



**13 November 2002**

Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Submitted Electronic to [www.fda.gov/dockets/ecomments](http://www.fda.gov/dockets/ecomments)

Dear Guidance Document Manager,

Re: Gilead Sciences Review Comments on Liposome Drug Product Draft Guidance

Gilead thanks the Agency for the opportunity to submit comments and suggestions on the proposed "Liposome Drug Product" guidance. Gilead is a leading manufacturer of Liposome drug products in the United States with a tradition of constructive consultation with the Agency on liposome technology. Please find enclosed Gilead comments to the above guidance document.

Our comments have been prepared based on strong science and Gilead long standing experience in commercial scale manufacture of liposomal parenterals. We hope that you will find the comments helpful in generating liposome guidance that is clear, appropriate and consistent with current advances in liposome science. The comments are summarized into "Issue," "Proposal" and "Objective of Proposal," for each line or section under reference. Current texts proposed for deletion are in ~~strike through~~ and proposed new texts are underlined.

If you have any question on these comments, please feel free contact me.

Sincerely,

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## REVIEW COMMENTS ON LIPOSOME DRUG PRODUCT DRAFT GUIDANCE

DOCUMENT	COMMENT
Lines 43-44	<p><b>Issue:</b> Definition of “Liposome drug products” is not adequate.</p> <p><b>Proposed Definition:</b> “Liposome drug products are defined as drug substances (active pharmaceutical ingredients) encapsulated, <u>intercalated or entrapped</u> in liposomes.”</p> <p><b>Objective of Proposed Definition:</b> To broaden modality of liposome drug interaction.</p>
Lines 44-47	<p><b>Issue:</b> Definition of “Liposome” is not adequate.</p> <p><b>Proposed Definition:</b> “A liposome is a microvesicle composed of <u>one or more bilayers</u> of lipidic amphipathic molecules <u>typically</u> enclosing an <u>equal number of</u> aqueous <u>compartments</u>.”</p> <p><b>Objective of Proposed Definition:</b> To bring in line with accepted literature definition.</p>
Lines 47-50	<p><b>Issue:</b> Statement on “drug substance in a liposome formulation” is not always intended as stated. Statement as written excludes liposome applications where formulations are intended to release drug immediately after administration.</p> <p><b>Proposed Statement:</b> Modification and addition to statement: “A drug substance in a liposome formulation is <u>typically</u> intended to exhibit a different pharmacokinetic and/or tissue distribution (PK/TD) <del>profile from the same drug substance (or active moiety) in a nonliposomal formulation given by the same route of administration.</del> <u>Liposome formulations which do not retain drug substance immediately after administration are not subject to the provisions of this guideline.</u>”</p> <p><b>Objective of Proposed Modification:</b> To make clear that this guideline does not apply to liposomal formulations not intended for PK and/or TD alteration.</p>
Line 61	<p><b>Issue:</b> The list of excluded formulations should include liposomal formulations not intended for PK/TD alteration. (See comment on lines 47-50).</p> <p><b>Proposal:</b> [Add bullet for]: <u>Liposome formulations not intended for PK and/or TD alteration.</u></p> <p><b>Objective of Proposal:</b> To clarify that these formulations fall in the excluded category.</p>

DOCUMENT	COMMENT
Lines 74-76	<p><b>Issue:</b> The “molar ratio” and “percentage by weight” of the lipid both express the same property of the lipid. In general, Gilead believes that lipid content in units of milligram (mg) per milliliter (mL) or per vial, along with similarly specified drug content specifications, adequately specifies the lipid quantity in the drug product and also the lipid-to-drug ratio. Gilead believes a separate specification based on ratio is redundant.</p> <p><b>Proposed Statement:</b> “The quantity of lipids in the formulation should be expressed as <u>milligram (mg) per milliliter (mL) or as mg per vial for each lipid component.</u> <del>the molar ratio and percentage by weight of the lipid to the drug substance as well as ....</del>”</p> <p><b>Objective of Proposed Statement:</b> To remove redundancy.</p>
Line 95	<p><b>Issue:</b> Requirement of “volume of entrapment in liposome vesicles” as a possible physicochemical property.</p> <p><b>Proposal:</b> Requirement should be changed to “<u>fraction of drug encapsulated.</u>”</p> <p><b>Objective of Proposal:</b> Based on Gilead experience with liposome drug products, the “Volume of Entrapment” is neither a reliable nor useful parameter.</p>
Line 100	<p><b>Issue:</b> Requirement of “Osmotic Properties” as a possible physicochemical property. It may be necessary for agency to clarify if ordinary osmotic properties (e.g. osmolarity or osmolality) are meant or if some other (defined) understanding is implied.</p> <p><b>Objective:</b> Enhance document clarity.</p>

