CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-942

Trade Name: Intralipid 30% Injection

Generic Name: (soybean oil)

Sponsor: Kabi Pharmacia, Inc

Approval Date: December 30, 1993

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-942

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-942

APPROVAL LETTER

6.1

NDA 19-942

DEC 30 1993

Kabi Pharmacia, Inc.
1899 Highway 70 East
P.O. Box 597
Clayton, North Carolina 27520-0597

Attention: Thomas L. Pituk
Director of Regulatory Affairs

Dear Mr. Pituk:

Reference is made to your new drug application submitted December 29, 1988, and resubmitted June 29, 1990, under section 505(b) of the Federal Food, Drug and Cosmetic Act for Intralipid® 30% I.V. Fat Emulsion Pharmacy Bulk Package.

We acknowledge receipt of your amendments and correspondence dated January 12, February 16, and October 25, 1989; March 11, May 3 and 20, and December 19, 1991; and September 4 and October 27, 1992; and June 30, July 22, and December 13, 1993. Additionally, we refer to our not approvable letters dated February 28, 1991; April 30, 1992; and March 19, 1993.

We have completed the review of this application, including the submitted draft labeling dated December 13, 1993, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling with the revisions listed below. Accordingly, the application is approved as amended effective on the date of this letter. As discussed by telephone on December 15, 1993, with Ms. Anna Marie Weikel of the division, you agreed to the following labeling revisions:

1. The following statements in the CONTRAINDICATIONS section should be capitalized:

   "INTRALIPID® 30% PHARMACY BULK PACKAGE IS NOT INTENDED FOR DIRECT INTRAVENOUS ADMINISTRATION. DILUTING INTRALIPID® 30% TO A 10% OR 20% CONCENTRATION WITH AN INTRAVENOUS FLUID SUCH AS NORMAL SALINE OR OTHER DILUENT DOES NOT PRODUCE A DILUTION THAT IS EQUIVALENT IN COMPOSITION TO INTRALIPID® 10% OR 20% I.V. FAT EMULSIONS, AND SUCH A DILUTION SHOULD NOT BE GIVEN BY DIRECT INTRAVENOUS ADMINISTRATION (FOR EXAMPLE, THROUGH A Y-CONNECTOR)."

2. The last statement in the DOSAGE AND ADMINISTRATION section under "Mixing Guidelines and Limitations" should be revised in bold letters to read, **"Failure to follow the Mixing Guidelines and Limitations below, including recommended storage temperature, storage time, order of mixing, etc., may result in an unstable admixture."** and inserted between the third and fourth paragraph under this section.

Please submit twelve (12) copies of the final printed labeling (FPL) identical to the draft labeling dated December 13, 1993, with the agreed upon revisions mentioned above, as soon as it is available. Seven of the copies should be individually mounted on heavy weight paper, or similar material. For administrative purposes this submission should be designated "FPL for Approved NDA 19-942." Approval of the submission by FDA is not required before the labeling is used. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug.

Please submit, in duplicate, the advertising copy that you intend to use in your proposed introductory promotional and/or advertising campaign. One copy should be sent to the Division of Medical Imaging, Surgical, and Dental Drug Products, and the second copy should be sent to the Division of Drug Marketing, Advertising, and Communications, HFD-240, 5600 Fishers Lane, Rockville, MD 20857. All proposed materials should be in draft form or mock-up form, not final print. Also, please do not use form FDA-2253 for this submission; that form is for routine use, not for proposed materials.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Patricia Y. Love, M.D., M.B.A.
Acting Director
Division of Medical Imaging,
Surgical, and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: NDA 19-942*
HFD-160/Div File*
HFC-130/D.O.*
HFD-80* *w/labeling
HF-2/Medwatch*
HFD-100
HFD-638*
HFD-735*
HFD-160/PLove
HFD-161/Sheinin/Koch
HFD-161/Weikel AMW 12.20.93
Concurrences: Sheinin-12-17-93/Cooney-12-17-93/
Koch-12-17-93/Cheever-12-16-93

F/T by: AChapman-12-20-93
NDA APPROVAL

12/29/93

12/28/93

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-942

NOT-APPROVABLE LETTER(S)

3.1

APR 30 1992

NDA 19-942

Kabi Pharmacia, Inc.
1899 Highway 70 East
P.O. Box 597
Clayton, North Carolina 27520-0597

Attention: Thomas L. Pituk
Director of Regulatory Affairs

Dear Mr. Pituk:

Please refer to your new drug application dated December 29, 1988, and your resubmission dated June 29, 1990, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intralipid 30% I.V. Fat Emulsion (Pharmacy Bulk Package).

We also acknowledge receipt of your correspondence and amendments dated February 16 and October 25, 1989, March 11, May 3, May 20 and December 19, 1991.

We have completed the review of this application and find that the information presented is inadequate and that the application as amended is not approvable. The deficiencies may be summarized as follows:

The application fails to include adequate chemistry, manufacturing, and controls information as required under section 505(b)(1) of the Act and 21 CFR 314.125(b) of the implementing regulations to assure that the finished drug product (or drug substance) conforms to appropriate standards of identity, strength, quality and purity. The specific deficiencies are as follows:

1. Your assurance is needed that the soybean oil raw material proposed for use in the manufacture of Intralipid 30% Pharmacy Bulk Package will meet all USP requirements for this article, and thereby may be referenced as soybean oil USP. Reasons for using (———) in place of Method II for Iodine Value should be explained, and the comparability of results shown. Comparability of the test results using the proposed method for the determination of free fatty acids with the method in USP should be shown. While the proposed procedure for the determination of fatty acid composition differs somewhat from that found in the USP XXII monograph, the process is sufficiently similar to warrant acceptance.

2. Provide us with the formal and complete method of analysis used by Kabi Pharmacia for determining pesticide residues in the purified soybean oil and the egg yolk phospholipids intended for use in the production of the subject drug product. The procedure should be presented in sufficient clarity and detail to permit duplication in our laboratories. This method as well as data demonstrating the validation of this method should also be made a part of the Methods Validation package.

3. The revised method of analysis entitled Identification and Quantification of Component Distribution in Egg Yolk Phospholipids by HPLC (p. 3.1.4.-9 through 3.1.4.-20) has not been included in the Methods Validation update packages in section 3.3 or in section 10.1 of this amendment. Both of these locations, however, contain the revised validation report for this method. The formal written procedure and its validation report should be made a part of the Methods Validation package.

4. The following comments and recommendations concern the finished drug product release and shelf-life controls:

   a. Acceptance criteria should include an evaluation or description of emulsion appearance, to include examination for evidence of discoloration and emulsion breakage or oil phase separation.

   b. We request that you demonstrate that monitoring for peroxide formation is not necessary over the shelf-life of this product.

   c. Release criteria should include testing for heavy metals. The testing performed should suitably control those heavy metals of concern. Our concern in this regard is based on the number and nature of the sources of these contaminants and their cumulative effect. A test for heavy metals has been proposed for inclusion in the USP monograph for Intravenous Fat Emulsion; please refer to the July-August, 1991 issue of Pharmacopeial Forum.

d. Please specify the acceptable fill volume range for this drug product; i.e., the minimum and maximum fill volumes which meet manufacturing instructions. Please refer to the USP General Chapter on Injections for guidance regarding the excess volume recommended for use in injection containers.

5. [redacted] Please provide us with stability data which demonstrate stability maintenance - primarily with regard to physical characteristics - when storage takes place at temperatures of 2° - 8°C for a period of not less than (NLT) 3 months.

6. The post-approval stability protocol provides for one production lot (after the series of 3 initial production lots) to be entered into a shelf-life stability study program every other year. We recommend that this stability protocol be revised to provide for the testing of NLT one production lot every year.

7. Aluminum levels in a parenteral drug product, particularly an LVP, should be established through appropriate studies using sensitive and specific methodology, adjustments made in these levels as indicated by the data, and subsequent lots monitored as warranted. We have been and will continue to review such data as voluntarily provided to us by the parenteral drug industry, thereby enabling us to gain a better understanding of the extent of this contamination, and the means and methods to control it. At present, we are asking that aluminum levels in parenteral drug products be monitored, and that the data accumulated therefrom be shared with this Agency. We also ask that a description of the analytical methodology used be provided.

8. [redacted]

[redacted]

Constant appraisal of upcoming changes which may influence the compatibility of these BHC products is essential so that studies may be conducted by Kabi Pharmacia to reestablish their acceptability prior to the implementation of the changes.

[redacted]

9. The revised and complete Methods Validation packages (refer to the **Guideline for Submitting Samples and Analytical Data for Methods Validation** for a list of information that should be included in this package) should be submitted to this file.

10. [redacted]

All reviews of the application have not been completed. Upon completion of these reviews, any resulting comments or deficiencies will be communicated under separate cover. We reserve comment on the labeling until the application is otherwise approvable.

In accordance with the policy described in 21 CFR 314.102(d) of the new drug regulation, should you so desire, you are invited to request an informal conference with members of the Division of Medical Imaging, Surgical and Dental Drug Products to discuss in detail the deficiencies in this application and what further steps you need to take to secure approval. The meeting is to be requested at least 15 days in advance. Should you wish this conference or a telephone report, please call Mrs. Regina Joyce, Consumer Safety Officer at (301) 443-3500.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other actions under 21 CFR 314.120. In the absence of such action FDA may take action to withdraw the application. We will not process a partial reply as a major amendment nor will the review clock be reactivated until the deficiencies have been addressed.

Sincerely,

WAC 4/30/92

Wiley A. Chambers, M.D.
Acting Director
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
NDA 19-942
HFD-160
HFD-82
HFD-100
HFD-735
HFD-160/DivDir/Chambers
HFD-160/MO/Kenealy
HFD-160/Pharm/Wilson
HFD-160/Micro/Cooney
HFD-160/Chem/Koch/Sheinin
HFD-160/CSO/Joyce RDJoyce 4/29/92
R/D by: RDJoyce 04-27-92
F/T by: AChapman 04-29-92
NOT APPROVABLE

ACKNOWLEDGEMENT ONLY: [illegible] 4/29/92
HFD-160/SMO/Kenealy [illegible] 4-29-92
HFD-160/SChem/Sheinin
HFD-160/SPharm/DeWitt JM DeWitt 4/29/92
HFD-160/SMicro/Cooney TH Cooney 4/29/92
HFD-160/SCSO/Rumble

FEB 28 1991

NDA 19-942

KabiVitrum, Inc.
P. O. Box 597
U.S. Route 70 East
Clayton, North Carolina 27520

Attention: Thomas L. Pituk
Director of Regulatory Affairs

Dear Mr. Pituk:

Please refer to your new drug application dated December 29, 1988, and your resubmission dated June 29, 1990, received on July 2, 1990 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intralipid 30% I.V. Fat Emulsion (Pharmacy Bulk Package).

We also acknowledge receipt of your correspondence dated February 12 16 and October 25, 1989.

We have completed our review and find that the information presented is inadequate and that the application as amended is not approvable. The deficiencies may be summarized as follows:

It fails to include adequate laboratory test procedures as required under section 505(b)(1) to assure that the finished drug product (or drug substance) conforms to appropriate standards of identity, strength, quality and purity. Specific deficiencies are as follows:

1. The following comments concern the synthesis, source, and/or control of both the active and inactive drug substances:

   a. State the expiration dating periods and applicable storage conditions assigned to the soybean oil and egg yolk phospholipids drug substances manufactured by KabiVitrum AB, Stockholm, Sweden.

b. The fatty acid composition of the soybean oil is given on p. 3.1-4.3 of the original submission of this NDA. The laboratory responsible for testing the soybean oil for conformance with these fatty acid component specifications should be provided. Please indicate (1) whether the Certificate of Analysis which accompanies the soybean oil drug substance as received from KabiVitrum AB also confirms that testing for the fatty acid composition has been successfully completed, and (2) whether testing for fatty acid composition is performed on each lot by KabiVitrum, Inc. in Clayton, N.C.

c. Assurance is needed that the soybean oil used in the manufacture of this finished drug product meets all the requirements of the current USP monograph for this active drug substance.

d. The testing routinely performed by your supplier on soybean oil for pesticides should be discussed; i.e., provide us with a list of the pesticides for which control testing is performed, the analytical methodology employed, and the specification limit established for each pesticide.

e. With reference to the egg yolk phospholipid controls, additional specifications and tests should be considered to further establish and/or define the composition, purity, and quality of this drug substance. We have the following comments in this regard:

(1) Materials which make up at least a portion of the greater than / of egg yolk phospholipid not yet identified should be characterized and controlled either through content limits imposed on (a) additional specific phospholipids (as active or inactive ingredients, or as impurities), or (b) natural components, such as sterols. A specification for total phospholipids may be of value.

(2) Impurities which should be controlled include / —— / residual solvents, and pesticides. Your supplier should provide you with a listing of all pesticides for which testing is performed and the specification limit established for each pesticide.

(3) Testing should be performed to control the water content, / —— / and the total bacterial count/pyrogens.

The percentage of phospholipid in the "Specifications for Component Composition of Purified Phospholipid" [p. 3.1.4-5] should be expressed in the appropriate terms; e.g., w/w.

f. Please provide us with your source of supply of glycerin, water for injection, and . Your confirmation is also needed that each lot of raw material glycerin, sodium hydroxide, , , and water for injection used in the production of Intralipid 30% Pharmacy Bulk Package meets all requirements of their respective monographs in the current USP/NF.

2. We have the following inquiries concerning the drug product container and its component parts:

a. Verify for us the use of container glass which is clear and colorless. Please describe the manner by which container glass used in the construction of these containers is rendered and confirmed to be pyrogen-free.

b. Please describe the criteria for evaluating the acceptability of both the (as stated on p. 3.2.5.-6 of the Method of Manufacture and Packaging), used in the

3. Please explain the role that emulsion particle size (oil globule particle size) plays in determining the number of Discuss the influence of a higher percentage of oil (as compared to that found for the 10% and 20% concentrations) on the overall manufacturing procedure, on the order of mixing ingredients, and on the

Please discuss in more detail the physical and chemical parameters followed during the emulsification process and your means of determining when the process is completed. Indicate how these important vary from batch to batch. A full review of the reprocessing criteria (if any) are needed; i.e., review the factors which determine whether a given batch is eligible for reprocessing should it fail to meet the necessary specifications at this stage of the manufacturing procedure, as well as the defects which you consider

correctable by way of reprocessing. Should you propose some form of reprocessing, present a comprehensive discussion of the entire procedure and include the extent to which fresh ingredients may be used and the accounting process.

4. The following information dealing with the finished drug product controls is requested:

   a. Criteria that must be satisfied prior to the release of the drug product, and throughout its shelf life, regarding the appearance of the fat emulsion should be counted among the finished drug controls. Color and physical state/condition should be among these appearance criteria.

   b. Consideration should be given to the addition of controls to limit the presence of peroxides and heavy metals. Indicate the heavy metal candidates for solution contamination and explain the capability of the chosen method to properly identify and quantify these metals. Comment on the advisability of controlling ~~~ in the finished drug product.

   c. The control of fluid particulate matter should be included essentially as performed by the appropriate USP XXII test procedure (see pp. 1596 - 1597).

   d. The fill volume limits should be expressed.

   e. The validation test procedures performed on the proposed finished drug product methods for the determination of soybean oil, the determination of glycerin, and the determination of [redacted] should be included in this new drug application.

   f. The listing of finished drug product specification and tests should include reference to the specific analytical test procedures by the method name and (if available) the laboratory test procedure number.

   g. With reference to controls for the emulsion particle size and based on the proposed specifications, discuss the numbers of particles that are permitted to be present in this drug product that are larger than [redacted] microns in diameter and larger than [redacted] microns in diameter.

