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# 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### *DRAFT GUIDANCE*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)  
August 2002  
CMC**

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Pharmacokinetics and Bioavailability; and Labeling  
Documentation**

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**U.S. Department of Health and Human Services  
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# GUIDANCE FOR INDUSTRY<sup>1</sup>

## Liposome Drug Products

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

*If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:*

- *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](mailto: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).<sup>2</sup> The recommendations in this guidance focus on the unique technical aspects of liposome drug products. Applicants should

<sup>1</sup> 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.

<sup>2</sup> 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.

37 refer to the forthcoming drug product guidance<sup>3</sup> for other recommendations on the CMC  
38 documentation that should be submitted in original NDAs. Applicants can contact the appropriate  
39 review division if they have questions on demonstrating bioequivalence and sameness of liposome  
40 drug products. The recommendations in this guidance should be considered, to the extent  
41 applicable, when a sponsor is submitting an investigational new drug application (IND).  
42

43 Liposome drug products are defined as drug products containing drug substances (active  
44 pharmaceutical ingredients) encapsulated in liposomes. A liposome is a microvesicle composed  
45 of a bilayer of lipid amphipathic molecules enclosing an aqueous compartment. Liposome drug  
46 products are formed when a liposome is used to encapsulate a drug substance within the lipid  
47 bilayer or in the interior aqueous space of the liposome. A drug substance in a liposome  
48 formulation is intended to exhibit a different pharmacokinetic and/or tissue distribution (PK/TD)  
49 profile from the same drug substance (or active moiety) in a nonliposomal formulation given by the  
50 same route of administration. The complete characterization of the PK/TD profile of a new  
51 liposome drug product is essential to establish the safe and effective dosing regimen of the  
52 product.  
53

54 The guidance does not provide recommendations on:

- 56 • clinical efficacy and safety studies
- 57 • nonclinical pharmacology and/or toxicology studies
- 58 • bioequivalence studies or those to document sameness
- 59 • liposomal formulations of vaccine adjuvants or biologics
- 60 • drug-lipid complexes<sup>4</sup>

61  
62

## 63 **II. CHEMISTRY, MANUFACTURING, AND CONTROLS**

64  
65 The recommendations provided on CMC documentation focus on the information specific to  
66 liposome drug products that should be submitted to CDER. An applicant should consult all  
67 relevant regulations and guidances for information on the type of documentation that should be  
68 submitted for drug substances and other aspects of documenting the identity, strength, quality,  
69 purity, and potency of the drug product.  
70

### 71 **A. Description and Composition**

72

---

<sup>3</sup> 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.

<sup>4</sup> 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.

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

## 81 **B. Physicochemical Properties**

82  
83  
84 The physicochemical properties of the liposome drug product are critical to ensuring drug  
85 product quality. Therefore, a detailed evaluation of these properties should be provided.  
86 Rigorous characterization of the physicochemical properties can also be beneficial in  
87 evaluating subsequent changes in manufacturing (see section II.G. on Changes in  
88 Manufacturing). The physicochemical characterization tests, which are critical to ensuring  
89 product quality of each batch of liposome drug product, should be identified. However, all  
90 the characterization tests need not be included in the specifications. Properties specific to  
91 liposome drug products that may be useful to assess include:

- 92
- 93 • morphology of the liposome, including lamellarity determination, if applicable
- 94 • net charge
- 95 • volume of entrapment in liposomal vesicles
- 96 • particle size (mean and distribution profile)
- 97 • phase transition temperature
- 98 • spectroscopic data, as applicable
- 99 • in vitro release of the drug substance from the liposome drug product
- 100 • osmotic properties
- 101 • light scattering index
- 102

## 103 **C. Description of Manufacturing Process and Process Controls**

104  
105 Liposome drug products are sensitive to changes in the manufacturing conditions, including  
106 changes in scale. This should be considered during the development process, and critical  
107 manufacturing parameters (e.g., scale, shear force, temperature) should be identified and  
108 evaluated. If there are changes in critical manufacturing parameters, complete  
109 characterization of the liposome drug product is recommended and in vivo studies may be  
110 warranted (see section II.G. on Changes in Manufacturing).

111  
112 The chemical and physical complexity of liposome drug products can provide unique  
113 challenges to the sterilizing filtration process. For example, constituents of the liposome  
114 may block adsorptive interactions of organisms with the filter matrix, effectively allowing  
115 organisms to pass through the sterilizing filter. Therefore, product-specific validation  
116 studies should demonstrate the microbial retentivity of the intended sterilizing filters.

118 **D. Control of Excipients: Lipid Components**  
119

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

127  
128 In addition to the information recommended by the drug substance guidance,  
129 recommendations specific to lipid components are provided below.