Lines 108-110	<p><b>Issue:</b> Need for additional agency clarification on the use of “in vivo studies in evaluation of manufacturing changes” requirement. Not all changes in critical manufacturing parameters would be expected to have in vivo effect on the liposome drug product. Physicochemical control testing for batch release ensures appropriate reproducibility of product characteristics, and such testing is adequate to assess the effects of manufacturing changes in many cases. Supplemental characterization, using an appropriate combination of methods outlined in section IIB, may be warranted for some critical manufacturing parameters. Gilead believes in vivo studies should only be considered if the physicochemical testing of product noted elsewhere in the guidance, or other elements of the change, indicate that an in vivo effect might be possible.</p> <p><b>Proposed Statement:</b> Additional statements and modification of existing statement after sentence ending “...should be identified and evaluated” in Line 108: <u>“To support manufacturing changes, physicochemical characterization of the liposome drug product is required. In general, this can be accomplished with the routine control tests for ensuring product quality of each batch, supplemented with additional tests from section IIB that are relevant to the nature of the manufacturing change and its potential effects on the product. If there are changes in critical manufacturing parameters, complete characterization of the liposome drug product is recommended, as outlined in section II.B. <del>If there are changes in critical manufacturing parameters, complete characterization of such</del> characterization indicates some change in the performance or characteristics of the liposomal drug product, is recommended and in vivo studies may be warranted (see section...”</u></p> <p><b>Objective of the Proposed Statement:</b> To clarify the requirement.</p>
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DOCUMENT	COMMENT
Line 115	<p><b>Issue:</b> The statement on “product-specific validation studies” requirement may require too much material to be feasible for investigational new drug (IND) products.</p> <p><b>Proposed Statement:</b> Additional statement at end of sentence in Lines 115-116. “.....of the intended sterilizing filters. <u>For liposome drug products in IND phases where adequate material may not be available, an appropriately justified surrogate with comparable physical and chemical characteristics may be used.</u>”</p> <p><b>Objective of Proposed Statement:</b> To clarify the requirement.</p>
Lines 121-122	<p><b>Issue:</b> Application of API level characterization to lipid components will, in most cases, be too stringent a requirement even for liposomes intended for PK/TD alteration. It has been Gilead experience that specifications and test methods used in demonstrating sufficient lipid product quality typically lie between those for more ordinary excipients and drug substances. The requirement to treat lipid components as a drug substance is certainly too stringent in cases where the liposome is utilized only as a solvent without intention or effect of altering PK/TD. Therefore, Gilead proposes to exclude such formulations from this guideline.</p> <p><b>Proposed Statement:</b> “Information concerning the CMC of the lipid components should be provided <del>at the same level of</del> <u>in sufficient detail expected for a so as to ensure the performance and integrity of the liposomal drug product produced, in some cases approaching the level of that provided for the drug substance.</u>”</p> <p><b>Objective of Proposed Statement:</b> To accommodate other lipid component uses and scenarios in the criteria for lipid characterization.</p>
Line 133	<p><b>Issue:</b> HSPC is a highly purified natural lipid and may also be cited in the statement.</p> <p><b>Proposed Statement:</b> “If the lipid is a well-defined synthetic, semisynthetic, or highly purified natural lipid, such as dimyristoylphosphatidylcholine (DMPC) or <u>hydrogenated soy phosphatidylcholine (HSPC).</u>...”</p> <p><b>Objective of Proposed Statement:</b> To include an example of a highly purified natural lipid.</p>
Lines 135-137	<p><b>Issue:</b> Regarding the statement on natural lipid mixtures and fatty acid composition, the fatty acid compositions of natural phospholipids conform to ranges of compositions, not absolute compositions.</p> <p><b>Proposed Statement:</b> “In the case of natural lipid mixtures (e.g. egg lecithin), <u>the natural range of the lipid composition (i.e., the percentage of each fatty acid) should be provided.</u>”</p> <p><b>Objective of Proposed Statement:</b> To clarify the requirement.</p>

