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October 24, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration (FDA)
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
U.S.A.

Re: Comments on the draft guidance "Guidance for Industry Liposome
Drug Products".

Dear Sir:

The enclosed document is the summary of our comments on the draft
guidance "Guidance for Industry Liposome Drug Products" issued by FDA.
This document prepared by using Microsoft(R) Word 98 is also sent to
FDA(coryj@cderr.fda.gov) by e-mail today.

We would be much obliged if you give us FDA review of our comments by
letter or by e-mail.

We sincerely hope that our comments will contribute to completion of the
finalized 'GUIDANCE'.

Sincerely,

A handwritten signature in cursive script that reads 'Masaharu Miyajima'.

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02D-0337

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Comments on Guidance for “Industry Liposome Drug Products”

**Terumo Corporation
2002.10.24**

1. (General):

Glossary and definition for important terms should be added into the guidance.

2. (General):

Although this guidance serves to identify the CMC information that should be submitted in an NDA, it also indicates that some information will also apply to the IND. We recommend that the guidance clearly indicate the extent of the requirements for the IND and the requirements for the NDA. For example, the guidance indicates that ‘the analytical procedures should be validated and the specification should include a stability-indicating assay.’ It would be more useful to indicate what level of validation/specification of the stability-indicating assay is required for the IND and what level is required for the NDA.

3. (Introduction)(Line 43):

Drug substances (active pharmaceutical ingredients) encapsulated in liposomes do not necessarily have a pharmacological action such as enzymes and hemoglobin. Therefore We feel that it would be better to change the words “drug substances (active pharmaceutical ingredients)” in Line 43 to the words “drug substances (active

pharmaceutical ingredients) or functional substances”.

4. (Introduction)(footnote 4):

The word "drug-lipid complexes" is defined as follows: “mixing a drug with lipids in such a way that true liposomes are not created”. Strictly speaking, liposomes are supposed to be formed under certain conditions in the mixing process. Therefore, we propose a more precise definition of "drug-lipid complexes" should be based on description of physicochemical properties. For example, drug-lipid complexes are formed by mixing a drug with lipids, which do not form a liposome structure.

5. (CHEMISTRY, MANUFACTURING, AND CONTROLS (A. Description and Composition))(Line 74-76):

It is not necessary to indicate all of four notations. Molar ratio and percentage, for example, are certainly different words, but both words describe the same quality of the liposome by using different physical unit. Therefore, we recommend changing “molar ratio and percentage” to “ molar ratio or percentage” and “per milliliter (mL) and per vial basis” into “per milliliter (mL) or per vial basis”.

6. (CHEMISTRY, MANUFACTURING, AND CONTROLS (A. Description and Composition))(Line 80):

This guidance states that any specified ranges for a component should be justified. Please include examples of what constitutes valid evidence or justification for specified ranges (e.g., based on actual measurement value of three Lots manufactured by production scale).

7. (CHEMISTRY, MANUFACTURING, AND CONTROLS (B.

Physicochemical Properties))(Line 94):

Please describe more concrete or specific examples of net charge (line 94) such as zeta-potential.

8. (CHEMISTRY, MANUFACTURING, AND CONTROLS (B. Physicochemical Properties))(Line 98):

Please describe more concrete or specific physicochemical properties that are determined by using “spectroscopic data”.

9. (CHEMISTRY, MANUFACTURING, AND CONTROLS (B. Physicochemical Properties))(Line 101):

Please describe more concrete or specific physicochemical properties that are determined by using “light scattering index”.

10. (CHEMISTRY, MANUFACTURING, AND CONTROLS (C: Description of Manufacturing Process and Process Controls))(Line 112-116):

“Sterility” and “Control of Endotoxin” are very important properties of liposome drug products. We recommend using such headings as “Sterility” and Control of Endotoxin” and we propose a more detailed description of these properties.

11. (CHEMISTRY, MANUFACTURING, AND CONTROLS (D. Control of Excipients: Lipid Components))(General):

Although there is a detailed description of lipid as an additive agent, there is no description about other ingredients. Other agents/ingredients can significantly influence the characteristics of the

liposome, (for example, PEG-lipid). Therefore, please also take into consideration the description of additive agents other than lipid.

12. (CHEMISTRY, MANUFACTURING, AND CONTROLS (D. Control of Excipients: Lipid Components))(Line 120):

Does the Lipid Components described in section II-D (Control of excipients) include every component of lipid, for example, PEG-lipid used as additive agent, etc.?

13. (CHEMISTRY, MANUFACTURING, AND CONTROLS (D. Control of Excipients: Lipid Components))(Line 142):

The definition of “starting material” should be added. For example, the definition of “starting material” shows interface with the definition in ICH Q7A.

14. (CHEMISTRY, MANUFACTURING, AND CONTROLS (D. Control of Excipients: Lipid Components): Line 157):

We recommend adding an example or a reference that describes the way to ensure the removal of animal proteins and viruses.

15. (CHEMISTRY, MANUFACTURING, AND CONTROLS (D. Control of Excipients: Lipid Components))(Line 165):

Please describe with an illustration or show by reference data how reference standard should be specified.