5. The review of submitted data concerning drug product stability has generated the following inquiries and recommendations:

   a. We are unable to properly assess the full effect of storage on the number and size of globule particles which are greater than [redacted] microns by using the data from the [redacted] without more specific information; i.e., the globule particle size test procedure [redacted] used in these studies does not evaluate this parameter to the extent needed. To reiterate, the fat globule particle size should be characterized in a more comprehensive fashion, and the specification revised to more closely control the full range of particles that may result from the manufacture of a product of this nature. In addition, we note that, [redacted]

   b. The criteria used to assess the "visual examination" specification should be provided so we may more closely monitor these properties throughout the stability study period.

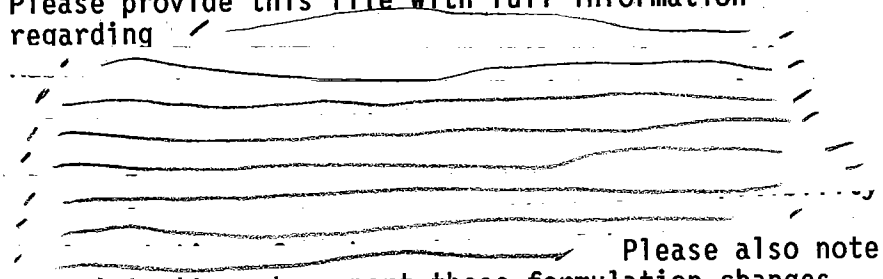
   c. Referring to the full term primary stability data provided, [redacted] Discuss the criteria used to establish this [redacted] as well as the probable exposure of this drug product during shipment and subsequent storage. [redacted]

   d. The marketed drug product stability commitment should be a self-contained part of this NDA which addresses the testing of drug lot samples manufactured after NDA approval. This commitment should specify the number of <u>initial</u> [minimum of three (3)] and subsequent production lots to be placed into this stability testing program, the temperatures at which samples are to be stored, the testing to be performed on these samples, the intervals at which each control test will be done, the frequency that test results will be submitted to this file, and the action pledged should a production lot or lots be found to fall outside the approved specifications in one or more ways within the expiration dating period.

e. The stability study protocol should review in detail the production lot stability testing to be performed and the manner by which this generated data is to be statistically analyzed and applied to support and/or extend the expiration dating period. Reference should be made to information contained in the Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics for further assistance in this regard. Alternatively, you may waive your option to extend the approved expiration dating period based on an approved stability protocol under the provisions of 21 CFR 314.70(d)(5) in favor of the submission and prior approval of a supplemental application providing for extension of the expiration dating period granted in the original application.

f. We recommend that aluminum levels be monitored in production lots of this drug production throughout the shelf life. We request that you share this information with us from time to time. A proposed rule has been published in the 5-21-90 Federal Register entitled "Parenteral Drug Products Containing Aluminum as an Ingredient or a Contaminant; Notice of Intent and Request for Information." These proposed regulations address the testing and labeling of parenteral drug products for the purpose of controlling aluminum contamination. The test procedures you intend to use to accomplish this testing should be submitted for our review and possible validation.

g. Please provide this file with full information regarding



Please also note your intentions to report these formulation changes, and the resulting testing performed, to us as they occur.

6. The environmental assessment statement should follow the format as indicated in 21 CFR 25.31a under the Environmental Impact Considerations regulations. This statement must be dated when signed by a responsible official.

Also, the following information and data are needed for sterility assurance:

1. In support of container/closure integrity you have referred to [redacted] these studies should be repeated using the 30% product since the effects of the higher lipid content are not known.

2. Concerning the proposed endotoxin test [redacted] please supply validation information and data demonstrating the suitability of this test for this product. Please also supply the specification for endotoxin limits for this drug product. The oil-in-water emulsion products may present unique problems relative to use of the [redacted] Please consider the following comments:

   (a) Endotoxins are complex lipopolysaccharides derived from Gram negative microorganisms. Such molecules have lipophilic portions which may preferentially associate with other lipophilic moieties.

   (b) The lipids which form the emulsion in this product are derived from soybeans (i.e., soybean oil). As a natural product, these may be contaminated with endotoxins. Is it possible that endotoxins may be copurified with the soybean oil and end up preferentially associated with the lipid phase of the emulsion?

   (c) If endotoxins were preferentially associated with the lipid phase of the emulsion, would they be detected using an [redacted] Since the [redacted] is [redacted] detection may not be possible if the endotoxins are not associated with the [redacted] Is any information available which addresses these issues? Could studies be devised which address these issues?

3. We note (p. 3.2.7.-3) that for purposes of the stability program, sterility assessment is performed only at the initial time point. Furthermore, this initial test is performed using [redacted] This testing should be part of the commitment provided for the marketed product stability protocol. The method described on p. 3.2.6.-28 [redacted]

We have the following preliminary comments concerning the labeling:

1. The label should be revised to the following extent:

   a. The boxed declaration reading "Pharmacy Bulk Package - Not for Direct Infusion," in the Product Title section should be highly visible through the use of bold face type and/or contrasting color, and the type size should be increased to not less than that of the drug product established name lettering. These recommendations also apply to the Product Title section in the package insert. Please also be reminded of the provisions of 21 CFR 201.10(g) regarding the type size relationship between the established name and the proprietary name.

   b.

   c.

   d. The label should include a warning statement against the use of the container contents if there appears to be a separation of the emulsion, i.e., an oiling out of the emulsion.

   e. If space permits on the immediate container label, provisions should be made to include the date and time the closure was entered: e.g.,

      Date Entered: _____
      Time of Entry: _____

2. The package insert should be revised to the following extent:

   a. The following comments concerning the DESCRIPTION section should be considered:

      (1)

      (2) The amount of individual fatty acids in soybean oil To represent these fatty acid concentrations in soybean oil in a more definitive manner, we recommend that they be expressed as the range of values within which they occur naturally.

      (3) Please correct the definition of the R_3 portion of the phospholipid general structure to that of "... primarily either the choline or the ethanolamine ester of phosphoric acid"

   b. The following comments concerning the MIXING GUIDELINES AND LIMITATIONS section of the package insert should be addressed:

      (1) In the first line of this section correct Intralipid 30 to the read Intralipid 30%.

      (2) With reference to the paragraph which cites compatibility studies with Intralipid and amino acid solutions, please state the concentrations of Novamine amino acids injection to which you are referring.

      (3) As stated in our approval letter for NDA 17-643/S-045 and NDA 18-449/S-013 dated September 19, 1988, the content of this section

If you have any questions, please contact:

Mrs. Regina D. Joyce
Consumer Safety Officer
Telephone: (301) 443-3500

Sincerely yours,

J Palmer 2-27-91

John F. Palmer, M.D.
Director
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Orig NDA 19-942
HFD-160/Division File
HFD-80
HFD-100/Dr. Botstein/L. Carter
HFD-231
HFD-160/Kenealy/Cooney/Koch/Wilson/Joyce/Sheinin
R/D by: RJoyce 1/29/90 (0879J/D-0017)
R/D init by: WRumble 02-04-91
PCooney 01-29-91
JKenealy 01-29-91
KMainigi 01-29-91
SKoch for ESheinin 01-31-91
RDJoyce 01-29-91
PGWalters 02-04-91
F/T by: AChapman 02-20-91

RDJoyce 2/20/91

WRumble 2/20/91
2/27/91

NOT APPROVABLE (5C)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-942

LABELING

DRAFT

71-6053-0
(Issued _____)

APPROVED DEC 30 1993

Intralipid® 30%

A 30% I.V. Fat Emulsion

Pharmacy Bulk Package
Not For Direct Infusion

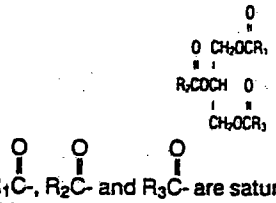
DESCRIPTION

Intralipid® 30% (30% I.V. Fat Emulsion) ~~in a~~ Pharmacy Bulk Package is a sterile, non-pyrogenic fat emulsion intended as a source of calories and essential fatty acids for use in a pharmacy admixture program.

It is made up of 30% Soybean Oil, 1.2% Egg Yolk Phospholipids, 1.7% Glycerin and Water for Injection. In addition, sodium hydroxide has been added to adjust the pH so that the final product pH is 8.0; pH range is 6.0 - 8.9.

Intralipid® 30% Pharmacy Bulk Package is not for direct infusion. It is a sterile dosage form which contains several single doses for use in the preparation of three-in-one or total nutrient admixtures (TNAs) in a pharmacy admixture program. [BOLD]

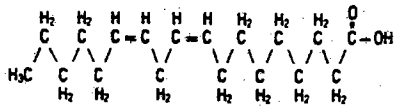
The soybean oil is a refined natural product consisting of a mixture of neutral triglycerides of predominantly unsaturated fatty acids with the following structure:



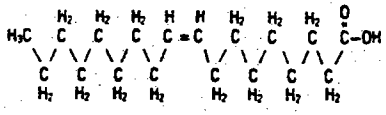
where R_1C-, R_2C- and R_3C- are saturated and unsaturated fatty acid residues.

The major component fatty acids are linoleic (44-62%), oleic (19-30%), palmitic (7-14%), linolenic (4-11%) and stearic (1.4-5.5%).[1] These fatty acids have the following chemical and structural formulas:

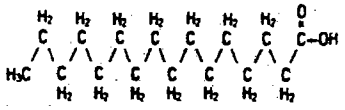
Linoleic acid
$C_{18}H_{32}O_2$



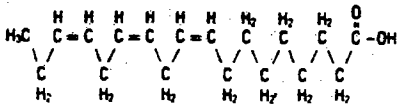
Oleic acid
$C_{18}H_{34}O_2$



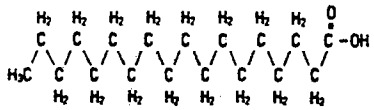
Palmitic acid
$C_{16}H_{32}O_2$



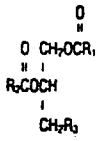
Linolenic acid
$C_{18}H_{30}O_2$



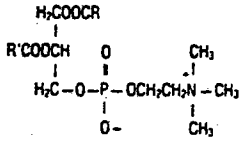
Stearic acid
$C_{18}H_{36}O_2$



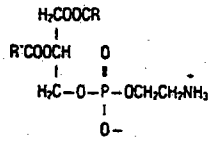
Purified egg phosphatides are a mixture of naturally occurring phospholipids which are isolated from the egg yolk. These phospholipids have the following general structure:



R_1C- and R_2C- contain saturated and unsaturated fatty acids that abound in neutral fats. R_3 is primarily either the choline or the ethanolamine ester of phosphoric acid

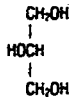


Phosphatidylcholine



Phosphatidylethenolamine

Glycerin is chemically designated $C_3H_8O_3$ and is a clear colorless, hygroscopic syrupy liquid. It has the following structural formula:



Intralipid® 30% (30% I.V. Fat Emulsion) has an osmolality of approximately 310 mOsmol/kg water (which represents 200 mOsmol/liter of emulsion) and contains emulsified fat particles of approximately 0.5 micron size.

The total caloric value, including fat, phospholipid and glycerin, is 3.0 kcal per mL of Intralipid® 30%. The phospholipids present contribute 47 milligrams or approximately 1.5 mmol of phosphorus per 100 mL of the emulsion.

CLINICAL PHARMACOLOGY

Intralipid® is metabolized and utilized as a source of energy causing an increase in heat production, decrease in respiratory quotient and increase in oxygen consumption. The infused fat particles are cleared from the blood stream in a manner thought to be comparable to the clearing of chylomicrons.

Intralipid® will prevent the biochemical lesions of essential fatty acid deficiency (EFAD), and correct the clinical manifestations of the EFAD syndrome.

INDICATIONS AND USAGE

Intralipid® a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods of time (usually for more than 5 days) and as a source of essential fatty acids for prevention of EFAD.

30% Pharmacy Bulk Package is indicated for use in a pharmacy admixture program for the preparation of three-in-one or total nutrient admixtures (TNAs) to provide

CONTRAINDICATIONS

The administration of Intralipid® is contraindicated in patients with disturbances of normal fat metabolism such as pathologic hyperlipemia, lipoid nephrosis or acute pancreatitis if accompanied by hyperlipidemia. Intralipid® 30% is not intended for direct intravenous infusion.

Intralipid® 30% Pharmacy Bulk Package is not intended for direct intravenous administration. Diluting Intralipid® 30% to a 10% or 20% concentration with an intravenous fluid such as normal saline or other diluent does not produce a dilution that is equivalent in composition to Intralipid® 10% or 20% I.V. Fat Emulsions, and such a dilution should not be given by direct intravenous administration (for example, through a Y-connector).

WARNINGS

Deaths in preterm infants after infusion of intravenous fat emulsion have been reported in the medical literature[2]. Autopsy findings included intravascular fat accumulation in the lungs. Treatment of premature and low birth weight infants with intravenous fat emulsion must be based upon careful benefit-risk assessment. Strict adherence to the recommended total daily dose is mandatory; hourly infusion rate of the admixture should be as slow as possible in each case and the total fat should not in any case exceed 1 g fat/kg in four hours. Premature and small for gestational age infants have poor clearance of intravenous fat emulsion and increased free fatty acid plasma levels following fat emulsion infusion; therefore, serious consideration must be given to administration of less than the maximum recommended doses in these patients in order to decrease the likelihood of intravenous fat overload. The infant's ability to eliminate the infused fat from the circulation must be carefully monitored (such as serum triglycerides and/or plasma free fatty acid levels). The lipemia must clear between daily infusions.

Caution should be exercised in administering Intralipid® to patients with severe liver damage, pulmonary disease, anemia or blood coagulation disorders, or when there is danger of fat embolism.

PRECAUTIONS

When Intralipid® is administered, the patient's capacity to eliminate the infused fat from the circulation must be monitored by use of an appropriate laboratory determination of serum triglycerides. Overdosage must be avoided.

During long term intravenous nutrition with Intralipid®, liver function tests should be performed. If these tests indicate that liver function is impaired, the therapy should be withdrawn.

Frequent (some advise daily) platelet counts should be done in neonatal patients receiving parenteral nutrition with Intralipid®.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies with Intralipid® have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

Pregnancy Category C: Animal reproduction studies have not been conducted with Intralipid®. It is also not known whether Intralipid® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Intralipid® should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Caution should be exercised when Intralipid® is administered to a nursing woman.

Pediatric Use: See DOSAGE AND ADMINISTRATION.

Make subheadings bold.

AVOID OVERDOSAGE ABSOLUTELY.

ADVERSE REACTIONS

The adverse reactions observed can be separated into two classes:

1. Those more frequently encountered are due either to a) contamination of the intravenous catheter and result in sepsis, or to b) vein irritation by concurrently infused hypertonic solutions and may result in thrombophlebitis. These adverse reactions are inseparable from the hyperalimentation procedure with or without Intralipid®.
2. Less frequent reactions more directly related to Intralipid® are: a) Immediate or early adverse reactions, each of which has been reported to occur in clinical trials, in an incidence of less than 1%: dyspnea, cyanosis, allergic reactions, hyperlipemia, hypercoagulability, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in the chest and back, slight pressure over the eyes, dizziness, irritation at the site of infusion and, rarely, thrombocytopenia in neonates.

b) Delayed adverse reactions such as hepatomegaly, jaundice due to central lobular cholestasis, splenomegaly, thrombocytopenia, leucopenia, transient increases in liver function tests and overloading syndrome (focal seizures, fever, leukocytosis, hepatomegaly, splenomegaly and shock).

The deposition of a brown pigmentation in the reticuloendothelial system, the so-called "intravenous fat pigment," has been reported in patients infused with Intralipid®. The causes and significance of this phenomenon are unknown.

