elimination, as appropriate, and quantify both parent drug and any metabolites present.

You should determine major metabolites associated with the therapeutic and toxic effects of the drug substance. We also recommend considering 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 and/or studies in specific populations.

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

b. Comparison Clinical Pharmacology Studies with Nonliposome Drug Product

[13] See 21 CFR 320.24(b)(1)(i).
[14] See 21 CFR 320.1(a).
[15] See FDA's guidance for industry on *Population Pharmacokinetics.*

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

If there are approved nonliposome formulations, 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 for a comparative study of 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 such 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 few examples exist, we encourage you to establish an IVIVC for the 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 contained and free drug substance (drug released from the liposome).[16]

d. Liposome-Protein Interaction

Depending on the type of lipids used in formulating liposomes, interactions between blood proteins and lipoproteins 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 on what to include in the labeling 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, you should refer to 21 CFR 299.4, USP General Chapter <1121> *Nomenclature*,[17] and the USP Nomenclature Guidelines.[18] 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]

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[16] See FDA's guidance for industry on *Bioanalytical Methods Validation*.

[17] According to USP General Chapter <1121>, the general format for a drug product monograph title is [DRUG][ROUTE OF ADMINISTRATION][DOSAGE FORM].

[18] See the following USP Web site: http://www.usp.org/sites/default/files/usp_pdf/EN/2014-12-01_nom_guidelines.pdf.

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.[19]

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 that the foregoing is not intended to apply to liposome drug products that have been determined by the 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.

For liposome drug products that require reconstitution, you should provide reconstitution instructions[20] and a statement regarding the appropriate in-use period. 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), you should also provide admixing instructions and a statement regarding the appropriate in-use period of the admixed product. The other issues that you should address, 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.

IV. REFERENCES

Guidance for Industry[21]

Bioanalytical Method Validation (or the current drug product guidance)

Changes to an Approved NDA or ANDA

[19] Note that with respect to ANDA submissions, the product name is the same as the nonproprietary or established name of the RLD.

[20] See 21 CFR 201.57(c)(3)(i)(J)(iv).

[21] 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.

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

Population Pharmacokinetics

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

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*