130  
131 *1. Description and Characterization*  
132

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

138  
139 *2. Manufacture*  
140

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

146  
147 A complete description of the synthetic process, extraction, and purification  
148 procedures should be provided, as applicable. Specifications should be provided  
149 for starting materials, raw materials, solvents, and reagents. The controls for  
150 critical steps and intermediates should be provided. Chromatographic purification  
151 procedures should be described, including the collection of desired fractions, and a  
152 sample chromatogram should be provided. For synthetic and semisynthetic lipids,  
153 the manufacturing controls that ensure positional specificity of acyl side chains  
154 should be provided, if applicable. (See the drug substance guidance for additional  
155 information on the manufacturing information that should be provided.)  
156

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

161  
162 *3. Specifications*  
163

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

171  
172 For synthetic lipids such as DMPC and semisynthetic lipids, the assay and impurity  
173 tests can be done by comparison with the reference standard (e.g., thin-layer  
174 chromatography (TLC)) when the analytical procedure can distinguish the desired  
175 lipids from possible impurities. If the analytical procedure cannot distinguish the  
176 desired lipids from impurities, then assays capable of confirming the fatty acid  
177 composition and positional specificity should be used.

178  
179 For natural lipid mixtures such as egg lecithin, the specifications should be  
180 sufficient to ensure that the lipid can perform adequately in the liposome drug  
181 product and conform to impurity limits. Based on the nature of lipid or lipid  
182 mixtures, the lipid composition (e.g., percentage of each lipid and fatty acid,  
183 positional specificity of acyl side chains, degree of fatty acid unsaturation) should  
184 be specified in some circumstances. For instance, if the degree of unsaturation of  
185 the fatty acid side chains is too high, stable liposomes might not be formed. If the  
186 data indicate that this is a critical factor, acceptance criteria for the degree of fatty  
187 acid unsaturation should be included in the specifications. Other examples of  
188 parameters that can be critical to the performance of the lipid are the amount of  
189 phosphatidylglycerol or phosphatidylserine in a *lecithin* preparation.

#### 190 191 4. *Stability*

192  
193 Lipids used to manufacture liposomes should undergo stability studies to establish  
194 the storage conditions and retest date or shelf life. Stress testing (i.e., high  
195 temperature, light, pH, and oxygen), should be performed to determine the  
196 degradation profile. The container and closure system for storage and shipment of  
197 the lipids should be described, and relevant stability data should be provided.

### 198 199 **E. Control of Drug Product: Specifications**

200  
201 For recommendations on specifications, applicants should consult the International  
202 Conference on Harmonisation (ICH) guidance for industry *Q6A Specifications: Test*  
203 *Procedures and Acceptance Criteria for New Drug Substances and New Drug Products:*  
204 *Chemical Substances*, where appropriate. Additional testing specific to liposome drug  
205 products is recommended over that which is typical of the nonliposomal dosage form.  
206 Additional tests may include, for example:

- 207  
208 • physicochemical parameters of the liposome determined to be critical to product  
209 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*<sup>5</sup> and the ICH guidance *QIAR 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.

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<sup>5</sup> 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.

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

263  
264 Before distributing the product made with a change, applicants must assess the effect of  
265 each manufacturing change (including site changes, changes to the lipid composition and  
266 lipid component specifications) on the identity, strength, quality, purity, and potency of the  
267 liposome drug product, as these factors relate to safety and efficacy (section 506A(b) of  
268 the Act). The liposome drug product resulting from these changes (i.e., postchange  
269 product) should usually be compared to the liposome drug product manufactured as  
270 approved in the application (i.e., prechange product). Comparison testing of prechange  
271 and postchange drug products should be performed to initially characterize the changed  
272 product but is not necessary for routine testing after the change is implemented. An  
273 applicant can contact the appropriate review division if it has questions on the type of  
274 information to generate or the appropriate reporting mechanism for a postapproval change.

### 275 276 277 **III. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY**

278  
279 When an NDA is submitted for a liposome drug product, the requirements to provide human  
280 pharmacokinetics and bioavailability data apply (see 21 CFR 314.50, 320.21, and 320.29). This  
281 guidance does not provide information on clinical pharmacology and/or clinical efficacy and  
282 safety studies that would be submitted in an NDA. Applicants should consult relevant guidance  
283 documents for recommendations on the information to be provided for these topics, or they can  
284 consult the appropriate CDER review division.

#### 285 286 **A. Bioanalytical Methods**

287  
288 Validated bioanalytical methods should be used when evaluating the pharmacokinetics and  
289 bioavailability of a drug substance.<sup>6</sup> For liposome drug products the bioanalytical method  
290 should also be capable of measuring encapsulated and unencapsulated drug substance. If a  
291 method that distinguishes between encapsulated and unencapsulated drug substance cannot  
292 be developed, a justification as to why it is not feasible to develop such a method should  
293 be provided.