OVERDOSAGE

In the event of fat overload during therapy, stop the infusion containing Intralipid® 30% until visual inspection of the plasma, determination of triglyceride concentrations, or measurement of plasma light-scattering activity by nephelometry indicates the lipid has cleared. Re-evaluate the patient and institute appropriate corrective measures. See WARNINGS and PRECAUTIONS.

DOSAGE AND ADMINISTRATION

Intralipid® 30% Pharmacy Bulk Package should be administered only as a part of a three-in-one or total nutrient admixture via peripheral vein or by central venous infusion.

Directions For Proper Use Of Pharmacy Bulk Package

INTRALIPID® 30% PHARMACY BULK PACKAGE IS NOT INTENDED FOR DIRECT INFUSION.

The container closure may be penetrated only once using a suitable sterile transfer device or dispensing set which allows measured dispensing of the contents. The Pharmacy Bulk Package is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area). Once the closure is penetrated, the contents should be dispensed as soon as possible; the transfer of contents to suitable TPN admixture containers must be completed within 4 hours of closure penetration. The bottle should be stored below 25°C (77°F) after the closure has been entered. Date and time of container entry should be noted in the area designated on the container label.

Admixtures made using Intralipid® 30% should be used promptly. See MIXING GUIDELINES AND LIMITATIONS section for admixture storage recommendations.

Adult Patients

The initial infusion rate of the nutrient admixture in adults should be the equivalent of 0.1 g fat/minute for the first 15 to 30 minutes of infusion. If no untoward reactions occur (see ADVERSE REACTIONS section), the infusion rate of the nutrient admixture can be increased to be equivalent to 0.2 g fat/minute. For adults, the admixture should not contain more than 330 mL of Intralipid® 30% on the first day of therapy. If the patient has no untoward reactions, the dose can be increased on the following day. The daily dosage should not exceed 2.5 g of fat/kg of body weight (8.3 mL of Intralipid® 30% per kg). Intralipid® should make up no more than 60% of the total caloric input to the patient. Carbohydrate and a source of amino acids should comprise the remaining caloric input.

Pediatric Patients

The dosage for premature infants starts at 0.5 g fat/kg body weight/24 hours (1.7 mL Intralipid® 30%) and may be increased in relation to the infant's ability to eliminate fat. The maximum dosage recommended by the American Academy of Pediatrics is 3 g fat/kg/24 hours.[3]

The initial rate of infusion of the nutrient admixture in older pediatric patients should be no more than 0.01g fat/minute for the first 10 to 15 minutes. If no untoward reactions occur, the rate can be changed to permit infusion of 0.1 g of fat/kg/hour. The daily dosage should not exceed 3 g of fat/kg of body weight.[3] Intralipid® should make up no more than 60% of the total caloric input to the patient. Carbohydrate and a source of amino acids should comprise the remaining caloric input.

Essential Fatty Acid Deficiency

When Intralipid® is administered to correct essential fatty acid deficiency, eight to ten percent of the caloric input should be supplied by Intralipid® in order to provide adequate amounts of linoleic and linolenic acids. When EFAD occurs together with stress, the amount of Intralipid® needed to correct the deficiency may be increased.

Administration

See MIXING GUIDELINES AND LIMITATIONS section for information regarding mixing this fat emulsion with other parenteral fluids.

Intralipid® 30% (30% I.V. Fat Emulsion) is not for direct infusion. It must be infused as part of an admixture into a central or peripheral vein. The flow rate of the admixture should be controlled with an infusion pump. Filters of less than 1.2 micron pore size must not be used with admixtures containing Intralipid® 30%.

Conventional administration sets and TPN pooling bags contain polyvinyl chloride (PVC) components that have DEHP (diethyl hexyl phthalate) as a plasticizer. Fat-containing fluids such as Intralipid® extract DEHP from these PVC components. Therefore, it may be advisable to use a non-DEHP administration set for infusing admixtures which contain Intralipid®.

Do not use any bottle in which there appears to be an oiling out on the surface of the emulsion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

MIXING GUIDELINES AND LIMITATIONS

INTRALIPID® 30% PHARMACY BULK PACKAGE IS NOT INTENDED FOR DIRECT INFUSION.

It must be combined with fluids so total parenteral nutrition (TPN) that the resulting admixture has a final concentration of not more than 20% fat (0.2 g fat per mL of admixture). The following table may be used as a guide:

Volume of Intralipid® 30%		Required Minimum Volume of Dextrose/ Amino Acid Solutions		Final Volume of Admixture	Final Fat Concentration
1 mL	+	0.5 mL	=	1.5 mL	20%
100 mL	+	50 mL	=	150 mL	20%
250 mL	+	125 mL	=	375 mL	20%
500 mL	+	250 mL	=	750 mL	20%

Investigations have been conducted which demonstrate the compatibility of Intralipid® 30% when properly mixed with either Novamine® (8.5%, 11.4% or 15%) or 8.5% Travasol® or 10% Travasol® Amino Acid Injections for use in Total Parenteral Nutrition (TPN) therapy.

Perform all manipulation in a suitable work area, such as a laminar flow hood.

The following proper mixing sequence must be followed to minimize pH related problems by ensuring that typically acidic Dextrose Injections are not mixed with lipid emulsions alone:

1. Transfer Dextrose Injection to the TPN admixture container
2. Transfer Amino Acid Injection
3. Transfer Intralipid® 30%.

Note: Amino Acid Injection, Dextrose Injection and Intralipid® may be simultaneously transferred to the admixture container. Admixing should be accompanied by gentle agitation to avoid localized concentration effects.

These admixtures should be used promptly with storage under refrigeration (2°-8°C) not to exceed 24 hours and must be completely used within 24 hours after removal from refrigeration.

It is essential that the admixture be prepared using strict aseptic technique as this nutrient mixture is a good growth medium for microorganisms.

Additives other than those named above may be incompatible. Complete information is not available. Those additives known to be incompatible should not be used. Consult with pharmacist. If, in the informed judgment of the prescribing physician, it is deemed advisable to introduce additives, use aseptic technique.

Mix thoroughly when additives have been introduced. Do not store solutions containing additives (e.g., vitamins and minerals).

Additives must not be added directly to Intralipid® and in no case should Intralipid® be added to the TPN container first. Bags should be shaken gently after each addition to minimize localized concentration.

If evacuated glass containers are used, add the Dextrose and Amino Acid Injections first, followed by Intralipid® and then additives. Bottles should be shaken gently after each addition.

Supplemental electrolytes, trace metals or multivitamins may be required in accordance with the prescription of the attending physician.

The prime destabilizers of emulsions are excessive acidity (low pH) and inappropriate electrolyte content. Careful consideration should be given to additions of divalent cations (Ca^{++} and Mg^{++}) which have been shown to cause emulsion instability. Amino acid solutions exert a buffering effect protecting the emulsion.

The admixture should be inspected carefully for "breaking or oiling out" of the emulsion. "Breaking or oiling out" is described as the separation of the emulsion and can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the admixed emulsion. The admixture should also be examined for particulates. The admixture must be discarded if any of the above is observed.

Failure to follow the above Mixing Guidelines and Limitations, including recommended storage temperature, storage time, order of mixing, etc., may result in an unstable admixture.

HOW SUPPLIED

Intralipid® 30% (30% I.V. Fat Emulsion) is supplied as a sterile emulsion in a Pharmacy Bulk Package in the following fill sizes:

250 mL	NDC 0338-0495-02
500 mL	NDC 0338-0495-03

STORAGE

Intralipid® 30% should not be stored above 25°C (77°F). Do not freeze Intralipid® 30%. If accidentally frozen, discard the bottle.

REFERENCES

1. Padley FB: "Major Vegetable Fats," *The Lipid Handbook*, (Gunstone FD, Harwood JL, Padley FB, eds.), Chapman and Hall Ltd, Cambridge, UK (1986), pp. 88-9.
2. Levene MI, Wigglesworth JS, Desai R: Pulmonary fat accumulation after Intralipid® infusion in the preterm infant. *Lancet* 1980; 2(8199):815-8.
3. American Academy of Pediatrics: Use of intravenous fat emulsion in pediatric patients. *Pediatrics* 1981; 68:5(Nov):738-43.

71-6053-0
(Issued _____)

Manufactured for
Clintec Nutrition Company
Affiliated with
Baxter Healthcare Corporation & Nestlé S.A.
Deerfield, IL 60015 USA

Manufactured by
Kabi Pharmacia Inc.
Clayton, NC 27520 USA

Kabi Pharmacia

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-942

CHEMISTRY REVIEW(S)

6.1

Division of Medical Imaging, Surgical and Dental Drug Products

Chemistry Review #4

OCT 13 1993

NDA 19-942

Date Completed: 9-30-93

Submission Type:
Original Amendment (AC) dated 6-30-93, HFD-160 date 7-2-93, Date assigned 7-8-93
Original Amendment (BC) dated 7-22-93, HFD-160 date 7-23-93, Date assigned 7-27-93

Applicant/Sponsor: Kabi Pharmacia Inc.
U.S.Route 70 East
P.O. Box 597
Clayton, N.C. 27520
Attention: Thomas L. Pituk
Director, Regulatory Affairs

Reviewer: Stan Koch

Product Name(s):

Proprietary: Intralipid 30% Pharmacy Bulk Package

Nonproprietary: Intravenous Fat Emulsion 30% Pharmacy Bulk Package

Official: none

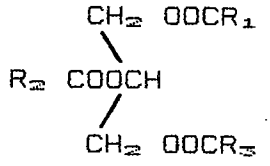
Code Name/Number:

Route of Administration: IV (fluid withdrawn from this package)
Dosage Forms: injection/infusion
Strength: 30%
Drug Category: LVP

Indications: Source of calories and essential fatty acids for patients requiring parenteral nutrition.

Chemical Name/Structural Formula:

soybean oil - triglycerides of oleic acid, linoleic acid, linolenic acid, palmitic acid, and stearic acid.



egg yolk phospholipids - mixture of phospholipids obtained from egg yolk

Supporting and Related Documents:

NDA 17-643	Intralipid (I.V. Fat Emulsion) 10%
NDA 18-449	Intralipid (I.V. Fat Emulsion) 20%

Remarks:

The original NDA is dated 12-29-88, received CDER 1-5-89, and ultimately withdrawn 2-2-89. KabiVitrum agreed to voluntarily withdraw NDA 19-942 in their 1-12-89 letter to FDA. The subsequent resubmission is dated 6-29-90, and Chemistry Review #1 is dated 11-15-90. A Not Approvable letter issued 2-28-91. Processing of the 12-19-91 AZ produced Chemistry Review #2 dated 3-10-92. Remaining deficiencies sent to the firm 4-30-92 generated 9-4-92 amendment. Inquiries from Chemistry Review #3 dated 11-10-92 sent to Kabi on 3-19-93. The subject 6-30-93 and 7-22-93 pair of amendments respond to this most recent letter.

As of 5-3-93 the KabiVitrum AB facilities in both Stockholm and Kungsangen, Sweden, and the KabiVitrum, Inc. plant in Clayton, NC., were evaluated by HFD-320 as acceptable from the standpoint of CGMPs. Another request for an update was initiated on 9-8-93.

The proposed expiration dating period for Intralipid 30% remains at 18 months/25°C.

The questions which we raised in the Agency's action letter dated 3-19-93 are addressed below under the Review Notes according to the responses contained in the firm's 6-30-93 and 7-22-93 amendments.

Conclusions and Recommendations:

This application is Approvable from the standpoint of the manufacturing & controls pending satisfactory response to EER update request sent to HFD-320 on 9-7-93. Methods have been validated to our satisfaction. Expiration dating period 18 months/25°C. Most recent versions of the draft package insert (in 6-30-93 amendment) and draft labels (in 9-4-92 amendment) are acceptable from standpoint of chemistry. Storage temperature specifically written for use with this drug product.

Stan Koch HFD-160

cc:
Orig NDA 19-942
HFD-160/Div File
HFD-160/PLove
HFD-160/SKoch
HFD-160/ESheinin
HFD-160/PCooney
HFD-161/AMWeikel
F/T SKoch
R/D init by ESheinin
HFR-SE100/ATL-DO

10-13-93

5 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 19-942
chemFT4

6.1

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Analysis
1114 Market Street, Room 1002
St. Louis, MO 63101
Tel (314) 539-2135
FAX Tel (314) 539-2113

Date: July 13, 1993

From: Henry D. Drew, Ph.D., Chief, Drug Monitoring Branch (HFH-300)

Subject: **Evaluation of NDA - MVP for Intralipid 30 % Emulsion (NDA: 19-942) Submitted by Kabi Pharmacia**

To: Stanley Koch, NDE Review Chemist (HFD-160)

The evaluation of the Particle Size Method for Intralipid 30 % Emulsion NDA - MVP has been completed and the method is acceptable for quality control and regulatory purposes. Please refer to specific comments from the evaluating chemist, Duckhee Y. Toler, presented on the attached memorandum and worksheets.

As per program requirements, we are forwarding the original worksheets. We shall **retain the reserve sample for 90-days before disposal of remaining sample.** If you feel that the reserve sample should be held longer, please contact DDA.

Henry D. Drew

Henry D. Drew, Ph.D.
Chief, Drug Monitoring Branch

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Division of Drug Analysis
1114 Market Street, Room 1002
St. Louis, MO 63101
Tel. (314) 539-2011 (ext.119)
FAX Tel. (314) 539-2011

DATE : July 12, 1993

FROM : Duckhee Y. Toler, Chemist (HFH-300)

SUBJECT : Method Validation for NDA 19-942
Intralipid 30% Fat Emulsion
Kabi Pharmacia

TO : Stan Koch (HFD-160)

THROUGH : Carol M. Kerner, Supervisor Lab B (HFH-300) C M Kerner 7/13/93

Particle size analysis was done by using ~~[redacted]~~ particle size analyzer. The detectable particle size ranges of ~~[redacted]~~ with our analyzer. With this ~~[redacted]~~

Duckhee Y. Toler
Duckhee Y. Toler
Chemist

2 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 19-942
MEMO, July 12

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 19, 1993

FROM: Stan Koch , Reviewing Chemist, HFD-_160
Through: _Eric B, Sheinin, PhD___, Supervisory Chemist, Division of Medical Imaging, Surgical & Dental Drug Products, CDER 4/19/93

SUBJECT: Laboratory Assignment(s) for NDA Methods Validation (MV)

TO: Henry D. Drew, Chief, Drug Monitoring Br., Div. of Drug Analysis, HFH-300

NDA No: 19-942 **Product:** Intralipid 30% Intravenous Fat Emulsion Pharmacy Bulk Package

Applicant: Kabi Pharmacia, 1899 Highway 70 East, Clayton, N.C. 27520

Enclosed you will find MV request forms (2871 & 2871a). The MV package for this NDA will be forwarded to you from the Southeast Regional Laboratory (HFR-SE660), Atlanta, GA together with a copy of the analytical reports representing the applicant's analyses of the lots represented by the drug product described above using the proposed NDA methods.

Stan Koch
Reviewing Chemist, HFD-160

Enclosures

MI/Method Validation Initiation

cc: Original NDA
HFD-_160 __/Division File
Division of Drug Analysis, HFH-300
Compliance Evaluation Staff, HFD-320
Division of Field Sciences, HFC-140

3.1 ctr.

Division of Medical Imaging, Surgical and Dental Drug Products

Chemistry Review #3

DEC 15 1992

NDA 19-942

Date Completed: 11-10-92

Submission Type: Original Amendment (AC) dated 9-4-92
HFD-160 date: 9-8-92
Date assigned:

Applicant/Sponsor: Kabi Pharmacia Inc.
U.S.Route 70 East
P.O. Box 597
Clayton, N.C. 27520
Attention: Thomas L. Pituk
Director, Regulatory Affairs

Reviewer: Stan Koch

Product Name(s):

Proprietary: Intralipid 30% Pharmacy Bulk Package

Nonproprietary: Intravenous Fat Emulsion 30% Pharmacy Bulk Package

Official: none

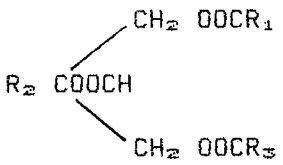
Code Name/Number:

Route of Administration: IV (fluid withdrawn from this package)
Dosage Forms: injection/infusion
Strength: 30%
Drug Category: LVP

Indications: Source of calories and essential fatty acids for patients requiring parenteral nutrition.

