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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TABLE OF CONTENTS

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 It finalizes the revised draft guidance for industry *Liposome Drug Products, Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation* that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.

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