16. (CHEMISTRY, MANUFACTURING, AND CONTROLS (F: Stability))(Line 222-223):

If “to address both physical and chemical stability of liposome itself” is important, “liposomes without a drug substance” instead of “liposomes to be combined with a drug substance before use” should be used as unloaded liposome.

17. (CHEMISTRY, MANUFACTURING, AND CONTROLS (F: Stability))(Line 234):

What does the integrity of the liposome mean specifically in line 234? Please indicate what kind of physicochemical properties show the integrity of the liposome. If such physicochemical properties are not listed in “CHEMISTRY, MANUFACTURING, AND CONTROLS (B. Physicochemical Properties”, please add the properties into that section.

18. (CHEMISTRY, MANUFACTURING, AND CONTROLS (G. Changes of Manufacturing))(Line 245-273):

As employed in SUPAC guidance, a relationship between the level of manufacturing changes and reporting mechanisms should be indicated in this guidance so that reader can easily understand.

19. (HUMAN PHARMACOKINETICS AND BIOAVAILABILITY (A: Bioanalytical Methods))(Line 289-293):

The information on the rate of encapsulation of drug in blood (= the stability of liposomes in blood) is important to assess the biodistribution and bioavailability of the liposome products. However, the stability of liposomes in blood can be assessed from the PK, TK study and in vitro study using human plasma (see III D). Therefore, we think that it isn't required to measure the encapsulation in blood.

20. (HUMAN PHARMACOKINETICS AND BIOAVAILABILITY (B: In Vivo Integrity (Stability) Consideration))(Line 314):

The in vivo stability of liposome products can be estimated based on in vitro study (III D) and PK, TK data. From this point of view, we think that the stability test in vivo is not necessary. Therefore you should accept this strategy and insert the sentences of such contents in this chapter. “If it is difficult to distinguish directly between encapsulated and unencapsulated drug substance, the stability of liposome in vivo should be clarified by indirect study.” In relation with this comment, line 321-325 should be deleted.

21. (HUMAN PHARMACOKINETICS AND BIOAVAILABILITY (C: Protein Binding))(General):

The interaction between liposome products and plasma components may cause the release of encapsulated drug or aggregation of liposome products in blood. But in this case, what should be clarified isn't protein but the changing of liposome products (i.e. aggregation or release of drug), and these properties can be assessed by in vitro study (III D) and PK, TK study. Furthermore, in the identification of protein, the criteria of “major” are unknown and it is difficult to set up the standard from the viewpoint of traceability. Therefore we think that this section isn't needed and should be deleted.

22. (HUMAN PHARMACOKINETICS AND BIOAVAILABILITY (D: In vitro Stability))(General):

Although lipoprotein and/or other plasma protein affect the stability of liposome in vivo, interaction between liposome and these proteins does not limit its stability exclusively. Stability of liposome can be examined with results of non-clinical studies, in vivo studies of stability exhibited

IIIA, IIIB and in vitro studies of stability exhibited in IIID. Then, we think it is not necessary to require identification and measurement of binding proteins on liposome for this purpose. Therefore, this item should be deleted.

23. (HUMAN PHARMACOKINETICS AND BIOAVAILABILITY (C: Protein Binding))(General):

In vitro studies are effective not only for evaluation of properties of the liposome but also for bridging the results of non-clinical studies and clinical studies by comparing interaction of liposome and animal blood (plasma) to that in humans. Therefore, to achieve the purpose of studies exhibited in IIIA-IIIC, studies to compare liposome stability in animal and human blood should be described in this item.

24. (HUMAN PHARMACOKINETICS AND BIOAVAILABILITY (E: Pharmacokinetics and Bioavailability))(General):

In the case of protein or peptide drugs, radioactive labeling and determination of radioactivity in blood, urine and feces is not considered sufficiently effective to trace the kinetics of these drugs. Further, the administration of a non-liposome drug can possibly cause a remarkably disadvantageous reaction to recipients. Therefore, a comparison of liposome and non-liposome drug should not be done. Consequently, we recommend adding to the description an exception to the procedure of mass balance study in such cases as described above.

25. (HUMAN PHARMACOKINETICS AND BIOAVAILABILITY (E: Pharmacokinetics and Bioavailability))(Line 379-):

The manufacturing of the liposome products containing drug substance tagged with a radioactive label (hot products) may almost be

a different manufacturing procedure than the cold products because of manufacturing scale or GMP and so on. As you know, it is very difficult to assure the bioequivalence between the products made by various manufacturing procedures. Therefore, a change in manufacturing method should not be required.

Furthermore, the study using hot products involves the risk of radiation exposure to subjects. Especially, in the case of using the liposome products having site-specificity and long circulation, the risk will be increased. In such case, mass balance study using hot products should not be performed. From these viewpoint, mass balance study should be performed using cold liposome product and not require the assurance of bioequivalence. Based on this view, the contents of this chapter should be changed.

26. (HUMAN PHARMACOKINETICS AND BIOAVAILABILITY (E: Pharmacokinetics and Bioavailability))(footnote):

As described in the footnote (remark No.7), historical pharmacokinetic data can be used in lieu of a comparative study in a single dose pharmacokinetics study. These points should be described in this chapter.