Chemical Name/Structural Formula:

soybean oil - triglycerides of oleic acid, linoleic acid, linolenic acid, palmitic acid, and stearic acid.



egg yolk phospholipids - mixture of phospholipids obtained from egg yolk

Supporting and Related Documents:

NDA 17-643 Intralipid (I.V. Fat Emulsion) 10%
NDA 18-449 Intralipid (I.V. Fat Emulsion) 20%

Remarks:

The original NDA is dated 12-29-88, received CDER 1-5-89, and ultimately withdrawn 2-2-89. KabiVitrum agreed to voluntarily withdraw NDA 19-942 in their 1-12-89 letter to FDA. The subsequent resubmission is dated 6-29-90, and Chemistry Review #1 is dated 11-15-90. A not approvable letter issued 2-28-91. Processing of the 12-19-91 AZ produced Chemistry Review #2 dated 3-10-92. Remaining deficiencies sent to the firm 4-30-92 generated the present amendment.

As of this date (10-30-92), the Swedish facilities for which a CGMP evaluation were requested are entered as Pending-On Hold in CIRTS. The Clayton, N.C. facility inspection status is Completed. The original EER form (current date entered adjacent to date originally submitted, with notation "request for update") was resubmitted to HFD-320 via HFD-100 for an update on 3-2-92. Another update request was sent on 10-26-92.

According to information contained in the 12-19-91 amendment Kabi Pharmacia has an

[redacted]

, Documents in hand serve to secure this working agreement and permit admixture statements in labeling regarding Travasol products which are supported by stability data.

The proposed expiration dating period for Intralipid 30% is 18 months/25°C.

Conclusions and Recommendations:

We have not been formally contacted by HFD-320 regarding the CGMP status of the KabiVitrum AB facilities located at Franzengatan, Stockholm and at Kraftvagen, Kungsangen, Sweden, used as the source of supply of soybean oil and egg yolk phospholipid, and the Kabi Pharmacia plant at Clayton, N.C. An EER update was initiated on 10-26-92. [CIRTS status data: Swedish firms Pending - On Hold, Clayton, N.C. Completed.]

10 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 14942

Chem #3

Division of Medical Imaging, Surgical and Dental Drug Products

Chemistry Review #2

APR 17 1992

NDA 19-942

Date Completed: 3-10-92

Submission Type: Original Amendment (AZ) dated 12-19-91
HFD-160 date: 12-24-91
Date assigned:

Applicant/Sponsor: Kabi Pharmacia Inc.
U.S.Route 70 East
P.O. Box 597
Clayton, N.C. 27520
Attention: Thomas L. Pituk
Director, Regulatory Affairs

Reviewer: Stan Koch

Product Name(s):

Proprietary: Intralipid 30% Pharmacy Bulk Package

Nonproprietary: Intravenous Fat Emulsion 30% Pharmacy Bulk Package

Official: none

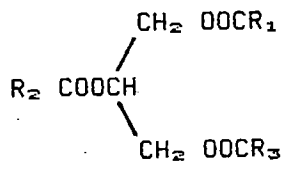
Code Name/Number:

Route of Administration: IV (fluid withdrawn from this package)
Dosage Forms: injection/infusion
Strength: 30%
Drug Category: LVP

Indications: Source of calories and essential fatty acids for patients requiring parenteral nutrition.

Chemical Name/Structural Formula:

soybean oil - triglycerides of oleic acid, linoleic acid, linolenic acid, palmitic acid, and stearic acid.



egg yolk phospholipids - mixture of phospholipids obtained from egg yolk

Supporting and Related Documents:

NDA 17-643 Intralipid (I.V. Fat Emulsion) 10%
NDA 18-449 Intralipid (I.V. Fat Emulsion) 20%

Remarks:

The original NDA is dated 12-29-88, received CDER 1-5-89, and ultimately withdrawn 2-2-89 after this Agency raised questions regarding the high concentration of fat, the use of the pharmacy bulk package for this application, and/or the unique combination of these two distinctions. KabiVitrum agreed to voluntarily withdraw NDA 19-942 in their 1-12-89 letter to FDA. The subsequent resubmission is dated 6-29-90, and Chemistry Review #1 is dated 11-15-90. The not approvable letter issued 2-28-91.

The original Intralipid (Intravenous Fat Emulsion) application (NDA 17-643) dated 8-9-74 for the 10% concentration of soybean oil was approved for marketing 10-7-75; the applicant at that time was Cutter Laboratories, Berkeley, CA, with the drug manufacturing operation located at Vitrum AB, Stockholm, Sweden. Cutter-Vitrum, Inc., Emeryville, CA, submitted NDA 18-449 for the 20% concentration on 1-11-80; the 1-23-81 approval provided for the manufacture to take place at both the Clayton, N.C. and Stockholm facilities.

This drug product is intended solely for the preparation of total nutrient admixtures (%age fat NMT —) in the pharmacy setting, and is not intended for direct administration. This 30% concentration offers a higher fat to volume ratio than the other Intralipid products, and is directed toward patients on a fluid volume restriction. The 30% product also differs from the 10% and 20% concentrations in

Request for CGMP evaluation of KabiVitrum AB facilities in Stockholm and Kungsangen, Sweden, and KabiVitrum, Inc. facilities in Clayton, N.C. sent to HFD-320 on 8-6-90. These inspections as of 3-2-92 are pending; request for update sent to HFD-320 on or about 3-4-92.

Conclusions and Recommendations:

This application remains not approvable from the standpoint of the manufacturing and controls. See the "Draft of Chemistry Part, Letter to Applicant" attached to this review.

Stan Koch

S.A.Koch, HFD-160

cc:
Orig NDA 19-942
HFD-160/Div File
HFD-160/SKoch/ESheinin
HFD-160/JWilson/JKenealy/PCooney
HFD-161/RJoyce
F/T SKoch 3/10/92
R/D init by ESheinin

4-17-92

14 Page(s) Withheld

1 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-19-942
Chem #2

21

Division of Medical Imaging, Surgical and Dental Drug Products

Chemistry Review #1

DEC 13 1990

NDA 19-942

Date Completed: 11-15-90

Application dated: 6-29-90
HFD-160 date: 7-2-90

CDER date: 7-2-90
Date assigned:

Submission type: resubmission

Reviewer: Stan Koch

Applicant/Sponsor: KabiVitrum, Inc.
U.S.Route 70 East
P.O. Box 597
Clayton, N.C. 27520

Product Name(s):

Proprietary: Intralipid 30% Pharmacy Bulk Package

Nonproprietary: Intravenous Fat Emulsion 30% Pharmacy Bulk Package

Official: none

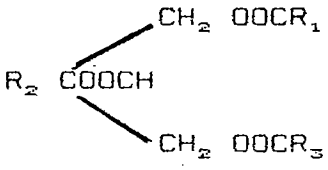
Code Name/Number:

Route of Administration: IV (fluid withdrawn from this package)
Dosage Forms: injection/infusion
Strength: 30%
Drug Category: LVP

Indications: Source of calories and essential fatty acids for patients requiring parenteral nutrition.

Chemical Name/Structural Formula:

soybean oil - triglycerides of oleic acid, linoleic acid, linolenic acid, palmitic acid, and stearic acid.



egg yolk phospholipids - mixture of phospholipids obtained from egg yolk

Supporting and Related Documents:

NDA 17-643	Intralipid (I.V. Fat Emulsion) 10%
NDA 18-449	Intralipid (I.V. Fat Emulsion) 20%

Remarks:

This original NDA is dated 12-29-88, received CDER 1-5-89, and ultimately withdrawn 2-2-89 after this Agency raised questions regarding the high concentration of fat, the use of the pharmacy bulk package for this application, and/or the unique combination of these two distinctions. KabiVitrum agreed to voluntarily withdraw NDA 19-942 in their 1-12-89 letter to FDA.

The original Intralipid (Intravenous Fat Emulsion) application (NDA 17-643) dated 8-9-74 for the 10% concentration of soybean oil was approved for marketing 10-7-75; the applicant at that time was Cutter Laboratories, Berkeley, CA, with the drug manufacturing operation located at Vitrum AB, Stockholm, Sweden. Cutter-Vitrum, Inc., Emeryville, CA, submitted NDA 18-449 for the 20% concentration on 1-11-80; the 1-23-81 approval provided for the manufacture to take place at both the Clayton, N.C. and Stockholm facilities.

This drug product is intended solely for the preparation of total nutrient admixtures (%age fat NMT) in the pharmacy setting, and is not intended for direct administration. This 30% concentration offers a higher fat to volume ratio than the other Intralipid products, and is directed toward patients on a fluid volume restriction. The 30% product also differs from the 10% and 20% concentrations in

Request for CGMP evaluation of KabiVitrum AB and KabiVitrum, Inc. facilities sent to HFD-320 on 8-6-90. Methods Validation proceedings not yet initiated.

Conclusions and Recommendations:

This application is not approvable from the standpoint of the manufacturing and controls. See the "Draft of Chemistry Part, Letter to Applicant" attached to this review.

S.A.Koch, HFD-160

cc:
Orig NDA 19-942
HFD-160/Div File
HFD-160/SKoch
HFD-161/RJoyce
R/D init by ESheinin

12-13-90

24 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 19-942 Chem #1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-942

PHARMACOLOGY REVIEW

3.1

NDA 19-942 JUN 2 1992

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Amendment AZ

Letter Date:	12/19/91	Reviewer:	J.E. Wilson
HFD-160:	12/24/91	Review Started:	5/18/92
		Review Completed:	6/02/92

Pharmacology Consult in Response to Request by Reviewing Chemist

APPLICANT: Kabi Pharmacia
Clayton, NC

DRUG: INTRALIPID® 30% I.V. Fat Emulsion (Pharmacy Bulk Package)

CATEGORY: Replenisher (fluid, nutrient)

COMPOSITION:

	Per 100 mL
Soybean Oil	30.0g
Egg Yolk Phospholipids	1.2g
Glycerin	1.7g
NaOH	(to adjust pH)
Water for Injection	q.s.
Osmolarity	200 mOsmol/L
pH	8.0 (6.0-8.9)

CONTAINER CHARACTERISTICS:

The 30% emulsion will be packaged in 250 mL and 500 mL glass bottles of USP Type II or better. The closure

RELATED NDAs: 17-643 and 18-449

DOSAGE:

INTRALIPID 30% in a Pharmacy Bulk Package is not intended for direct infusion.

Daily dosage in the adult should not exceed 2.5 g of fat/kg of body weight (8.3 mL of INTRALIPID 30% per kg).

Daily dosage in pediatric patients should not exceed 3 g of fat/kg of body weight.

EVALUATION:

The amendment of December 19, 1991, is in response to our deficiency letter of February 28, 1991. The reviewing chemist requested that the

methodology for the testing of pesticides in soybean oil be discussed and that a specification be listed for each pesticide residue. A similar request was made for the pesticides in egg yolk phospholipid.

— batches of fully refined soybean oils used in the production of INTRALIPID during 1991 were analyzed by the ——

— batches of —— Egg Phospholipids also used in the production of INTRALIPID during 1991 were analyzed by the same institution.

Detection limits (mg/kg) and quantification —— the detection) limits as established by the —— are presented for 46 permitted pesticides on soybeans and a total of 20 pesticides that may be found in egg yolk phospholipids. Results indicated that none of the pesticides listed for either product were in sufficient quantity to be detectable.

The applicant states that the refinement of soybean oil consists of —

Each year FDA publishes the results of their pesticide monitoring. The 1990 results (J Assoc Off Anal Chem 74: 136A-139A, 1991) are shown in the following table:

Commodity Group	No. of Samples	Percent Samples with No Residues	Percent Samples Over Tolerence
Domestic samples			
Soybeans	59	59	0
Crude vegetable oil	9	44	0
Refined vegetable oil	11	100	0
Imported samples			
Crude vegetable oil	11	82	0
Refined vegetable oil	31	77	0

The vegetable oils in the above table include other oils beside soybean oil. Further, the tolerances in the above table are based on the oral route of administration. The tolerance for the pesticides by the intravenous route may be lower than by the oral route, and hence the percent of samples over tolerance in the above table may not necessarily be zero. Until the individual tolerances of pesticides by the intravenous route are known, no detectable residues for any pesticide should be present in the purified soybean oil used in the present product. Likewise, no detectable residues should be present in the egg yolk phospholipids.

Removal of pesticides during the purification of soybean oil and the absence of detectable pesticide residues in either this item or egg yolk phospholipids makes both these components acceptable for use in the applicant's drug product. The high percentage of samples of refined vegetable oil that contain no pesticide residues when analyzed by FDA further supports the safety of the soybean oil.

CONCLUSION:

The inability to detect pesticides residues in either the soybean oil or egg yolk phospholipid components used in INTRALIPID® 30% Fat Emulsion (Pharmacy Bulk Package) supports the safe use of the applicant's product.

Recommended changes in labeling are presented in the DRAFT OF COMMENTS TO APPLICANT.

J E Wilson 6/2/92
James E. Wilson, Ph.D.

Linda M. DeWitt 6/2/92

cc:
Orig. NDA 19-942
HFD-160/Division File
HFD-160/Pharm/JEWilson
HFD-160/MO/JKenealy
HFD-160/Chem/SKoch
HFD-160/CSO/AMWeikel
R/D Init. by LMDeWitt 5/27/92
F/T by JEWilson 6/02/92

DRAFT OF COMMENTS TO APPLICANT:

Please revise the package insert in accordance with 21 CFR 201.57 as follows:

The following subsections should be added to the PRECAUTIONS section:

"**Carcinogenesis, mutagenesis, impairment of fertility:** Studies with INTRALIPID® have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility."

"**Nursing Mothers:** Caution should be exercised when INTRALIPID® is administered to a nursing woman."

"**Pediatric use:** See DOSAGE AND ADMINISTRATION."

NDA 19-942
DIVISION OF MEDICAL IMAGING, SURGICAL AND DENTAL DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
~~Resubmission of 6/29/90~~

Review Date: 2/15/91

APPLICANT: KabiVitrum Incorporated, Clayton NC

ORGANIZATION PERFORMING TOXICITY STUDIES: FEB 19 1991

Ref. Firm 1: KabiVitrum AB, Stockholm, Sweden

FOREIGN PRECLINICAL STUDIES: Yes

DRUG: INTRALIPID 30% I.V. Fat Emulsion (Pharmacy Bulk Package)

CATEGORY: Replenisher (fluid, nutrient)

COMPOSITION:

	Per 100 mL
Soybean Oil	30.0g
Egg Yolk Phospholipids	1.2g
Glycerin	1.7g
NaOH	(to adjust pH)
Water for Injection	q.s.
Osmolarity	200 mOsmo/L
pH	8.0 (6.0-8.9)

CONTAINER CHARACTERISTICS:

The 30% emulsion will be packaged in 250 mL and 500 mL glass bottles of USP Type II or better. The closure

RELATED NDAs: 17-643 and 18-449

DOSAGE:

INTRALIPID 30% in a Pharmacy Bulk Package is not intended for direct infusion.

Daily dosage in the adult should not exceed 2.5g of fat/kg of body weight (8.3 mL of INTRALIPID 30% per kg).

Daily dosage in pediatric patients should not exceed 3g of fat of body weight.

