

# Lipoid

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Dockets Management Branch (HFA-305)  
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## Guidance for Industry: Liposome Drug Products (1 08/21/2002)

Dear Sirs,

Lipoid highly supports the publication of a Guidance for Industry focused on lecithins and phospholipids, in this case for the liposome drug products.

Lipoid GmbH produces the whole range of lecithins and phospholipids that are used in pharmaceutical including liposomal formulation. Lipoid is the largest independent producer of these lipids. More than eighty percent of our products are used in parenteral pharmaceuticals. The product line includes lecithins and phospholipids derived from egg yolk and soy bean, hydrogenated lecithins and phospholipids, as well as synthetic phospholipids.

Based on our more than 25 year lasting experience we would like to comment this draft, mainly the part describing the lecithins and phospholipids.

- According to A (line numbers 73 and 74) lipids are considered to be inactive ingredients. In contrast to that in line number 118 – 127 it is referred to *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*. On the other hand a Type IV Drug Master File (for excipients) is requested. We therefore propose to refer to IPEC's Good Manufacturing Practice Guide for Bulk Pharmaceutical Excipients as published in USP 25 (General Chapter [1078]).

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- Line 172 – 177: The fatty acid composition, the position isomerism (for mixed fatty acid phospholipids) and the configuration are essential to be tested for.
- Line 179 – 189: For partially hydrogenated phospholipids the percentage of trans-fatty acids has to be determined. If the Iodine Value is not more than 2, the analysis for trans-fatty acids is not required because the phospholipid can be seen as fully

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hydrogenated. Partially hydrogenated and hydrogenated phospholipids should be analyzed for residual catalyst.

The phospholipids have to be analyzed for degradation products as peroxides (for unsaturated phospholipids), lysophospholipids, free fatty acids and glycerophospholipids.

- Line number 182-187: the positional specificity of acyl side chains should not be part of the release specification for natural lecithins and phospholipids. It has to be tested for detailed characterisation (structural investigation) during validation and for characterisation as in the Drug Master File, but on a routine base other parameters as Iodine Value can be taken to control the grade of saturation/unsaturation and/or the fatty acid composition respectively.  
Depending on the way of synthesis it should be tested of residual catalyst and/or residual enzyme respectively.  
The stability of polar phospholipids as phosphatidy glycerols and phosphatidyl acids depends on the kind of salt (e.g. Sodium- or ammonium salt, or free acid) specifications have to be set for that.  
As bivalent ions can have a strong influence on the solubility of the phospholipids and of the final liposomal formulation, limits have to be set for them, e.g. Calcium.
- Line number 188-189: natural purified lecithins mainly consists of phosphatidyl choline and phosphatidyl ethanolamine.
- Line 190: Specifications have to be set for heavy metals, residual solvents (used in the last two production steps), bacteriology and endotoxins or pyrogens respectively.
- Line number 192-197: The stability study should be performed according to the ICH guideline. As highly purified lecithins and phospholipids should be stored at  $-18\text{ }^{\circ}\text{C}$ , the stability study is to be performed at  $-18\text{ }^{\circ}\text{C}$  and  $+4\text{ }^{\circ}\text{C}$ . The stability of the lecithins and phospholipids strongly depends on the composition of the final formulations (e.g. pH, other ingredients etc). Therefore it is required to perform intense stability testing on the final formulation also in regard to the degradation of the lipids.

These comments are also sent as Word document by e-mail to [coryj@cder.fda.gov](mailto:coryj@cder.fda.gov).

If you have any question, please do not hesitate to contact me.

Sincerely  
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