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SENT VIA EMAIL [Zhoul@cder.fda.gov]

April 24, 2003

Dr. Liang Zhou
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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm, 1061
Rockville, MD 20852

RE: Guidance for Industry, Liposome Drug Products (Draft Guidance)

Subject: Comments and suggestions

Dear Dr. Zhou:

To follow up on our telephone conversation of April, 23, I wanted to thank you for offering to review my comments and suggestions on the Draft Guidance concerning Liposome Drug Products. I regret I was unable to provide these comments at an earlier date. I have extensive personal experience in the preclinical and clinical development of liposomal drug products over the past 15 years, and hope these comments can be of use in developing your final Guidance.

In general, the Draft Guidance is well written, and identifies the most important issues in developing liposomal drug products. My comments apply mainly to the Pharmacokinetics and Bioavailability section, and focus on how to characterize liposomal products in a way that provides relevant information for understanding the unique safety, activity and clinical properties of each liposomal drug.

I have summarized the comments in the following tabular format. Please feel free to contact me if you have any questions concerning any of the comments.

Again, many thanks for the opportunity to offer this input.

Sincerely,

Robert M. Fielding
Biologistic Services

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Comments and Suggestions, Draft Guidance for Industry, Liposome Drug Products

Line No./ Text reference	Comments	Proposed Change
Line 47-50 (also Lines 392-394) "A drug substance in a liposome formulation is intended to exhibit a different pharmacokinetic and/or tissue distribution (PK/TD) profile from the same drug substance...in a nonliposomal formulation given by the same route..."	While this is frequently true, it is not always the case. Liposome formulations have been under development whose function is primarily to provide an improved formulation vehicle. For example, to replace potentially toxic excipients such as Cremophor, to provide aqueous preparations of extremely insoluble drugs, or to increase drug product stability or quality. In such cases, drugs may be formulated in liposomes that rapidly release the drug after administration, with no intended alteration in drug disposition versus a non-liposomal form. In addition, some liposomal formulations may claim to significantly alter the disposition of encapsulated drug, when in fact they do not. Some formulations of so-called "long circulating" liposomes have been shown to leak extensively after i.v. administration.	I would suggest the following addition to your recommendation in line 52: "It is also important to compare the PK/TD profiles of the liposomal drug with a nonliposomal or conventional formulation to demonstrate if and to what extent the liposomal formulation alters the disposition of the drug substance in its intended use."
Lines 93-101 List of Physicochemical Properties unique to liposome drug products	I would suggest the addition of "Percent or Amount Encapsulated or Liposome-associated Drug". In some instances, this would be a measure of the fraction of total drug contained inside the liposomal bilayers or aqueous compartment. For some drugs there may be more than one pool of liposome-associated drug, an encapsulated pool and a surface-bound pool.	Add: "Percent or Amount Encapsulated or Liposome-associated Drug".
Lines 310-319 "The liposome is considered stable in vivo if, over the time course of the single-dose study, the: drug substance, when in circulation, remains substantially in the encapsulated form, [or the] ratio of unencapsulated to encapsulated drug substance remains constant.	While I agree in principle with the intent of this section, I believe it is likely to be unworkable in practice, and would strongly recommend that the Guidance Document be reworded to suggest a case-by-case approach to the issues of liposome stability, and measurement of total vs. unencapsulated drug fractions, for the following reasons. First, the definition of liposome stability presented is neither clear-cut nor amenable to simple quantitation. Liposomes undergo multiple interactions upon injection that can alter their	Change to: "The stability of the liposomal drug product should be evaluated in vivo, after administration by its intended route. The residence times of liposomes and liposomal drug in the circulation, and the extent and rate at which encapsulated drug is lost from the liposomes should be evaluated to determine which measurements are necessary to establish the disposition profile of the liposomal drug.