ACUTE TOXICITY IN MICE (Ref. Firm 1):

Technical Report: 84 98 262
Test Material: INTRALIPID 30%

No. of Animals/Level: 10M & 10F

Dosage Levels (Ml/Kg): 30, 40, 50 and 60

Route of Administration: I.V. dorsal tail vein

Rate of Administration: 0.5mL/min (approx 1500 mL/kg/hr)

General Behavior: Only clinical sign observed in those animals dying was a morbid condition 3 to 6 hrs after administration until death.

Mortality:

Ml/Kg	Males	Females
30	0	0
40	0	0
50	0	0
60	7	3

LD_{50} (combined sexes) = 60 mL/kg

SUBACUTE TOXICITY:

RAT (Sprague-Dawley): Ref. Firm: 1
Technical Report: 85-99-053
Protocol:

Group	Material	Ml/kg/Day	*Gm Fat/Kg/Day
T	INTRALIPID 30%	60	18
K	INTRALIPID 20%	90	18

No. of Animals/Group: 9 males

Duration and Route: Intravenous for 28 consecutive days via a catheter inserted in to the vena cava via the jugular vein.

Rate of Infusion:

Group	Ml/Kg/Day	Hours	Ml/Kg/Hr
T	60	20	3.0
K	90	20	4.5

Growth Effects: The reference group (K) showed a slightly higher increase in body weight (3.48 g/day) compared with the test group (2.99 g/day). The difference was not considered significant.

Mortality: One rat in each group was sacrificed because of catheter related problems.

Food Consumption: Average intake was 7.7 g/kg and 7.3 g/day in the test and reference groups respectively.

Hematology: Two rats in the reference (K) group showed an increased number of reticulocytes. One rat in test group and one rat in reference group had a white count above 20,000/mm^3 due to an enhanced number of lymphocytes.

Clinical Chemistry: One test rat (T8-2365) receiving INTRALIPID 30% had markedly increased aspartate aminotransferase, alanine aminotransferase, and lactic dehydrogenase activities. Slightly enhanced alanine aminotransferase, activity was seen in another rat (T3-2352) from the test group and in one animal (K5-2349) from the reference group.

Organ Weights: Three animals had spleen weights weighing well above 2 grams.

Agent	Animal No.	Abs. Spleen Wt.
INTRALIPID 30%	T9-2367	2.10g
INTRALIPID 20%	K1-2353	2.69g
	K4-2355	2.85g

Gross Pathology: Significantly enlarged spleens in animals noted above.

Histopathology:

Lung: Very slight to slight fatty change in both test and reference groups except one reference group animal who had no fatty change. The fat droplets were deposited in macrophages or as casts in small blood vessels.

Thymus: Fatty changes in all animals with degree and incidence similar to lung. Fatty droplets deposited mainly in macrophages.

Spleen: With the exception of reference rat that showed a slight fatty change, all others in both groups possessed between a slight-moderate fatty change.

Slight vacuolation of cells in the red pulp in all rats except the same reference rat as above due to lipid deposition and a slight deposition of a yellowish pigment in macrophages. Part of this pigment showed a positive reaction when stained for iron. An increased hematopoietic activity occurred in the red pulp in two INTRALIPID 20% rats.

Liver: Fatty changes were observed in single hepatocytes and reticuloendothelial cells and groups of hepatocytes in all animals in both groups. Occasionally, hepatocytes with fatty changes were accompanied by mononuclear cell infiltration, by slight focal neurotic changes and slight granulomatous

reactions. Slight to moderate deposition of iron-containing pigment was seen predominantly in 3 of 9 rats in the INTRALIPID 20% group and a very slight deposition in 2 of 9 rats in the INTRALIPID 30% group.

Extramedullary hematopoietic foci were seen in one INTRALIPID 20% rat.

DOG (Beagles): Ref. Firm: 1

Technical Report:
Protocol: 84-94-168

Infusion Solution	Ml/Kg/Day	Triglyceride Gm/Kg/Day	Hours	Infusion Rate Ml/Kg/Hr
INTRALIPID 30%	30	9	6	5.0
INTRALIPID 20%	45	9	6	7.5
Ringer-acetate	45	0	6	7.5

No. of Animals/Group: 2M & 2F

Duration and Route: An intravenous cannula was inserted daily into a peripheral vein. Infusions were daily for 28 days.

Growth Effects: Males receiving INTRALIPID 30% showed an increase in body weight gain mainly during the first two weeks of the test period. Weight gain in the remaining two groups was similar to pre-test period.

Mortality: None

Food Consumption: Dogs in the test and reference groups gradually reduced their food intake during the test period.

Hematology: Nucleated erythrocytes were observed in blood smears from most of the dogs after administration of the two fat emulsions. Slight anisocytosis and a rather high reticulocyte count was observed in one female from the INTRALIPID 30% group.

A marked decrease occurred in the number of lymphocytes after administration of the two fat emulsions. A less pronounced decrease occurred in the Ringer-acetate controls.

Clinical Chemistry: Moderately decreased serum urea levels were observed in all fat emulsions on treated dogs. A moderate increase in alkaline phosphatase activity occurred in the two fat emulsions groups.

Serum cholesterol levels were increased after 28 days of infusion of both fat emulsions. INTRALIPID 30% produced a smaller increase (1.3-2.0-fold) than its INTRALIPID 20% counterpart (2.3-2.7-fold). The factor

contributing to the increase in total cholesterol was the low density lipoprotein (LDL) fraction and not the high density lipoprotein (HDL) fraction.

INTRALIPID 20% produced increased (1.9-2.3-fold) serum levels of phospholipid; whereas, INTRALIPID 30% produced no significant change in total serum phospholipid levels. The changes were related to an increase in the LDL phospholipids.

Urinalysis: All dogs receiving INTRALIPID 30% had decreased urinary osmolality and density. One male dog given INTRALIPID 20% had a likewise decrease. The changes were of moderate degree and only one male in the INTRALIPID 30% group had values below normal. A slight reduction in urinary osmolality and density was also observed in 2 of 4 dogs in the Ringer-acetate controls.

Opthalmological Exam: No abnormalities were detected as a result of administration of the infusion solutions.

Organ Weights: No definite trends revealed.

Gross Pathology: Both males and one female in the INTRALIPID 30% group had single superficial mucosal erosions of 3-5 mm in the duodenum. Further, 1 of 2 males in the INTRALIPID 20% group had a single superficial mucosal erosion of 5mm in the duodenum. There were no duodenal erosions in the control group.

Histopathology:

Liver: Lipid deposits of a slight degree in centrolobular hepatocytes and hepatic reticuloendothelial cells were found in both fat emulsions treated groups. Focal proliferation of mononuclear cells in the liver of a slight degree are stated to be treatment related. Lipoid pigments in the hepatic reticuloendothelial cells were also slight and were found in the fat emulsion groups.

Spleen: Lipid phagocytosis of the reticuloendothelial cells in the spleen and the mesenteric lymph nodes are also treatment related. The changes were graded as slight or moderate in both reference and test groups. Slight lipoid pigments were found in the same organs and groups and were considered treatment related.

Duodenum: Erosion of the mucosa (3-5 mm in diameter) was seen in the 1 of 2 males and 1 of 2 females in the INTRALIPID 30% and in 1 of 2 males in the INTRALIPID 20% group.

Clinical Behavior: One INTRALIPID 30% male dog had small sores around the ears form day 4 to day 9. One INTRALIPID 20% male dog had sores on the fore-and hind legs from day 1 to day 11. This same dog had loss of hair on the legs and from day 8 to day 11 a swelling on the right side of the jaw.

PLASMA HALF-LIVES FOR INTRALIPID (Ref. Firm 1):

Technical Reports: 84 98 263 and 82 99 026

Dosage: 100mg fat/kg

Rate of I.V. Administration: 1 mL/min or 20 mL/kg/hr

Results:

Test Material	Species	Strain	Number Sex	Half-life (Min)
INTRALIPID 30%	Rabbit	NZ White	4F	9.0
INTRALIPID 10%	Mouse	/ — /	12M	11.3
	Rat	Sprague Daw	5M	9.7
	Rabbit	NZ White	8M	10.3
	Dog	Beagle	4M	13.5
	Cat	/ — /	1M	10.2
	Man		M	11.4
			F	9.7

CARDIOVASCULAR EFFECTS IN THE CAT (Ref. Firm 1):

Preparation of Test Animal: / — / (1.3 mL/kg) was given intramuscularily followed by intravenous / — / (2 mL/kg of a / — / solution).

No. of Animals/Level: 2 males, 3 unspecified sex for controls.

First Experiment (84 98 264):

Dosing	Minutes After start of dosing	Dosage (mL/Kg)	Rate (mL/Kg/hr)
		INTRALIPID 30%	
Bolus 1 mL/kg	0	1	60
Bolus 1 mL/kg	15	1	60
Continuous infusion 1 mL/min for 90 min	30	27.8	0.5
		Saline Controls	
Bolus 1 mL/kg	0	1	60
Bolus 1 mL/kg	15	1	60
Continuous infusion 1 mL/min for 90 min	30	34.7	0.6

Second Experiment (85 98 061):

Test Material: INTRALIPID 30%
No. of Animals/Level: 1M & 1F
Protocol:

Dosing	Min after start of dosing	Rate
Continuous Infusion 0.03 mL/kg/min for 90 min	0	1.8 mL/kg/hr
Continuous infusion 0.1 mL/kg/min for 90 min	120	6.0 mL/kg/hr

Results:

Neither the bolus or continuous infusion of INTRALIPID 30% caused any significant change in blood pressure, heart rate, or respiratory volume from control and pretreatment values. Blood flow in the central mesenteric artery was decreased 30 minutes following cessation of the continuous administration of 27.8 mL/kg of INTRALIPID 30% and it eventually declined to 73% of the pretreatment value at 90 minutes. Hematocrit was also depressed 15% below pretreatment values 30 min after initiation of continuous infusion dose of INTRALIPID 30%. None of the foregoing effects were seen in connection with the continuous infusion of INTRALIPID 30% in the second experiment.

The S-T segment and T-wave were elevated in the EKG for both INTRALIPID 30% and saline control animals with the magnitude and incidence being greater in the treated animals.

BIOLOGIC TESTING OF [redacted] CLOSURE (Ref. Firm 2):

Test Material: [redacted]

Procedure: National Formulary XIV for [redacted]

Acute Systemic Injection in Mice:

Extraction Medium	Route	NF Results
0.9% NaCl	1V	Pass
Cotton Seed Oil	1P	Pass

INtracutaneous Reactivity in Rabbits:

Extraction Medium	Route	NF Results
0.9% NaCl	1C	Pass
Cotton Seed Oil	1C	Pass

EVALUATION:

The proposed product, INTRALIPID 30% I.V. Fat Emulsion (Pharmacy Bulk Package) is, as the applicant states, not for direct infusion. Rather, it is meant for administration only as part of an intravenous nutrition admixture via peripheral vein or by central venous infusion.

KabiVitrum has submitted additional pharmacologic and toxicologic data for the 30% emulsion that was collected by the parent firm in Sweden in studies performed between 1982 and 1985. Apparently these studies are submitted in the event that INTRALIPID 30% is injected inadvertently undiluted into a peripheral vein. Blood in-vitro compatibility studies supporting the peripheral infusion of undiluted INTRALIPID 30% have gone unreported.

One of the recently submitted toxicity studies was one in which the same amount of fat (18g/kg/day) was administered to two groups of rats for 28 days. The first group received 60 mL/kg/hr of INTRALIPID 30% at 3.0 mL/kg/hr and the second group received 90 mL/kg/day of INTRALIPID 20% at 4.5 mL/kg/hr. Enlarged spleens (weighing over 2 g) were seen in 1 of 9 males receiving the 30% concentrate ion and 2 of 9 males receiving the 20% concentration. Fatty changes were observed in single hepatocytes and reticuloendothelial cells of the liver and groups of hepatocytes in all animals in both groups.

Occasionally hepatocytes with fatty changes were accompanied by mononuclear cell infiltration, by slight focal necrotic changes, and slight granulomatous reactions. Further, deposition of iron-containing pigment was seen predominantly in the Kupffer cells of both groups of rats.

Slight vacuolation of cells in the red pulp of the spleen occurred in rats of both groups and was the result of lipoid deposition and slight deposition of a yellowish pigment in macrophages. Part of the pigment showed a positive reaction when stained for iron. Two INTRALIPID 20% rats showed an increased hematopoietic activity in the red pulp of the spleen. Evidence of hemolysis was thus present and if prolonged could lead to an anemia.

Another submitted study was a 28-day intravenous one in dogs that entailed three groups: (1) INTRALIPID 30% at 30 mL/kg/day at an infusion rate of 5.0 mL/kg/hr; (2) INTRALIPID 20% at 45 mL/kg/day at an infusion rate of 7.5 mL/kg/hr; and (3) a Ringer-acetate control group at 45 mL/kg/hr and an infusion rate of 7.5 mL/kg/hr. The amount of triglyceride administered to the two fat emulsion groups was 9 g/kg/day.

Nucleated erythrocytes were a by-product of the administration of the two fat emulsions indicating a sightly stimulating effect on erythropoiesis. A marked decrease in the number of lymphocytes was evident after the administration of the two fat emulsions.

Clinical chemistry findings included a moderate increase in alkaline phosphatase activity in both fat emulsion groups. The investigators noted that in this study and in previous studies with INTRALIPID 20% and INTRALIPID 10%, the higher the concentration of fat, the less pronounced was the increase in serum cholesterol. Those increases in cholesterol that did occur were in the low density lipoprotein (LDL) fraction. The same amount of fat (9g) gave rise to higher serum phospholipid values when administered as INTRALIPID 20% than when administered as INTRALIPID 30%. There was no significant increase when INTRALIPID 30% was administered.

The liver of dogs revealed lipoid deposits in the hepatocytes and lipoid deposits and pigments in the reticuloendothelial cells. Evidence of lipid phagoctosis was found in the spleen and mesenteric lymph nodes in both fat emulsion groups and was treatment related. A slight amount of lipoid pigments in these same organs was considered treatment related.

Perhaps the most serious findings in dogs at necropsy were superficial mucosal erosions (3-5 mm in diameter) in the duodenum in 3 of 8 animals receiving fat emulsions. The incidence in males was higher than females.

The presence of small sores around the ears of one male receiving INTRALIPID 30% and another male receiving INTRALIPID 20% with sore on the fore-and hind limbs plus a swelling on the right side of the jaw may indicate an interference with the immune defense mechanism.

The half-life of the triglycerides in the plasma of six mammalian species ~~in~~ luding humans was fairly short and relatively constant at 9-13 minutes.

The [redacted] closure on the 250 mL and 500 mL glass bottles is [redacted] The [redacted] passed the NF XIV tests for [redacted]

[redacted]

INTRALIPID 30% in a pharmacy bulk package when diluted and administered at the prescribed dosages is not believed to be more toxic to patients requiring parenteral nutrition than INTRALIPID 20% now appearing on the market.

CONCLUSION:

The applicant is approvable from the standpoint of pharmacology, but additional recommendations to the applicant are proposed.

Labeling conforms to the Labeling Revision Program and is adequate from the standpoint of pharmacology.

J. E. Wilson 02-15-91

cc:
Orig. NDA 19-942
HFD-160/Division File
HFD-160/JEWilson
R/D by: JWilson
R/D init by: KDMainigi 02-19-91
F/T by: AChapman 02-20-91
Wang 5111Y

HFD-160 CSO

J Palmer 2-26-91

DRAFT OF PHARMACOLOGY PORTION OF LETTER TO APPLICANT:

1. The source of soybean oil for use in INTRALIPID at all concentrations should be one that supplies a pesticide-free product. Since data for the evaluation of the toxicity of pesticides by the intravenous route are not available, a zero (0) level of acceptance is recommended, i.e., below the detection limits of current methodology.

