

Pharmaceutical  
Division

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

**RE: Docket No. 02D-0337  
Draft Guidance for Industry on Liposome Drug Products: Chemistry,  
Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability;  
and Labeling Documentation; Availability**

Dear Sir or Madam:

The Bayer Corporation Pharmaceutical Division has reviewed the FDA's Draft Guidance for Industry on Liposome Drug Products noted above. At this time we are providing our comments to this draft guidance.

If you have any questions please contact me at (203) 812-2681.

Sincerely,



Frederich K. Sundermann  
Deputy Director, Regulatory Affairs

02D-0337

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**Comments on FDA's Draft Guidance for Industry on Liposome Drug Products:  
Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and  
Bioavailability; and Labeling Documentation; Availability**

**I. Introduction**

*47-52 "A drug substance in a liposome formulation is intended to exhibit a different pharmacokinetic and/or tissue distribution profile..."*

A differentiation should be made between liposome drug products intended to achieve drug targeting and/or to modify PK/TD profile and immediate release products (liposomes solely for solubilization purposes). If a liposome formulation is chosen, for a drug substance with a low solubility, to dissolve the drug substance for parenteral administration only a reduced characterization of the physicochemical properties and a reduced PK program should be required. If it can be shown *in vivo* that the liposomes release the entire amount of drug immediately, a number of the additional studies mentioned in the guideline would not be necessary. Therefore, it would be useful to divide the guideline into two sections:

- i. liposomes intended for modified release and/or drug targeting and,
- ii. liposomes intended for immediate release and solubilization of poorly soluble drugs,

and outline the study program for both scenarios.

**B. *In-Vivo* Integrity**

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

The statement "stable *in-vitro* if, over the time course of the single dose study" is unclear. This could be the study day including or excluding follow-up, (e.g. it could be a 24 hr or 48 hr interval).

*316 "When the liposome is stable in-vivo..."*

The definition of "stability" in this draft guideline relates to liposomes intended for drug targeting. The definition of 'stability' should also take into consideration instances where the liposomes are manufactured strictly as a vehicle for i.v. administration of a poorly soluble drug and thus, are not stable *in-vivo*.

#### **D. *In-Vitro* Stability**

337-348

Since the conditions of such an *in-vivo* test (matrix, number of replicates, timing of sample collection etc.) have not been defined in Pharmacopoeias, it would be helpful to outline the experimental plan of the proposed experiment.

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

350-444

This section only refers to the case where a marketed non-liposome formulation of a given drug is already available and the liposome formulation is developed secondary to the approved formulation. Comparing both formulations is the main focus in this section. This guideline should also reflect situations where the liposome formulation is developed as the first formulation of the drug to be approved.