Line No./ Text reference	Comments	Proposed Change
When the liposome is stable in vivo, the total drug substance concentration can be measured to determine the pharmacokinetics and bioavailability. However, for an unstable liposome drug product, the concentration of both encapsulated and unencapsulated drug substance should be measured"	composition, drug content and other properties. Liposomal distribution is often non-linear with dose and/or time. While some liposomes display mono-exponential plasma profiles, the presence of rapid and slow elimination for other liposomes has been taken as evidence for non-homogeneity in composition, saturation of uptake mechanisms or other non-linear properties. Second, even the fact that most of the circulating drug is encapsulated does not demonstrate liposome stability. For example in a clinical study of liposomal daunorubicin which measured total and nonliposomal drug, nearly all the drug in plasma appears to be liposomal[1]. However, further analysis of the short half-life (5 hr), and the reported exposures to free drug and metabolite suggest that a substantial fraction of the drug "leaked" rapidly from the liposomes. Yet because the non-liposomal drug has a volume of distribution much higher than the liposomes, most of the nonliposomal drug rapidly entered the tissue compartment after being leaked. Thus, while a comparison of liposomal vs. nonliposomal drug in plasma would suggest stability, a comparison of liposomal to nonliposomal drug in the body would suggest otherwise. Third, using the ratio of unencapsulated to encapsulated drug to define stability may also be difficult in practice. Even for a relatively stable liposome, this ratio may change over time, as the concentrations of liposomal and nonliposomal drug change over time at different rates[2]. For example, a recent study quantitated pools of liposomal, protein-bound and free drug after administration of liposomal Amphotericin B to volunteers[3]. These long-circulating liposomes maintained liposomal drug in the plasma for over one week after administration, clearly demonstrating their stability. Yet the ratio of liposomal drug to total drug in plasma was never constant, and fell from 97% initially to 55% at the end of the one week study.	These may include measurements of total drug, liposome-associated drug, free drug , protein bound drug or total nonliposomal drug over time in the circulation and in the appropriate tissues. The disposition of liposomal drug should be compard to that of nonliposomal drug when possible, to establish how the liposome alters the drug's disposition."

Line No./ Text reference	Comments	Proposed Change
	Rather than attempting to define "stable", I would suggest treating the issue of stability as one of degree. The Guidance should emphasize that PK data needed to support a liposomal drug should include an adequate characterization of the in vivo disposition of the liposomes, the liposomal drug and the non-liposomal drug over time in the circulation and in the appropriate tissue compartments[4]. The fraction of the administered liposomes remaining in circulation at various time points, and the fraction of liposomal drug released from the liposomes over time would be important components of this analysis. The relative plasma or blood exposures (Cmax, AUC) to liposome-associated and nonliposomal drug should be determined and, when possible, compared to the exposures achieved after a similar dose of nonliposomal drug.	
Line 327 "Protein Binding"	This section should be clarified by dividing it into two sections, "Protein Binding" and "Protein Interactions". The "Protein Binding" section should recommend that the protein binding characteristics of the drug substance be determined for liposomal drugs, as they would for nonliposomal drugs. These characteristics are intrinsic to the drug substance, and are important for defining the disposition of the drug after it is released from the liposome. In some cases, high concentrations of liposomes, or liposomal lipids could affect binding of nonliposomal drugs, especially to lipoproteins. If thought to occur, these interactions should also be characterized. The section "Protein Interactions" would include data from investigations on the interaction of plasma proteins with liposomes in vivo, transfer of liposomal lipids to(lipo)proteins or altered levels of plasma proteins caused by liposomes.	"Protein Binding. After release from liposomes in vivo, drugs may interact with plasma proteins. As for nonliposomal drugs the plasma protein binding of drugs used in liposome products should be determined. Plasma protein binding may need to be determined in the presence of liposomes or liposomal lipids. Protein Interactions. Liposome stability in vivo can be affected by interactions with plasma components, including proteins and lipoproteins. Since these interactions depend on liposome composition and properties, it may be necessary to evaluate the extent to which plasma proteins and lipoproteins interact with the liposomal product at therapeutic concentrations, to identify the protein species involved, and to measure the extent of transfer of liposomal lipids to plasma (lipo)proteins."

Line No./ Text reference	Comments	Proposed Change
Line 363 "The disposition and pathways of elimination ... and several important pharmacokinetic measures (Cmax, AUC) and parameters (clearance, volume, half-life)"	The Guidance makes an important distinction between PK measures (Cmax, AUC) which are directly observed, and parameters (CL, Vd, half-life) which are calculated. This is especially important for characterization of liposomal products. While directly observed measures (Cmax, Ct, AUC) appear unequivocal, the calculation and interpretation of PK parameters such as clearance and volume assumes a certain physiologic relevance, which may not apply to liposomes. While it is essential to characterize the PK profile of liposomal drugs, it is important to realize that calculation of PK parameters by plugging data into "standard" equations may yield numbers with little physiologic relevance. For example, it has been shown that "standard" pharmacokinetic volumes of distribution for liposomal drugs can differ substantially from their physiologic volume of distribution[5]. A similar limitation may apply to the calculation of liposomal "clearance", especially in cases of multi-exponential plasma disposition. For these reasons, pharmacokinetic comparisons of liposomal drug formulations with nonliposomal formulations (and with other liposomal formulations) should justify the parameters used in the comparison and their method of calculation. ADME studies of liposomal drugs should be designed to provide detailed information on the disposition of the liposomes, liposomal drug and nonliposomal drug, rather than to provide uninterpreted values of "standard" PK parameters.	"The disposition and elimination (including metabolism and excretion) of liposomal drugs should be investigated under conditions of intended use. Disposition of the liposomal drug should be compared to nonliposomal drug administered by the same route to established the effect of the liposomal formulation, if any, on disposition. The amount of drug in liposomal and nonliposomal pools should be measured over time. The use of empirically observable measures (Cmax, Ct, AUC and half-life) is preferred. The calculation of clearance, volume of distribution and other PK parameters for liposomal drugs should be justified on a physiologic basis. The disposition of the liposomes, and/or liposomal lipid should be considered in the mass balance study, as the plasma residence times of liposomal drug and lipid may differ"