2. FDA filed a Notice of Intent (FR, May 21, 1990, p. 20799) for comments on adopting an upper limit for aluminum content in large volume parenterals. The specification currently being considered is 25 micrograms per liter or 25 parts per billion. This value should be achieved when INTRALIPID 30% I.V. Fat Emulsion (Pharmacology Bulk Package) is diluted for intravenous administration as part of a Total Parenteral Nutrition (TPN) admixture.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-942

STATISTICAL REVIEW(S)

HFD-160

Statistical Review and Evaluation

NDA #: 19-942

Date: SEP - 2 1993

Applicant: KabiVitrum, Inc.

Name of Drug: Intralipid 30% I.V. Fat Emulsion (Pharmacy Bulk Package)

Documents Reviewed: Volumes 1.1, 1.4 and 1.5 Dated 2 July 1990

Introduction

For the purpose of showing equivalency between Intralipid 30% manufactured in the USA and in Sweden, KabiVitrum has submitted analyses and data on three studies with varying degrees of participation for both manufacturing and laboratory sites.

Design

Three studies were undertaken. First, with unknown study conditions, — batches of Intralipid 30% manufactured in the USA and analyzed in the USA, were compared with — batches produced and analyzed in Sweden. Second — batches produced in the USA and stored for / months at / degrees Centigrade were analyzed by both laboratories in the USA and in Sweden. Third, in a similar way, except for storage at / degrees Centigrade, — batches which were manufactured in Sweden were analyzed both in the USA and in Sweden.

Sponsor's Analyses

The Sponsor stated that the data from the initial analyses of — batches of Intralipid 30% manufactured and analyzed in the USA and from — batches produced and analyzed in Sweden show a small but significant difference in the amount of / —— / —— / With respect to the — batches produced in the USA and stored for /months at / degrees Centigrade, both laboratories in the USA and in Sweden analyzed the samples. The results indicated that there is on average —— higher values for / —— for the determination in the USA than in Sweden. Also, in a similar way, the / — batches manufactured in Sweden were analyzed in both the USA and in Sweden. The Sponsor concluded that the USA results are on average 0.34 mmol/1 higher than the Swedish ones.

Reviewer's Analyses

With respect to the first study, that of the / — /batches of

Intralipid 30% manufactured in the USA and analyzed in the USA which were compared with / — / batches produced and analyzed in Sweden, the results of the our statistical analysis is not free of the confounded effects of the laboratories. However, statistical analyses were performed on six response variables and the two production sites were compared with the results as follows:

Response Variable	P-Values for the Production Sites
——————— (mmol/1)	0.0005
pH	0.3286
Droplet Size Distribution	0.0068
——— (mg/ml)	0.0013
Phospholipids (mg/ml)	0.0032
Triglycerides (mg/ml)	0.0022

Therefore, in this study, there exists differences between the production sites (given the confounded effects of laboratories) with respect to ——————— droplet size distribution, glycerol, phospholipids and triglycerides for Intralipid 30%.

With respect to the second study, that of the —— batches produced in the USA and stored for — months at — degrees Centigrade with both of the laboratories in the USA and in Sweden analyzing the samples, statistical analyses were performed on three response variables and the two laboratory sites were compared with the results as follows:

Response Variable	P-Values for the Laboratory Sites
——————— (mmol/1)	0.2010
pH	0.6376
Droplet Size Distribution	0.6376

Thus, with respect to the three response variables that the Sponsor provide data for (i.e. / ——————— / pH and droplet size distribution), there were no differences between the analyzing laboratories.

With respect to the third study, that of the / —— / batches which

were manufactured in Sweden and analyzed both in the USA and in Sweden, statistical analyses were performed on the six response variables and the two laboratory sites were compared with the results as follows:

Response Variable	P-Values for the Laboratory Sites
——————— mmol/1)	0.0139
pH	0.2943
Droplet Size Distribution	0.2420
—— (mg/ml)	0.1836
Phospholipids (mg/ml)	0.2992
Triglycerides (mg/ml)	0.0129

Therefore, the Reviewer found that of the six response variables (i.e. ——————— pH, droplet size distribution, ——— phospholipids and triglycerides), there were no differences between the analyzing laboratories except in the case of ——— and triglycerides.

Further, the estimated differences (US laboratory minus the Swedish laboratory) from the means by study are as follows:

Response Variable	Study # 2	Study #3
——————— (mmol/1)	0.400	0.340
pH	0.025	-0.080
Droplet Size Distribution	-0.025	-0.080
—— (mg/ml)	-----	0.140
Phospholipids (mg/ml)	------	0.026
Triglycerides (mg/ml)	------	4.400

From least squares means estimates, the adjusted estimated differences in Study #1 (US manufactured minus Sweden manufactured adjusted for laboratory differences but, not the varying storage conditions of the three studies) are as follows:

Response Variable	Adjusted estimated differences between manufacturing sites	P-Value
——— (mmol/1)	0.133	NS
pH	0.097	NS
Droplet Size Distribution	-0.294	0.017
——— (mg/ml)	-1.215	0.0006
Phospholipids (mg/ml)	-0.960	0.0004
Triglycerides (mg/ml)	-21.025	0.0003

The estimated differences, without accounting for the confounding effects of the varying storage conditions, for ——— Phospholipids and Triglycerides are based solely upon ——— batches manufactured in Sweden and analyzed in both Sweden and the U.S.laboratories, since data for these variables on the product manufactured in the U.S. and analyzed in both the U.S. and Sweden are not available.

Summary

For the purpose of showing equivalency between Intralipid 30% manufactured in the USA and in Sweden, KabiVitrum has submitted analyses and data on three studies with varying degrees of participation for both manufacturing sites.

These studies were, first, ——— batches of Intralipid 30% manufactured in the USA, with unknown storage conditions, and analyzed in the USA, were compared with ——— batches produced and analyzed in Sweden. Second, ——— batches produced in the USA and stored for ——— months at ——— degrees Centigrade were analyzed by both laboratories in the USA and in Sweden. Third, in a similar way ——— batches which were manufactured in Sweden and stored at ——— degrees Centigrade were analyzed both in the USA and in Sweden.

The Sponsor stated the data from the initial analyses of ——— batches of Intralipid 30% manufactured and analyzed in the USA and from ——— batches produced and analyzed in Sweden show a small but significant difference in the amount of ——— With respect to the ——— batches produced in the USA, both laboratories in the USA and in Sweden analyzed the samples. The results indicated that there is on average 0.4 mmol/1 higher

values for [redacted] for the determination in the USA than in Sweden. Also, in a similar way, the [redacted] batches manufactured in Sweden were analyzed in both the USA and in Sweden. The Sponsor concluded that the USA results are on average 0.34 mmol/1 higher than the Swedish ones.

The Reviewer found that, in the first study, there existed differences between the production sites (given confounded effects of laboratories) with respect to [redacted] droplet size distribution, [redacted] phospholipids and triglycerides for Intralipid 30%. With respect to the second study given only the three response variables that the Sponsor provide data for (i.e. [redacted] pH and droplet size distribution), there were no differences between the analyzing laboratories. In the third study, with data from the six response variables (i.e. [redacted] pH, droplet size distribution, [redacted] phospholipids and triglycerides), there were no differences between the analyzing laboratories except in the case of [redacted] and triglycerides.

However, the adjusted estimated differences in Study #1 (US manufactured minus Sweden manufactured adjusted for laboratory differences but not storage conditions) are as follows:

Response Variable	Adjusted estimated differences between manufacturing sites	P-Value
[redacted] (mmol/1)	0.133	NS
pH	0.097	NS
Droplet Size Distribution	-0.294	0.017
[redacted] (mg/ml)	-1.215	0.0006
Phospholipids (mg/ml)	-0.960	0.0004
Triglycerides (mg/ml)	-21.025	0.0003

Mordecai Friedberg,
Mathematical Statistician

Concur: WR 7 9/2/93
William R. Fairweather, PhD, Branch Chief, SARB,

cc: Original NDA 19-942
HFD-160
HFD-160/Dr. Woodbury
HFD-710/Chron
HFD-715/Chron
HFD-715/Dr. Fairweather/Dr. Lin/Mr. Friedberg
HFD-715/DRU 2.5 Intralipid 30%, KabiVitrum, Inc.
HFD-715/MF 8/13/93 Memo108

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-942

MEDICAL REVIEW

DIVISION DIRECTOR COMMENTS TO THE FILE

NDA: 19942
DRUG: Intralipid 30# Pharmacy Bulk Pack
INDICATION: Total Parenteral Nutrition
SPONSOR: Kabi Pharmacia Inc.
SUBMITTED: July 2, 1993

RELATED MEDICAL OFFICER REVIEW: September 23, 1993

BACKGROUND:

Intralipid 30% Pharmacy Bulk Pack was originally submitted in December 29, 1988 and was withdrawn within one month (January 12, 1989) because of the lack of clinical trials to support safety and efficacy. The NDA was resubmitted on June 29, 1990 and received a Not Approvalable Letter" on March 19, 1993. Three safety considerations, two chemistry/manufacturing and two labeling omissions were noted. The current amendment contains an adequate response to all deficiencies; however, the current labeling requires considerable strengthening as noted in the attached revisions.

Of concern during the review process is that the 30% Intralipid solution could be directly administered to a patient. In the amendment the sponsor indicates that direct infusion is not intended. In subsequent conversations (see t-con minutes of December 8, 1993), the sponsor indicated that the product is only for use in a three-in-one total admixture program. This was not clarified in the package insert or the current submission.

Of additional concern, is that if the 30% Intralipid is diluted to 10% or 20% concentrations, it is not identical to the 10 or 20% marketed intralipid solutions. The latter will have higher osmolarities and higher egg yolk phospholipid concentrations. These differences are probably negligible in a three-in-one admixture program with high osmolarity amino acids and dextrose. The difference would be important in a direct infusion of the diluted bulk pack. Therefore, the 30% intralipid Pharmacy Bulk Pack should contain stronger labeling which indicates that:

1) it is a pharmacy bulk pack and is not intended for direct infusion.
2) it should only be should as part of a three-in-one admixture program
3) it is not to be diluted with saline or dextrose for direct infusion via a Y connector
4) when diluted it is not a substitute for the marketed 10% or 20% intralipid solutions

See attached revised labeling for details.

Also as noted by the group leader, fat embolism as a syndrome should be added to the adverse reaction sections of all the intralipid products. This should be sent as a class labeling request to all fat emulsion manufacturers.

12/17/93

Patricia Y. Love, M.D.
Acting Division Director; HFD-160

6.1

Medical Officer's Review NDA Amendment

NDA # 19942

Document Date 6/30/93
Date Received 7/02/93
Review Date 9/23/93

Agent: Intralipid 30% I.V. Fat Emulsion
(Pharmacy Bulk)

DEC 17 1993

Sponsor: Kabi Pharmacia Inc.
P.O. Box 597
1899 Highway 70 East
Clayton, N.C. 27502

Resume:

The original NDA submission for Intralipid 30% I.V. Fat Emulsion was submitted December 29, 1988. The company was contacted and informed that the NDA might not be filed because labeling indicated the agent v

submitted documenting the safety and efficacy of the fat emulsion in the proposed concentration for use in humans. In addition there were significant reservations raised by chemistry and microbiology with the proposed new formulation.

On January 12, 1989 a letter was received from the sponsor requesting withdrawal of the NDA without prejudice, and requesting a meeting to review the deficiencies and plan for a future submission. A meeting with the company was held March 22,1989.

The sponsor resubmitted the NDA June 29, 1990. In order to address a variety of concerns from chemistry, microbiology, and questions relative to the stability of the emulsion, correspondence and amendments have been submitted February 16 and October 25, 1989; March 11, May 3, May 10 and December 19, 1991; September 4 and October 27, 1992.

A "Not Approvable Letter" was sent to the sponsor March 19, 1993. This letter was based on three safety considerations, two chemistry and manufacturing deficiencies, and two labeling omissions that the Agency felt had not been adequately addressed in the above submissions.

The amendment under review dated June 30, 1993 is the sponsor's item by item response to the concerns listed in the letter of March 19, 1993.

Summary of Responses:

the group administered Intralipid 30%; five were recorded from the Intralipid 20% group. All patients who could be followed had complete recovery of abnormal laboratory or clinical responses.

The two questions under **Chemistry, Manufacturing and Controls** were answered to the satisfaction of the chemist (Koch); this section was approved December 15, 1992.

Microbiology signed the submission approvable 01/22/92
Pharmacology signed the submission approvable 06/02/92.

Under **Labeling**, requests were made to add additional information under: Carcinogenesis,Mutagenesis and Fertility; Pediatric use. Request was also made to include information to prevent "cracking" of the All-in-One Admixture. This information was added to the new label insert (Att. # 4).

Pre-approval inspection observations:

During the pre-approval inspection 3 procedural questions were raised. The sponsor submits replies or changes initiated by these requests in significant detail.

Reviewer's Evaluation.

Intralipid 10% and Intralipid 20% have previously been approved by the FDA for intravenous administration to patients in need of total parenteral nutrition. The current submission is to utilize the product Intralipid 30% in bulk form to be diluted to 20% fat concentration for IV administration. The sponsor specifically states that the 30% concentration is not for direct, undiluted, administration.

Most of the safety questions raised pertained to the possibility that the 30% admixture may inadvertently be infused into patients. Six separate studies wherein the 30% and 20% admixtures were injected into separate cohort of patients (male and female). The incidence of biochemical changes were similar in each group. The incidence of adverse reactions thought possibly due to the fat emulsions (6) was significantly higher in the 20%(approved) emulsion than in the 30%(experimental) emulsion (5/6).

Questions raised by Chemistry and other reviewing disciplines were answered to the satisfaction of those reviewers.

Suggested additions and changes in the label insert were made.

The agency requested data on the following issues:

1. "Reports of any instability problems occurring after the letter of December 1988, relating to the stability of Intralipid I.V. Fat Emulsions in Total Parenteral Nutrition (TPN) All-In-One Admixtures, identified as admixture breakage and cracking of the admixture".

In response to this request the sponsor collated all complaints received related to admixture breakage or cracking during the period 1/1/89 through 6/25/93. A total of 174 complaints were received from hospitals and home care facilities during that period. All complaints were investigated; when possible, aliquots of the same drug lot were studied at the in-house laboratory. From these investigations sufficient information was received to evaluate 170 of the complaints; of these 92% (156/170) were found to be caused either by "usage outside labeled recommendations or usage of component/quantities that were untested or known to cause admixture instability". The breakdown was:

- admixture stored outside of recommendations 71% (123/174).
- known incompatible components, improper mix 19% (33/174).
- information insufficient for evaluation 2% (4/174).
- in-house testing of formulation did not confirm admixture breaking when refrigerated for 24 hours, then room temp for 24 hours 8% (14/174).

From the above the sponsor concludes:"..all reports of cracked admixtures that could be evaluated were attributed to user problems, i.e., misuse....for every complaint that identified a specific lot number of Intralipid a complete manufacturing record review was conducted by our Quality Assurance department. No problems that would negatively impact emulsion stability were noted".

2. "Information on the clinical outcome of any patients who have received cracked admixture at any time".

The sponsor reviewed their records of admixture cracking complaints and found that 51 (29%) of the defects were noted during the infusion of the admixture. Of the 51 patients so infused, one patient developed an adverse reaction; this reaction was redness and focal pyrexia at the site of

infusion of a peripheral vein. The patient was treated with Vancomycin and recovered without consequence.

The sponsors initiated an extensive literature search (att.1b) through multiple computer data base searches for world wide reported incidences of adverse reactions with the intact or cracked admixture of fat emulsions. This search produced no reference citations. (Supposedly the literature referenced was for concentrations of 10% and 20% fat emulsions).