DOCUMENT	COMMENT
Lines 194-196	<p><b>Issue:</b> The statement on stress testing assumes predictive chemical properties of lipids above the transition temperature.</p> <p><b>Proposed Statement:</b> Additional statement at end of sentence in Lines 194-196: “...should be performed to determine the degradation profile. <u>Testing at temperature(s) near or above the phase transition temperature(s) may not be relevant to storage below this (these) transition temperature(s).</u>”</p> <p><b>Objective of Proposed Statement:</b> To account for potential issues in temperature studies.</p>
Lines 220-221	<p><b>Issue:</b> The requirement on application of CDER and ICH stability testing guidances to liposome drug products does not recognize that specific provisions in these guidance documents may not be relevant or applicable to liposome products.</p> <p><b>Proposed Statements:</b> Modification of statement in Lines 218-221 and additional statement at end of sentence: “.....New Drug Substances and Products apply <u>generally</u> to the design of stability studies for liposome drug products. <u>However, there may be limitations to the value of data collected at accelerated temperatures if and when lipid bilayer phase transitions are occurring between the storage and proposed accelerated temperature conditions.</u>”</p> <p><b>Objective of Proposed Statements:</b> To account for potential issues in temperature studies.</p>
Lines 223-224	<p><b>Issue:</b> Regarding stability study of unloaded liposomes, Gileads believes that the study of empty liposomes should only apply to remote loaded drug products.</p> <p><b>Proposed Statement:</b> “.....before use) should also be performed. <u>Such testing only applies to drug products that include empty liposomes (e.g. remote loaded products).</u>”</p> <p><b>Objective of Proposed Statement:</b> Clarification as the study of empty liposomes is of limited value and relevance to non-remote loaded liposomal drug products.</p>
Lines 228-229	<p><b>Issue:</b> The statement on the physical stability of liposome drug product being a function of integrity and size distribution of the lipid vesicles is scientifically inaccurate.</p> <p><b>Proposal:</b> Delete statement.</p> <p><b>Objective of Proposal:</b> To enhance document clarity.</p>
Lines 229-230	<p><b>Issue:</b> The statement on liposome susceptibility “to fusion, aggregation, and leakage” is not always true.</p> <p><b>Proposed Statement:</b> “Liposomes <u>may</u> be susceptible to fusion, aggregation, flocculation, and/or leakage of the encapsulated drug substance during storage.”</p> <p><b>Objective of Proposed Statement:</b> To enhance accuracy and clarity of statement.</p>
Lines 230-231	<p><b>Issue:</b> The statement “For instance, small unilamellar vesicles are more susceptible to size changes than are multilamellar vesicles” is incorrect.</p> <p><b>Proposal:</b> Deletion of statement.</p> <p><b>Objective of Proposal:</b> To remove a statement that is incorrect.</p>

DOCUMENT	COMMENT
Lines 231-234	<p><b>Issue:</b> Statement on “The type of lipids in the bilayer” could be improved for better clarification.</p> <p><b>Proposed Statements:</b> “Also <u>The type of lipids in the bilayer or the encapsulated drug substance, and the particle size, are some of the many factors that 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 drug retention and size of liposomes.</u>”</p> <p><b>Objective of Proposed Statements:</b> To enhance accuracy clarity and of statement.</p>
Lines 261-262	<p><b>Issue:</b> The in vivo studies requirement statement needs to be associated with the language proposed for lines 108-110 above.</p> <p><b>Proposed Statement:</b> “In vivo studies may be warranted to demonstrate that the changed product is equivalent to the original product with respect to safety and efficacy <u>e.g. for cases where physicochemical testing indicates some change in the properties of the drug product.</u>”</p> <p><b>Objective of Proposed Statement:</b> To provide consistency with the proposed changes in lines 108-110.</p>
Page 7, Footnote 6	<p><b>Issue:</b> The statement in the footnote needs further agency clarification.</p> <p><b>Objective:</b> Enhance document clarity.</p>
Section III Line 277	<p><b>Issues:</b> Gilead has the following general comments for this section.</p> <ol style="list-style-type: none"> <li>1. This section should include recommendations that apply to both nonclinical ADME studies and Human pharmacokinetics.</li> <li>2. The term bioavailability utilized throughout this section appears to have been used in place of the term “delayed release”. If there is no metabolism of a drug substance, the bioavailability of it in a liposome encapsulated formulation will be 100%.</li> </ol> <p><b>Proposals:</b> See more specific proposals covering Lines 277–444 below.</p> <p><b>Objective of Proposal:</b> To clarify objectives of this section</p>

