

November 18, 2002



Management Dockets, N/A
Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

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**Re: Docket Number 02D-0337
Draft Guidance for Industry on Liposome Drug Products: Chemistry, Manufacturing, and
Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation**

Dear Sir or Madam:

Enclosed please find the comments from GlaxoSmithKline, both general and specific, for the CMC sections of the Draft Guidance for Industry on Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation. These comments are presented for consideration by the FDA. The specific comments are presented in order by the section of the guidance.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for the CMC sections of this guidance. I am submitting this document both electronically (Dockets Management, Electronic Comment Submission Form) and by hardcopy. Therefore, you will receive a paper copy of this letter and two copies of the comments through the USPS.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

A handwritten signature in cursive script that reads "Mary Faye S. Whisler".

Mary Faye S. Whisler, Ph.D.
Assistant Director
New Submissions, North America

02D-0337

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General Comment:

Overall, the guidance appears reasonable and scientifically sound. It should ensure production of a consistent product. Some additions and revisions, as detailed in the following specific comments section, are desired.

Specific Comments:

The following comments would clarify and verify the information required in the guidance.

Section I.B. Physicochemical Properties

Given the inconsistency in obtaining reproducible data (Zeta potential) regarding "net charge", this physicochemical property should be deleted from those required, if the results will be used to release batches.

Light scattering index should not be a required test.

Section I.D.2. Control of Excipients: Lipid Components, Manufacture

There is no guidance on the use of natural lipids derived from genetically modified source materials (e.g. soybeans). Add a statement about information that should be submitted with respect to the use of these natural lipids.

Section I.D.3. Control of Excipients: Lipid Components, Specifications

A specification for positional specificity of acyl side chains in natural lipids is not necessary because natural synthetic pathways for the specific lipid and the isolation process will control this parameter. Remove the statement about positional specificity.

Section I.E. Control of Drug Product: Specifications

Routine measurement of lipid degradation products should not be required if the lipid component content is determined using a stability indicating method. Lipid degradation products are generally molecules that are naturally present in foods and the body and do not present significant risk. The lipid component assay and specification will ensure that degradation product levels remain sufficiently low. Add text to state that routine measurement of lipid degradation products should not be required if the lipid component content is determined using a stability indicating method.

Section III.C. Protein Binding

Protein binding levels when speaking about liposomes are very specific to the lipid constituents of liposomes. If one consistently uses the same lipids for several products (e.g. different actives) this should not be a requirement for different drugs. If it can be shown that protein binding levels are the same for the same liposomes regardless of the drug being delivered then it should be possible to use historical data to cover this item. However, different lipids used to deliver the same active will have different protein binding profiles and generating this data for a "new liposome" could be important. Clarify the text to allow for the inclusion of historical data to support requiring limited data.