3. " A safety update report as described in 21 CFR 314.50(d)(5)(vi) about the safety of Intralipid I.V. Fat Emulsion".

As part of the safety up date the sponsor submitted two phase 1 trials performed in Sweden as part of the NDA submission (trial reference nos. 8504200 and 8708900, section 7 of NDA 19942).

In addition to the above studies the results of four additional clinical trials were performed in Europe to support the application of Intralipid 30%. Attachment #2 of the amendment details the specifics of these four trials by charts, tables and individual data sets. Brief summary of these data follows:

Seventy-two patients took part in the four studies; data from two patients are not included for failure to complete the study. Two studies were open but randomized, one study was a double-blind parallel comparison of the metabolism and tolerance of Intralipid 30% and Intralipid 20%.

Patients, post abdominal resection for neoplasia, received intravenous injections of both Intralipid 30% and 20% at separate times. Forty -six patients received 30% and twenty-four patients received 20% Intralipid IV.
"statistically significant, but not clinically significant elevations in ALP, SGOT, platelet and triglyceride levels were observed in both treatment groups. This elevation of liver enzymes is not unexpected in patients receiving lipid base TPN".

There were 54 adverse events recorded among patients receiving 30% Intralipid, and 26 adverse events among patients receiving 20% Intralipid. Of this number only 6 were felt by the investigators to be due to the drug infusions; the other events were thought due to the underlying malady. One adverse event was recorded from

Regulatory Recommendation:

Approval of the NDA with the current amendment.

D.H.Woodbury M.D
10/14/93

I agree.
See my note Dec 1, 1993
D.E. Jones M.D.

Agree with approval. The package insert, however, needs considerable strengthening in order to clarify that 1) the 30% is a pharmacy bulk pack, 2) it should not be diluted to 10% or 20% + administered by a "Y" intravenous set. 3) it should not be diluted with saline or dextrose 4) it should only be given in a three-in-one admixture program and diluted only with mixtures approved for this program.

12/1/93
see my
memo 12/12/93

Division Director's Comments on NDA 19-942

NDA 19-942 **Review date:** 11/28/92

Sponsor: Kabi Pharmacia NOV 28 1992

Drug: Intralipid 30% Intravenous Fat Emulsion (Pharmacy Bulk Package)

Proposed Indication: Intralipid® is indicated as a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods of time (usually for more than 5 days) and as a source of essential fatty acids for prevention of EFAD.

Related Reviews: Medical Officer's Review dated 12/21/90

Background: [From NDA Clinical Data Summary]

"Intralipid® 30% is a lipid emulsion of soybean oil stabilized with egg yolk phospholipids. The formula is similar to that of Intralipid 10% and 20% emulsions which have been used clinically for more than 25 years as energy sources for patients in need of parenteral nutrition."

Comparison of Intralipid Products

Each 100 milliters contains:	10%	20%	30%
Soybean Oil (g)	10.0	20.0	30.0
Phospholipids (g)	1.2	1.2	1.2
Glycerin, USP (g)	**2.25**	**2.25**	**1.7**
pH (approximate)	8.0	8.0	8.0
Caloric density (kcal/mL)	1.1	2.0	3.0
Osmolality (mOs/kg H_2O)			
Droplet Diameter (approx) (micron)	0.5	0.5	0.5
Phosphorus from phospholipids (mMol/100 mL)	1.5	1.5	1.5

Intralipid 30% I.V. Fat Emulsion is a Pharmacy Bulk Pack intended to be used for compounding total nutrient admixtures (TNAs). Intralipid 30% is not intended for direct infusion (unlike Intralipid 10% and 20%). In patients where low fluid volume in combination with high caloric need is required (e.g., patients with severely compromised renal or cardiac function requiring intravenous nutrition via TNA), this new emulsion may be preferable to the older ones. Additionally, a more concentrated fat emulsion is more convenient in the hospital pharmacy since fewer units of this fat emulsion can be used when mixing the TNAs.

Reviewer's Comments: *In order for patients to receive a higher caloric intake with less volume than the 20%, it would be necessary for the final concentration to be higher than 20%. A significant safety data base has not been established for final formulations above 20%.*

... in a March 22, 1989 meeting the FDA expressed concern over the possibility that this product could be misused and infused directly into a patient. Because of this potential FDA requested clinical evidence of the safety of directly infused Intralipid 30%. Additionally, FDA agreed at the March 22, 1989 meeting that European clinical studies would be acceptable to demonstrate safety of Intralipid 30% provided that KabiVitrum established that Intralipid 30% produced in Stockholm, Sweden and Clayton, NC are comparable.

Reviewer's Comments: *FDA meeting minutes state that clinical data would be required. "One aspect that would have to be done would be a clearance rate with various volunteers. ... worst case scenario which would be 30% directly infused. ... would also want some data on the 30% admixture which would include adult and pediatric patients."*

"Two controlled Phase 1 clinical trials using Stockholm manufactured Intralipid 30% were conducted in which a total of 44 healthy volunteers were entered into study. A report showing the equivalency of Stockholm and Clayton produced Intralipid 30% was also provided.

Other studies that are relevant to the evaluation of the safety and effectiveness of the product have not been conducted. However, two similar products, Intralipid 10% (NDA 17-643) and Intralipid 20% (NDA 18-449), are both currently marketed in the US. ... The use of Intralipid 30% in TNAs is justified by its similarity in formulation and in clearance rate (similar or more rapid clearance) to Intralipid 10% and 20%. In addition, Intralipid 30% will be labeled to indicate that the fat content of TNAs prepared using Intralipid 30% can be no more than 20%."

Reviewer's Comments: *Details of each study will be addressed individually.*

Study 1

Randomized, cross-over study in 20 healthy male volunteers (19-49 years old). Each patient was given a single intravenous bolus of either 0.5 mL/kg body weight of Intralipid 20% or 0.33 mL/kg body weight of Intralipid 30% on day 1. On the following day, each patient received the alternate emulsion.

Sponsor's Results

"For the variables measured before the start of the treatment, an analysis of variance indicated statistically significant differences ($p < .05$) for leukocytes, mean corpuscular volume and triglycerides. However, all means were within normal ranges. Therefore, it was felt these differences are due to chance and are not clinically significant."

Reviewer's Comments:

This paragraph represents a lack of understanding with respect to the use of statistics. The p value is a reflection of the probability of the event occurring by chance. A p value of less than .05 means that there is less than a 1 in 20 chance of difference being due to chance.

"The were eight statistically significant differences. Five of the eight are due to differences between treatment day 1 and day 2; i.e., the day of treatment rather than the treatment itself appears to be the influencing factor in these cases. Only two, Y_o and CK are statistically significant differences between the two treatments. The CK difference is not considered to be of clinical significance. (Two patients had high CK values during the whole study). The Y_o value being 50% lower in the Intralipid 20% compared to Intralipid 30% is probably a reflection of a better distribution of the 30% within the circulatory system.

Three other important findings from the study are:

1. Intralipid 30% is eliminated from the blood stream at a rate similar to that of Intralipid 20% (i.e., k_2, %/min for 30% is 5.93 ± 1.36 vs. 5.12 ± 1.17 for 20%).

2. There were no changes in liver function, hematology or renal function with either of the two emulsions.

3. Serum TG and cholesterol concentrations remained constant during the study period."

Reviewer's Comments:

1. *The period interaction detracts from making comparisons between products. There obviously should have been a washout period in between treatments. Differences between hematology, liver and renal function may be masked.*

2. *Patients with elevated Creatinine Kinase (CK) levels sufficient to prevent comparisons should been removed from the study.*

3. *It is not clear how the sponsor arrived at the conclusion that a different Light Scattering Index (Y_o) represents a better distribution of the Intralipid 30%. The Medical Officer's review quotes the sponsor as stating the difference in volume of distribution is in all probability due to the smaller globule size of the 20% emulsion allowing distribution to more tissues while the larger globules of the 30% emulsion cause it to remain confined to circulation. Differences in distribution may lead to different safety issues.*

4. *Triglycerides were reported to be unequal at baseline. Comparisions between groups should account for the unequal baseline.*

5. *The clearance rate for the 30% was faster than for the 20%, although not reported as statistically significant. This difference is reproduced in the second study.*

6. *There were no female patients and no children in this study.*

Study 2

Randomized, cross-over study in 24 healthy male volunteers (20-47 years old). Each patient was given a intravenous bolus followed 40 minutes later by an infusion of 100 grams over 6 hours of either 0.5 mL/kg body weight of Intralipid 20% or 0.33 mL/kg body weight of Intralipid 30% on day 1. On the following day, each patient received the alternate emulsion.

Sponsor's Results

"Blood pressure, heart rate, body temperature and respiratory rate measurements were not significantly different between the two fat emulsions. The body temperatures increased 0.2 - 0.3°C in most patients for both fat emulsions. One patient while on Intralipid 30% had a temperature rise of 0.9°C but no other symptoms.

There were no significant differences in the response to the two emulsions in the hematological, kidney and liver function tests, even though individual alterations were observed after the fat emulsions were infused.

The fractional elimination rate, k_2 (%/min), was higher for both emulsions on day 2 as compared to day 1. Between the two emulsions the mean elimination rate for Intralipid 30% was 5.3 $\pm$ 1.4 compared to a mean for Intralipid 20% of 4.4 $\pm$ 1.4. There is a significant difference between these values (emulsions). This is in contrast to another study ... [Study 1] ... [where] the rates were 5.91 $\pm$ 1.46 for the Intralipid 30% vs. 5.11 $\pm$ 1.27 for Intralipid 20%.

Both phospholipid concentration and cholesterol concentrations increased more during use of Intralipid 20% than use of the Intralipid 30%. ... This is presumably due to the greater phospholipid/triglyceride ratio in Intralipid 20% compared to Intralipid 30%.

Reviewer's Comments:

1. *The sponsor failed to identify in the summary, that Bilirubin, Gamma-GT and Creatinine were statistically significantly lower only on Intralipid 30% treatment days.*

2. *The fractional elimination rate in this study is not in contrast to Study 1, but is in the same direction. In both studies, elimination is faster with the Intralipid 30%.*

3. *There were no female patients and no children in this study.*

4. *This study also points out differences between the 20% and 30% formulations.*

Additional Comments:

Summary:

Based on my review of the clinical information:

1. Neither study demonstrates:
   a) Use as an admixture
   b) Use for more than 6 hours (indication of product is for patients in need of parenteral nutrition for more than 5 days)
   c) Use in children
   d) Use in women
   e) Use in patients (as opposed to normal volunteers)
   f) Use in subjects greater than 50 years old

2. Each study had an insufficient washout time leading to carryover effects.

3. The 30% formulation has a non-proportional concentration of glycerin compared to the 10% and 20% formulations and therefore all dilutions of the 30% will be different than the 10% or 20%.

4. The clearance rate of the 30% is different (faster) than the 10% or 20% formulations.

5. A variety of laboratory abnormalities or differences between formulations were noted. The clinical relevance is not clear.

Conclusions:

It appears from the written record, that Drs. Kenealy (Group Leader), Walters (Deputy Division Director) and Palmer (Division Director) concluded that the application was clinically approvable. However, the deficiencies noted above would suggest that the submitted studies are not adequate to justify approval based on equivalency between Intralipid 30% and Intralipid 20%. [redacted] I do not believe that there is sufficient clinical information to support the safety of this product.

Recommendation:

[redacted], the application as submitted is **not recommended** for approval.

Wiley A. Chambers MD

Wiley A. Chambers, M.D.
Acting Director, HFD-160

cc: Orig NDA 19-942
HFD-160
HFD-161/CSO/Joyce
HFD-160/CHEM/Koch
HFD-160/PHARM/Wilson
HFD-160/MO/Kenealy
HFD-420/Gordin

w/6-29-90
Vol. 2.1

JAN 3 1991

NDA 19-942

MOR of Original NDA

Completed 12/21/90

Sponsor: KabiVitrum Inc.

JAN 3 1991

Drug: Intralipid 30% I.V. Fat Emulsion (Pharmacy Bulk Pack)

Category: Parenteral Nutrient

Dosage Form: Sterile Emulsion

Route of Administration: Central or Peripheral Venous Infusion

Proposed Indication: Parenteral Nutrition

Submitted: 6/29/90
Received: 7/2/90
Assigned: 7/5/90

Type of Submission: Original NDA

General Comment: This NDA was originally submitted in December of 1988 and subsequently withdrawn due to lack of any clinical data on the use of lipid emulsions of this concentration. It is meant to be a pharmacy bulk pack, There was significant concern on the part of the Division that direct infusion could readily occur, and that some clinical data to determine possible consequences of inadvertent direct infusion should be made available. Phase I clinical protocols were designed and, with these data, the application is now resubmitted.

Chemistry: The major concern about the chemistry of this drug product is the possible effects of a 30% concentration on the stability of the particle size of the emulsion, especially following dilution in TPN admixtures. The sponsor was asked to submit stability data to support stability data under various conditions of admixing and storage. These data will be reviewed and evaluated in the Chemist's review.

The composition of the emulsion is as follows:

Soybean oil 300 g
Egg phospholipids 12 g
Glycerol 17g
Water for injection ad 1000 ml

Pharmacology: See Pharmacologist's review.

Clinical Background: Various lipid emulsions ranging in concentration up to 20% have enjoyed wide clinical acceptance for many years throughout the world. There has not been approval of a 30% emulsion. The recent shift in hospital pharmacies to the use of pharmacy bulk packaging as a means of reducing medical expenditures has prompted the sponsor of this application to seek approval of this high concentration to be diluted in the hospital pharmacy by admixture with appropriate sources of carbohydrates and amino acids. These admixtures are to be subsequently administered either at home or in the hopsital to the appropriate patients. This type of program is designed to reduce the number of 250 and 500 ml containers required in a large practice where volumes of 100ml or less may be all that is required for a single patient infusion. There is no doubt that such a pharmacy bulk package would translate to significant financial savings if safety can be established.

Another anticipated advantage is use in patients having severely compromised renal or cardiac function who are unable to tolerate large fluid volume but who require parenteral caloric sources. Such patients should be able to receive more calories per unit volume of infusion.

In addition, it is known that longterm total parenteral nutrition patients tend to develop hypercholesterolemia. There is suggestive evidence that this may be less of a problem in the presence of the lower content of phospholipids in this product.

Clinical Studies:

Study I.

Invesigator: Stephan Rossner, MD, PhD.
Assoc. Prof. of Internal Medicine

Dr. Rossner's CV is presented and he appears well qualified.

Study Title: Clinical Tolerance of Intralipid 30% - A New Fat Emulsion - Clinical Trial # 85 04200

Objective: To study tolerance and fractional elimination rate of Intralipid 30% given as single injection and compare the fractional turn over rate with Intrelipid 20%.

Study Design: This was an open label, randomized,two period cross-over study of 20 adult male volunteers. Subjects were 18 - 70 years of age. Physical examination, pre-study, was performed. Laboratory data included blood chemistry, liver and kidney function evaluation and routine hematology.

Subjects were grouped as in the following table:

	Day 1	Day 2	Day 3
Group I n=10	Intralipid 20% 0.5 mL/kg BW	Intralipid 30% 0.33 mL/kg BW	-
Group II n=10	Intralipid 30% 0.33 mL/kg BW	Intralipid 20% 0.5 mL/kg BW	-

On days 1, 2, and 3 fasting blood samples were drawn and studied for hematology, liver and kidney function, electrolytes, triglycerides and cholesterol. In addition nephelometry for light scattering index was performed.

Patients were then subjected to the intravenous fat tolerance test as described by Rossner 1974.(Reprint copy of this publication is supplied with this submission.) Test emulsion was injected, according to the above schedule, as fast as possible. Starting at the mid-point of the injection, blood samples were draw at 5, 10, 15, 20, 25, 30, 40, 50 and 60 minutes following injection.