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Lines 279-282	<p><b>Issues:</b></p> <ol style="list-style-type: none"> <li>1. The requirement to provide bioavailability data specifically for a liposome drug product is unnecessary. Liposome encapsulation will not affect bioavailability since these products are administered parenterally. Assessment of bioavailability of the encapsulated/intercalated drug substance, for example as a result of metabolism, would be expected in accordance with routine ADME requirements.</li> <li>2. In addition to the usual requirements, ADME assessment for a liposome encapsulated drug product must also take into consideration data from either or both the drug substance and liposome structure if they have been included in submissions for previously approved drug products.</li> </ol> <p><b>Proposed Statements:</b> Addition of the following statements immediately after sentence ending "...and bioavailability data apply (see 21 CFR 314.50, 320.21, and 320.29)" in Line 280.</p> <ol style="list-style-type: none"> <li>1. <u>Additionally, pharmacokinetic assessment of both the liposome encapsulated and unencapsulated forms of the drug substance (active pharmaceutical ingredient) may be necessary, particularly if liposomal formulation produces delayed or controlled release of the drug substance into plasma and/or tissues.</u></li> <li>2. <u>If either or both the drug substance and liposome structure of the new formulation is/are identical to other approved drug product formulation(s), comparison with this data may be necessary to delineate differences in drug metabolism, distribution, or excretion of the new formulation.</u></li> </ol> <p><b>Objectives of proposed Statements:</b> To enhance document clarity.</p>
Lines 298-325	<p><b>Issue:</b> The concept of <i>in vivo</i> stability as described in this section is not applicable to most liposomal formulations. Liposomal encapsulation generally produces delayed release of the drug substance. The structure of the liposomal membrane may be altered to produce very fast or very slow release. Therefore, it is more appropriate to conduct single and repeated dosing studies to establish the concentration profiles of total, encapsulated and unencapsulated forms of the drug substance in plasma (if possible).</p> <p><b>Proposals:</b> See specific line proposals below.</p> <p><b>Objectives of proposals:</b> To enhance document accuracy and clarity</p>
Lines 298	<p><b>Proposal:</b> Modify title text to: <b><i>In Vivo</i> Integrity (Stability) Considerations Disposition of Drug Substance</b></p>
Lines 300-301	<p><b>Proposal:</b> Delete sentence beginning "In addition to the general stability considerations of the..." in Line 300 and replace with following. "<u>Since liposomal encapsulation generally produces delayed release of the drug substance, the PK profile should, when possible, include measurements of both encapsulated and unencapsulated drug substance in single-dose and repeated-dosing studies. The applicant should provide justification if bioanalytical methods to distinguish between encapsulated and unencapsulated fractions of the drug substance cannot be developed.</u>"</p>

DOCUMENT	COMMENT
Lines 303-308	<b>Proposal:</b> Delete sentences within whole paragraph and replace with following. <u>“If bioanalytical methods are available to measure both encapsulated and unencapsulated drug substance, the <i>in vivo</i> PK profile of both fractions in plasma should be determined. Both single-dose and repeated dosing studies should be performed. Whenever possible, measurements should be obtained for both fractions at a sufficient number of timepoints to establish an accurate profile for the liposome form of the drug substance. The measurements should also be used to confirm the profile of free drug released from the liposomes as expected from studies of non-liposome active.”</u>
Lines 310-319	<b>Comment:</b> The consideration that a liposome is stable or unstable based upon its PK profile is not useful for interpretation of its ADME. In Gilead’s experience it would be highly unusual for the ratio of unencapsulated to encapsulated drug substance to remain constant. The liposomes may be formulated to release drug by leakage at various rates and the released drug may be one that clears rapidly. Furthermore, liposomes may rupture in plasma releasing drug substance directly into the plasma or be cleared intact by the mononuclear phagocytic system after which the drug substance is exported back into the plasma. <b>Proposal:</b> Delete whole section within Lines 310-319 since they are redundant to proposed lines 303-308.
Lines 323-325	<b>Issue:</b> Additional agency clarification is required on what “bioavailability” means in this guidance as this term typically derives from oral, not parenteral, dosage forms. If the degree of encapsulation <i>in vivo</i> is meant by “bioavailability,” this needs to come out clearer. See comments above for Line 277 and for Lines 279-282. <b>Objective:</b> Enhance document clarity and accuracy.

