

Aventis Pharmaceuticals



November 15, 2002

Via fax and UPS

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Draft Guidance for Industry on Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation [67FR 54220, August 21, 2002]

Dear Sir/Madam:

Aventis Pharmaceuticals Inc. appreciates the opportunity to comment on the above-referenced draft guidance entitled "Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation".

This draft guidance provides recommendations to applicants on the chemistry, manufacturing, and controls (CMC); human pharmacokinetics and bioavailability; and labeling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. The development of the draft guidance on liposome drug products is welcomed. The underlying principles are generally sound and acceptable. We offer the following comments/clarification for your consideration.

02D-0337

CS

I. INTRODUCTION

Page 2, lines 47 to 50

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 (or active moiety) in a nonliposomal formulation given by the same route of administration.

We agree that a drug substance in a liposome formulation is usually intended to exhibit a different PK/TD profile from the same drug substance in a nonliposomal formulation given by the same route of administration, but a liposome formulation could also be developed for solubilization purpose only (with immediate drug release). We propose rewording this sentence as follows:

*A drug substance in a liposome formulation is **not exclusively** intended to exhibit a different pharmacokinetic and/or tissue distribution (PK/TD) profile from the same drug substance (or active moiety) in a nonliposomal formulation given by the same route of administration.*

II. CHEMISTRY, MANUFACTURING, AND CONTROLS

B. Physicochemical Properties

Page 3, line 95

- *volume of entrapment in liposomal vesicles*

We agree that the volume of entrapment is an important property that is useful to assess for a drug substance encapsulated in an inner aqueous compartment. However, for a hydrophobic drug substance located in the lipid bilayer, this characteristic is less relevant, and as a consequence its characterization not critical.

We propose rewording this bullet point as follows:

- *volume of entrapment in liposomal vesicles, **if applicable***

C. Description of Manufacturing Process and Process Controls

Page 3, lines 115 to 116

Therefore, product-specific validation studies should demonstrate the microbial retentivity of the intended sterilizing filters.

We would like to have further clarification on what kind of product-specific validation is needed. What does the Agency expect more than for classic sterile drug products produced by aseptic processing?

D. Controls of Excipients: Lipid components

3. Specifications

Page 5, lines 169 to 170

The level that would warrant identification and qualification will be determined on a case-by-case basis.

Would it be possible to indicate a target level for impurities identification and qualification (or a range depending on whether the lipid is from a natural or synthetic origin)?

Page 5, lines 179 to 189

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

For natural lipid mixtures, does the Agency expect a target purity (minimal value) for the main lipid component?

E. Controls of Drug products: Specifications

Page 6, line 212

- *assay of lipid components*

Would it be possible to precise to which extent lipid components need to be assayed in the drug product?

For instance, would the Agency accept that for natural phospholipids only the main component is assayed in the drug product itself, in addition to degradation by-products, based on the fact that the full characterization is performed on the excipient itself?

III. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

D. In Vitro Stability

Pages 8 and 9, lines 339 to 348

A validated in vitro test method should be established that uses an appropriate simulated physiological medium and/or human plasma and acceptance criteria for the in vitro release of the drug substance from the liposome. An in vitro test that measures the release of the drug substance from the liposome can be important for assessing the (1) quality of a liposome drug product, (2) adequacy of the process controls, (3) release characteristics of the product over time, and (4) the effect of CMC changes (e.g., minor manufacturing process changes or change in site of manufacture). As experience is gained in the manufacturing of a liposome drug product, an in vitro test, rather than an in vivo test, may be useful in characterizing the liposome drug product when manufacturing changes are made.

The Agency is expecting an in vitro test method using appropriate simulated physiological medium and/or human plasma. Does this mean that a correlation needs to be established between in vitro and in vivo behaviours? What does the Agency expect to be part of the validation for this in vitro method?

On behalf of Aventis Pharmaceuticals Inc. we appreciate the opportunity to comment on the draft guidance for Industry on Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation and are much obliged for your consideration.

Sincerely,



Steve Caffé, M.D.

Vice President, Head US Regulatory Affairs