---

<sup>6</sup> 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.

295 Additional information on validation of methods can be found in CDER's guidance for  
296 industry *Bioanalytical Method Validation*.  
297

## 298 **B. In Vivo Integrity (Stability) Considerations**

299  
300 In addition to the general stability considerations of the drug substance in a biological  
301 fluid, the stability of the liposome in vivo should be considered.  
302

303 If the bioanalytical method can distinguish between encapsulated and unencapsulated drug  
304 substance, the in vivo stability of the liposome should be determined. A single-dose study  
305 is recommended to assess the in vivo stability of the liposome. The concentration-time  
306 profile should be evaluated at multiple time points over an adequate period of time. The  
307 concentration of encapsulated and unencapsulated drug substance should be determined at  
308 each sampling time point.  
309

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

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

314  
315 When the liposome is stable in vivo, the total drug substance concentration can be  
316 measured to determine the pharmacokinetics and bioavailability. However, for an unstable  
317 liposome drug product, the concentration of both encapsulated and unencapsulated drug  
318 substance should be measured.  
319

320  
321 If an applicant uses a bioanalytical method that does not distinguish encapsulated and  
322 unencapsulated drug substance, this method should be justified (see section III.A on  
323 Bioanalytical Methods). When the applicant justifies the use of such a method, the total  
324 drug substance concentration can be measured to determine pharmacokinetics and  
325 bioavailability.  
326

## 327 **C. Protein Binding**

328  
329 The stability of liposomes in vivo can be affected by interactions with lipoproteins and  
330 other proteins in the blood. Such interactions can have safety implications if dose dumping  
331 occurs as a result of premature release of the drug substance from the liposomes.

332 Interactions of liposomes with serum proteins and lipoproteins can be dependent on the  
333 type of lipids used in formulating the liposomes. The protein (including lipoprotein)  
334 binding of the drug substance and liposome drug product should be determined over the  
335 expected therapeutic concentration range. The major binding proteins should be identified.  
336

## 337 **D. In Vitro Stability**

338  
339 A validated in vitro test method should be established that uses an appropriate simulated  
340 physiological medium and/or human plasma and acceptance criteria for the in vitro release

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

## 349 **E. Pharmacokinetics and Bioavailability**

350 To adequately characterize the pharmacokinetics and bioavailability of a drug substance  
351 after administration of liposome drug product, the following studies should be performed:  
352

### 353 1. *Mass Balance Study*

354  
355 The Agency recommends a comparative mass-balance study be performed to define  
356 and assess the differences in systemic exposure and pharmacokinetic measures or  
357 parameters between liposome and nonliposome drug products when (1) the two  
358 products have the same active moiety, (2) the two products are given by the same  
359 route of administration, and (3) one of the products is already approved for  
360 marketing. The disposition and pathways of elimination (including metabolism and  
361 excretion) and several important pharmacokinetic measures (C<sub>max</sub>, AUC) and  
362 parameters (clearance, volume, half-life) of a liposomal formulation administered  
363 intravenously can be different from that of a nonliposomal formulation given by the  
364 same route of administration. Although no examples currently exist, absorption  
365 could also be altered for liposome drug product when given via non-intravenous  
366 routes. For these reasons, if satisfactory<sup>7</sup> mass balance information is already  
367 available for the approved drug product, a limited mass balance study can be  
368 undertaken for the proposed drug product. In such a study, the quantity of the drug  
369 substance excreted via the major route should be compared in sufficient subjects by  
370 giving the liposomal and the nonliposomal formulations, using a crossover or a  
371 parallel study design.  
372

373  
374 Comparison of the absorption, distribution, metabolism, and excretion (ADME) of  
375 the liposome and nonliposome drug product form should be made, using a  
376 crossover or noncrossover study design that employs an appropriate number of  
377 subjects. Depending on the drug substance under investigation, the dose of the  
378 liposome and nonliposome drug product may be different. The mass balance study  
379 should be based on drug substance tagged with a radioactive label (e.g., <sup>14</sup>C, <sup>3</sup>H)  
380 before its incorporation into liposomes to allow for sensitive monitoring of  
381

---

<sup>7</sup> 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.