Line No./ Text reference	Comments	Proposed Change
Line 366 "Although no examples currently exist, absorption could also be altered for liposome drug product when given via non-intravenous routes".	Administration of liposomes by non-intravenous routes has been widely investigated. Inhaled and injectable depot formulations have reached clinical trials, and topical liposomes are marketed in some countries. A recent study compared the absorption and distribution profiles of one liposome formulation after i.v., i.p., i.m., s.c. and i.t. administration[6]. The results demonstrate that liposomes altered the disposition of the drug after all routes of administration, and that significant differences exist between routes.	Replacing the sentence with the following: "Liposomes can be systemically absorbed after non-intravenous administration, and/or alter the absorption pattern from that of nonliposomal drug and from intravenous liposomal drug. The pharmacokinetic profile of liposomes administered by extravascular routes should be evaluated as described above, and compared to intravenously administered liposomes if there is evidence that the liposomes are systemically absorbed."
Line 384 "Both parent drug substances and any metabolites present should be quantitated"	In addition to drug and metabolites, the fate of the liposomal lipids should be investigated during the ADME and mass balance studies. The maximum levels of lipids in plasma and their form (i.e., liposomes vs. lipoprotein-bound) should be determined during maximum exposure safety studies. The extent of further studies could be guided by safety and pharmacokinetic information. For example, non-naturally occurring lipids, lipids with known pharmacologic activity or highly elevated lipid levels may necessitate more detailed studies on metabolism and excretion of liposomal lipids to support the product's safety.	Add: "ADME studies to address the fate of liposomal lipids should be performed where appropriate, for example where there are safety issues, novel lipids or very high lipid concentrations in plasma."
Line 423 "Additional Pharmacokinetic Studies"	To those listed, the following studies should also be considered, on a case-by-case basis: 1) Studies to define the extent of interindividual variability in liposome disposition (previous human and animal studies have shown occasional instances of individuals with markedly higher or lower AUCs for liposomal drugs). 2) Studies to determine the sensitivity of liposomal drug disposition to formulation changes (some formulations have been shown to be more sensitive to changes in particle size, drug loading etc. than others)	Add: "1) Studies to define the extent of interindividual variability in liposome disposition 2) Studies to determine the sensitivity of liposomal drug disposition and safety to changes resulting from lot-to-lot differences or during ageing."

REFERENCES

[1] Mukwaya G, Grasela TH, Fiedler-Kelly J, Jiang C, Chan K and Ross ME. A Population pharmacokinetics study of liposomal daunorubicin (Daunoxome) in patients with AIDS-related Kaposi's sarcoma. NCI-EORTC meeting, March 1996, Abstr. 339.

[2] For example, the ratio of free to encapsulated drug depends on the rate of leakage from liposomes, the residence time of the liposomes and the rates at which nonliposomal drug is distributed to and eliminated from the body.

[3] Bekersky I, Fielding RM, Dressler DE, Lee JW, Buell DN, Walsh TJ. Plasma protein binding of amphotericin B and pharmacokinetics of bound versus unbound amphotericin B after administration of intravenous liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate. Antimicrob. Agents Chemother. 46: 834-840 (2002).

[4] At the present time, methodology for determining free and liposomal drug concentrations in tissues is limited.

[5] Fielding RM. Relationship of Pharmacokinetically-Calculated Volumes of Distribution to the Physiologic Distribution of Liposomal Drugs in Tissues: Implications for the Characterization of Liposomal Formulations. Pharm. Res. 18: 238-242 (2001).

[6] Fielding RM, Moon-McDermott L, Lewis RO. Bioavailability of a Small Unilamellar Low-Clearance Liposomal Amikacin Formulation after Extravascular Administration. J. Drug Targeting. 6: 415-426, 1999.