DOCUMENT	COMMENT
Lines 327-335	<p><b>Issue:</b> The “Protein Binding” studies requirement is in conflict with current positions throughout the liposome literature. There are currently no broadly acceptable methods or firm conclusions on liposome protein binding phenomena. While the issue remains an important academic question, the science so far generated has not afforded anything of utility in the development of pharmaceutical drug products along the lines indicated in lines 327-335. The core issues at hand are the safety and PK/TD of the drug which are directly evaluated, rather than protein binding which is part of a large body of mechanistic considerations.</p> <p><b>Proposal:</b> Replace sentences within Lines 329-335 with the following. <u>“If a particular construct can only be stabilized against in vivo degradation by coating it with a surface modifier to minimize or prevent protein binding, protein binding studies of this stabilizing effect maybe relevant. In general, however, in vivo studies of toxicity and PK/TD are sufficient for assessing the fate of liposomal drug on injection. Additional more detailed studies of such factors as tissue distribution, cellular uptake and protein binding may be required for specific formulations.”</u></p> <p><b>Objective of Proposal:</b> Enhance document clarity and accuracy.</p>
Line 350	<p><b>Issue:</b> This section describes assessment of parameters other than PK and bioavailability</p> <p><b>Proposal:</b> Change title text to: <u>“ADME and Clinical Pharmacokinetics and Bioavailability”</u></p> <p><b>Objective of Proposed Statement:</b> To enhance document clarity.</p>
Lines 355-388	<p><b>Issue:</b> Entire section on “Mass Balance Study” requirements is needs additional Agency clarifications. Isotopic labels of the type desired are not always available and exclusion of new chemical entity (NCE) from the requirements is essential. If therapeutic efficacy and safety are being determined de novo, it may be redundant to require more than the normal clinical/non-clinical evaluation relative to other IV formulations.</p> <p><b>Proposal:</b> Agency may need to revise section for clarity and practicality considerations.</p> <p><b>Objective of Proposal:</b> To enhance document clarity and accuracy.</p>
Line 375	<p><b>Issue:</b> The use of Absorption (in ADME) as stated in Line 375 is not a term typically applied to parenteral drugs. Additional agency clarification may be required by users of this guidance on what is meant by “absorption” in this context.</p> <p><b>Objective:</b> Enhance document clarity.</p>
Line 429.	<p><b>Issue:</b> In its over 10 years of experience, Gilead has not become aware of any evidence in which food has an impact on the PK/TD of liposome parenterals relative to other parenterals.</p> <p><b>Proposal:</b> Provision of additional agency clarification on this concept will greatly assist users of this guidance.</p> <p><b>Objective:</b> Enhance document clarity.</p>

Lines 455-462	<p><b>Issue:</b> The section on “Product Name” needs further agency clarification. Of note is the subjectivity with which such labels have been applied in the past, and the general disagreement within the academic liposome community with respect to the meaning of such subjective labels. For example, the term “Conventional” or terminology reflecting proposed interaction of the liposome with the RES/MPS system are both subjective and of minimal value in use on a product label. It is also important to note that liposomes of very different origin can exhibit similar performance properties in vivo. In this regard, both so-called “conventional” liposomes (e.g. Gilead’s investigational product MiKasome) and commercial liposomal products (e.g. Doxil), exhibit very long half lives in Man. Consequently, even if these categories are constructed as guides for classification, there will probably not be adequate data soon to distinguish between general characteristics of approved drug products.</p> <p><b>Proposal:</b> Provision of additional Agency clarification. Perhaps provision of a “Guides” for liposome type classification in a “Glossary” to assist manufacturers in generating accurate labeling statement for their liposome formulation as demanded by this guideline.</p> <p><b>Objective of Proposal:</b> Enhance document clarity.</p>
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