382 radioactive label after administration. Blood (plasma or serum as appropriate),  
383 urine, and fecal samples should be collected and assayed for radioactive label.  
384 Other routes of elimination should be monitored as appropriate. Both parent drug  
385 substances and any metabolites present should be quantitated. If feasible, mass  
386 balance studies can use nonlabeled drug moieties and ingredients. However,  
387 CDER recommends that a applicant contact the appropriate review division before  
388 conducting studies using nonlabeled drug substance.  
389

## 390 2 Pharmacokinetic Studies

391  
392 When given by the same route of administration, the pharmacokinetics of a drug  
393 substance in a liposomal formulation are expected to be different from the same  
394 drug substance in a nonliposomal formulation. For this reason, the pharmacokinetic  
395 studies should include a study to compare the ADME of a liposome and  
396 nonliposome drug product when (1) the two products have the same active moiety,  
397 (2) the two products are given by the same route of administration, and (3) one of  
398 the products is already approved for marketing. This information can be useful in  
399 establishing dosing regimens and in developing dose-concentration-response  
400 relationships. The detailed design of the study should be based on the anticipated  
401 dosing regimen in the intended patient population. These measures or parameters  
402 should include area under the plasma concentration versus time curve, peak plasma  
403 concentration, time to peak plasma concentration, elimination half-life, volume of  
404 distribution, total clearance, renal clearance, and accumulation, as appropriate.  
405 (See section III.B on In Vivo Integrity Considerations for recommendations on  
406 whether the pharmacokinetic measures or parameters should be based on total drug  
407 substance or both encapsulated and unencapsulated drug substance.) Major  
408 metabolites associated with the therapeutic or toxic effects of the drug substance  
409 should be determined. The following pharmacokinetic studies should be  
410 conducted:

- 411
- 412 • a single-dose pharmacokinetic study; this should be a comparative study  
413 between the liposome and nonliposome drug product, when appropriate (see  
414 above)
- 415 • a multiple-dose study evaluating the pharmacokinetics of the drug substance  
416 after administration of the liposome drug product
- 417 • a dose-proportionality study over the expected therapeutic dose range after  
418 administration of the liposome drug product
- 419

420 A population-pharmacokinetics approach can be used where appropriate. See  
421 CDER's guidance for industry *Population Pharmacokinetics*.  
422

## 423 3. Additional Pharmacokinetic Studies

424  
425 The following pharmacokinetic studies should be considered:

- 426 a. Food-Effect Studies
- 427

428  
429 Food intake can affect the lipid composition of plasma, which may affect  
430 the disposition of liposome drug products. The applicant should consult  
431 with the Agency if there are questions regarding the conduct and design of  
432 food studies.

433  
434 b. Drug Interactions and/or Special Populations

435  
436 Depending on the results of the mass balance and the pharmacokinetic  
437 studies, investigation of drug-drug interactions and/or pharmacokinetics in  
438 special populations may be warranted. The applicant should consult with  
439 the Agency if there are questions regarding the conduct and design of these  
440 studies.

441  
442 c. Exposure-Response Studies

443  
444 Exposure-response studies should be provided when available.

445  
446  
447 **IV. LABELING**

448  
449 Information on labeling requirements can be found in sections 502(e)(3) and 508(a) of the Act (21  
450 U.S.C. 352(e)(3) and 358(a)) and in parts 201 and 299 (21 CFR parts 201 and 299). Guidance  
451 specific to liposome drug products is provided below

452  
453 **A. Product Name**

454  
455 The product name should include the established name, dosage form, terminology to  
456 describe that it is a liposome drug product, and, if desired, a proprietary (i.e., brand) name.  
457 The descriptive terminology should include the term *liposome* and, when appropriate, such  
458 terms as *Type A*, *Type B*, and *Type C*, to distinguish one liposome product from other  
459 liposomal formulations of the same drug substance that are not therapeutically equivalent.  
460 For example:

461  
462 BrandX (Acetaminophen) Liposome-Type A For Injection

463  
464 **B. Cautionary Notes and Warnings**

465  
466 Liposome encapsulation can substantially affect a drug product's functional properties  
467 relative to those of the unencapsulated or nonlipid-associated drug substance. In addition,  
468 different liposome products with a common drug substance can vary from one another in  
469 the chemical composition and physical form of the lipid component. Such differences may  
470 affect the functional properties of these drug products. CDER recommends that when  
471 warranted:

- 472  
473
- A cautionary note should be included in the description section of the labeling

474 regarding the fact that liposome drug products may behave differently from  
475 nonliposome drug products.  
476 • A warning should be included in the labeling that the liposome drug product is not  
477 equivalent to or cannot be substituted for other drug products containing the same drug  
478 substance.

479  
480 **C. Dosage and Administration**

481  
482 Under § 201.57(j), reconstitution instructions with supporting data are required for  
483 lyophilized liposome drug products (21 CFR 201.57(j)). This information should be  
484 provided for both unloaded lyophilized liposomes that are reconstituted with a drug  
485 substance-containing solution at the time of use, as well as products in which the drug  
486 substance is loaded into the liposome by the manufacturer and then lyophilized. Other  
487 issues that should be addressed, as warranted, include storage conditions for the  
488 reconstituted drug, robustness of the liposome drug product under varied reconstitution  
489 conditions (e.g., degree of shaking), and appropriateness of using in-line filters.  
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