Results: The following table is excerpted directly from the application.

Statistically significant differences ($p < 0.05$) due to the day sequence (period), treatment, and treatment by day interaction effects with respect to observations during day 1 and day 2.

Parameter	Unit	Effect Tested			Diff.	p-value
		Interaction	Period	Treatment		
y_0 (LSI)	--			X	22.48-33.4	< 0.001
Platelets	10^9/L		X		173.5-192.3	< 0.005
MCV	fL	X			89.9- 86.4	< 0.5
Albumin	g/L		X		40.4- 42.0	< 0.001
S-Sodium	mmol/L		X		141.1-143.5	< 0.05
S-Potassium	mmol/L		X		3.9- 4.1	< 0.001
S-Calcium	mmol/L		X		2.36- 2.44	< 0.05
S-Creatinine Kinase	ukat/L			X	2.2- 2.7	< 0.05

Of the statistically significant differences tabulated, the treatment differences are of the greatest clinical concern. The sponsor points out that the difference in volume of distribution is in all probability due to the smaller globule size of the 20% emulsion allowing distribution to more tissues while the larger globules of the 30% emulsion cause it to remain confined to the circulation . There is no evidence that this difference is of any advantage or detriment.

The fractional elimination rates were not significantly different.

Serum cholesterol and triglycerides were not significantly different. The fractional elimination rate was similar for each emulsion.

There were no adverse reactions observed.

Conclusion: This Phase 1 study of 30% Intralipid given by rapid intravenous injection tends to confirm the contention of the sponsor that this drug product is safe.

Study II.

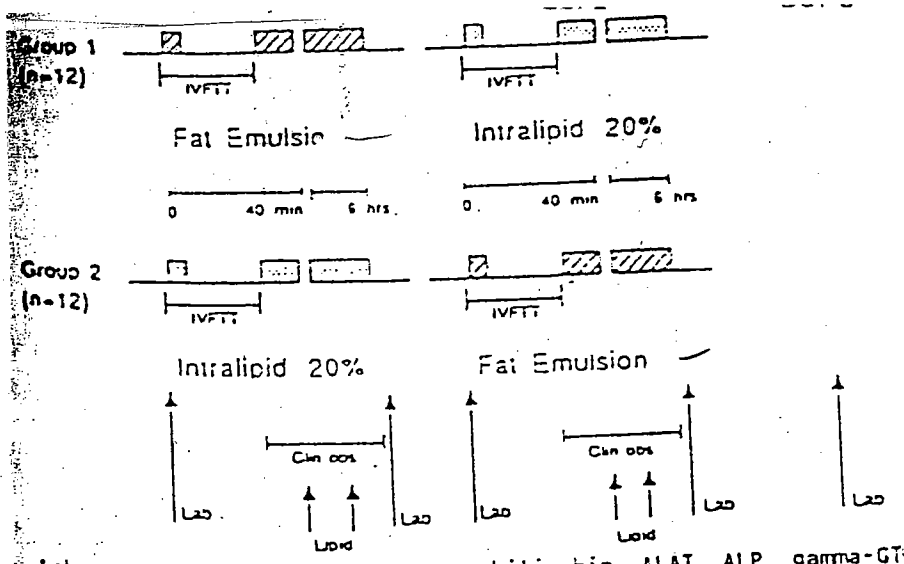
Investigators: Assoc. Prof. Jorgen Nordenstrom
and
Doctor Anders Thorne

Assoc. Prof. Marianne Lindholm
Medical Department
KabiVitrum Nutrition AB
S-112 87 Stockholm

Study Title: Tolerance and Elimination of Fat Emulsion — in Healthy Volunteers

Objective: To investigate the tolerence, safety and fat metabolism of Fat Emulsion — in comparison with Intralipid 200 mg/mL in healthy adult volunteers.

Study Design: This was an open label, randomized, two period cross-over study in which Fat Emulsion — was compared to Intralipid 20%. Twenty-four healthy adult male volunteers were divided into two groups. On day 1, group 1 received the study emulsion and group 2 received Intralipid 20%. On day 2 the treatment order was reversed. On day 3, no drug was administered, but serum samples were drawn.
Following an over night fast, the cubital vein was catheterized and an intravenous fat tolerance test was performed by bolus injection of 0.1 g fat/kg BW (i.e. 0.33 ml/kg BW study emulsion or 0.5ml/kg BW 20% Intralipid). Serum samples were drawn for determination of fractional elimination rate as calculated from light scattering index every 5 minutes during the following 40 minutes (8 samples total). At 40 minutes, a constant infusion of the same emulsion was begun at the rate of 330 ml/hr for test emulsion or 500 ml/hr for intralipid. The infusion rate was 16.6 g/hr for each emulsion.
On day 2, the identical procedure was followed, reversing the emulsion in each group. On day 3, subjects fasted for 8 hours and blood samples were drawn. No fat was infused. The following table (vol.1.4, pg.7.5.2.4.-7) diagrams the study plan and outlines the clinical and laboratory variables recorded.



Lab: Hb, EVF, WBC, platelets, bilirubin, ALAT, ALP, gamma-GT, Normotest, TG, cholesterol, FFA, phospholipid, lipoprotein (conc of TG and cholesterol) and creatinine

Lipid: TG, cholesterol, FFA and phospholipid (every second hour)

Clin Obs: BP, temp, HR and resp rate (every hour)

IVFTT: Intravenous fat tolerance test (See text p. 8)

Results: Vital signs - There were no clinically significant changes in BP, heart rate, respiratory rate or temperature, although there was slight increase in body temperature in most subjects. This is an anticipated change during the administration of fat emulsion in general.

Laboratory Data - Tables 2A and 2B, excerpted from vol.1.4 pg 7.5.2.4.-19 & 20, summarize the pertinent laboratory data. It is to be noted that there was a significant rise of ALAT (SGPT) following infusion of either emulsion, although there was no significant difference between the emulsions. This type of response to lipid emulsion infusion has been described frequently. The remainder of the clinical laboratory values did not show clinically significant variations.

Intravenous Fat Tolerance Test (IVFTT) - The fractional elimination rate for Fat Emulsion 4315 was higher than that of Intralipid 20%, being 5.3 +/-1.4% /min as opposed to 4.4 +/-1.4% /min. This difference was statistically significant.

Serum Triglycerides, Cholesterol, Free Fatty Acids and Phospholipid Concentrations - As may be seen in Table 5, taken from vol. 1.4,pg.7.5.2.4.-23, there are pre- and post infusion differences, as anticipated, in the concentrations of triglycerides, cholesterol and free fatty acids. There was, however, a significant difference in the phospholipid concentrations in the post infusion period. This difference should also be anticipated as the concentration of phospholipids in Intralipid 20% is approximately 50% greater than that in the test emulsion.

Adverse Events: There were no adverse events reported in this study that have not been previously reported with the infusion of lipid emulsions. One volunteer vomited the night between day 2 and day 3, approximately 10 hours following the end of the Intralipid 20% infusion. One subject experienced a temperature rise from prestudy

Table 2A. Descriptive statistics of measured variables
Hematological variables. Mean ± SD

		Study Group									
		Fat Emulsion Intralipid 20% n=12					Intralipid 20%/ Fat Emulsion n=12				
		Day 1		Day 2		Day 3	Day 1		Day 2		Day 3
		pre	post	pre	post		pre	post	pre	post	
Hemoglobin (g/L)	mean	145	150*	142	147*	141	147	154*	143	150*	143
	SD	4	7	6	12	8	8	8	6	7	5
Hematocrit (%)	mean	42	41	41	40	41	43	42	42	41	42
	SD	1	2	2	2	2	2	3	2	2	2
WBC 10^9/L	mean	5.2	6.1*	5.0	5.6*	4.6	5.5	6.9*	5.2	6.7*	5.4
	SD	0.8	0.9	0.7	0.7	0.8	1.5	1.9	1.4	2.4	1.9
Platelets 10^9/L	mean	228	219	194	201	216	239	244	225	227	223
	SD	35	32	33	60	36	46	60	48	69	51
Normotest** (%)	mean	99	87	98	82*	94	105	95*	91	98	107
	SD	14	16	16	14	16	19	15	30	19	17

*Statistically significant difference ($p<0.05$) when post vs pre values were compared for each fat emulsion.

**Prothrombin complex screening test - Factors II, VII and X

Table 2B. Descriptive statistics of measured varibles
Hepatic variables and creatinine. Mean ± SD

		Study group									
		Fat Emulsion Intralipid 20% n=12					Intralipid 20%/ Fat Emuluion n=12				
		Day 1		Day 2		Day 3	Day 1		Day 2		Day 3
		pre	post	pre	post		pre	post	pre	post	
Bilirubin (umol/L)	mean	11.1	9.3*	11.3	12.1	9.1	12.6	11.3	12.9	8.3*	10.3
	SD	7.0	2.8	6.1	7.5	4.6	8.5	5.6	7.2	4.1	4.6
ALAT (ukat/L)	mean	0.21	0.29*	0.26	0.34*	0.25	0.46	0.54*	0.47	0.55*	0.48
	SD	0.10	0.08	0.23	0.20	0.16	0.33	0.39	0.30	0.28	0.29
GAMMA-GT (ukat/L)	mean	0.25	0.19*	0.24	0.17	0.24	0.33	0.52	0.29	0.26*	0.32
	SD	0.07	0.05	0.06	0.06	0.06	0.12	0.92	0.13	0.13	0.13
ALP (ukat/L)	mean	2.5	2.1*	2.4	2.1*	2.4	2.5	2.3*	2.5	2.2*	2.5
	SD	0.5	0.4	0.4	0.4	0.4	1.0	1.1	1.1	1.0	1.0
Creatinine (umol/L)	mean	87	81*	89	82	87	85	76	84	76*	85
	SD	8	6	7	8	8	10	12	11	11	12

Table 5. Descriptive statistics of measured lipid variables.
Mean ± SD

		Study Group									
		Fat Emulsion ----- Intralipid 20% n=11					Intralipid 20%/ Fat Emulsion — n=12				
		Day 1		Day 2		Day 3	Day 1		Day 2		Day 3
		pre	post	pre	post		pre	post	pre	post	
S-Triglycerides (mmol/L)	mean	1.1	5.3*	0.8	4.6*	0.9	1.0	4.9*	1.0	3.2*	0.8
	SD	0.5	5.1	0.3	3.8	0.6	0.5	1.6	0.6	1.5	0.4
S-Cholesterol (mmol/L)	mean	4.1	4.0	3.9	4.0	4.1	4.6	4.6	4.4	4.3	4.5
	SD	1.0	1.0	0.7	0.7	0.8	1.2	1.2	1.3	1.1	1.2
P-Free fatty acids (umol/L)	mean	609	1099*	680	1137*	399	474	1079*	465	975*	510
	SD	314	248	269	349	158	109	172	121	177	136
P-Phospholipids (mmol/L)	mean	2.42	2.74*	2.21	3.04*	2.52	2.52	3.45*	2.50	2.72*	2.51
	SD	0.44	0.49	0.37	0.39	0.45	0.36	0.52	0.43	0.52	0.40

* Statistically significant difference ($p<0.05$) when post vs pre infusion values were compared for each fat emulsion.

of 36.8 C. to 37.7 C. at four hours into the Fat Emulsion 4315 infusion. At termination of the infusion, the temperature was 37.3 C. Neither of these is to be considered a serious reaction.

Summary and Conclusion:

As previously noted, the original submission of this NDA was withdrawn at the request of this Division. The reason for that request was lack of any clinical study data to document safety. In addition,

The sponsor stated at a meeting with members of this division that this was to be a pharmacy bulk package intended only for dilution. However, it was felt that inadvertent administration of the 30% emulsion was a distinct possibility in the clinical setting and the there should be some clinical data to support the statement that such an error would not produce severe adverse event. Two phase one studies in adult volunteers were requested and are reported in this submission.
The first study involved direct bolus injection of the 30% emulsion and similar injection of the approved emulsion, Intralipid 20%. There were no clinically significant differences in the response to the different emulsions and there were no serious or unexpected adverse events.

The second study also involved bolus injection of both emulsions but this was followed up with infusion of the emulsions over a 6 hour period. Again, there were not clinically significant differences in the response to the treatments and there were no serious nor previously unreported adverse reactions.

Package Insert Review:

The draft of the proposed package insert for this NDA is similar in the majority of areas to the approved package insert for Intralipid 10% and 20%. The principle areas of difference involve the admonition of all pharmacy bulk pack that they are not intended for direct infusion and the they must be discarded within 4 hours of initial entry. /the guidelines for mixing have been revised in accord with the use as a pharmacy bulk pack and, as we suggested to the sponsor, a table has been incorporated suggesting admixture volumes that will maintain final concentrations at 20%.

Title:---------- Satisfactory

Description:---------- Satisfactory

Clinical Pharmacology:---------- Satisfactory

Indications and Usage:---------- Satisfactory

Contraindications:---------- Satisfactory

Warnings:---------- Satisfactory

Precautions:---------- Satisfactory

Adverse Reactions:---------- Satisfactory

Dosage and Administration:---------- Satisfactory

Mixing Guidelines and Limitations: As noted above, this section has been revised to present a table of fluid volumes that will produce a final admixture containing no more than 20% fat emulsion. This table should be of value to the pharmacist in a busy hospital pharmacy and, hopfully may avoid admixing errors that would otherwise result in TPN mixtures that could lead to fat overload.

Satisfactory

How Supplied:---------- Satisfactory

Recommendation:

1. NDA 19-942 is clinically approvable.

John C. Kenealy, M.D.

PGW 1-2-91

J Palmer 1-3-91

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-942

MICROBIOLOGY REVIEW

Division of Medical Imaging, Surgical and Dental Drug Products
Microbiologist's Review No. 2
January 22, 1992

A. 1. **Application Number:** NDA 19-942 AZ

Applicant: Kabi Vitrum, Inc.
P.O. Box 597
U.S Route 70 East
Clayton, NC 27520

JAN 22 1992

2. **Product Name:** Intralipid 30% (30% I.V. Fat Emulsion)

3. **Dosage Form:** Sterile emulsion in 250 and 500 ml Pharmacy Bulk Package.

4. **Method of Sterilization:**

5. **Pharmacological Category and/or Principle Indication:** Source of calories and essential fatty acids.

6. **Drug Priority Classification:** 5C

B. 1. **Initial Submission:** June 29, 1990 (Resubmission)

2. **Amendments:** December 19, 1991 (Subject of This Review)

3. **Supporting Documents:** NDA 17-643 Intralipid 10%
NDA 18-449 Intralipid 20%

C. **Remarks:**

The subject drug product is a 30% fat emulsion to be marketed as a Pharmacy Bulk Package. As such it is intended to be used in the preparation of total nutrient admixtures and is not intended for direct infusion. The composition of the product is similar to Intralipid 10% and 20% except that the soybean oil concentration is increased to 30% and the glycerin content is decreased from 2.25% to 1.7%.

The product is to be manufactured by KabiVitrum at the Clayton, NC facility. According to the applicant, "The facilities, equipment, containers and closures, and packaging procedures to be used in the production of Intralipid 30% are the same as those currently used (and approved) for KabiVitrum's Intralipid 10% (NDA 17-643) and Intralipid 20% (NDA 18-449)." It is further stated that the sterilization process is the same as that currently used for Intralipid 10% and 20%.

The current Amendment responds to the Agency letter of February 28, 1991. Three items in that letter were derived from the first Microbiologist's Review. The comments and the applicant's responses are discussed below under "Review Notes".

D. **Conclusions:** Recommend approval on the basis of sterility assurance.

Peter H Cooney 1/22/92

Peter H. Cooney, PhD
Supervisory Microbiologist

MRC 2/7/92

cc: NDA 19-627
HFD-160/Div File
HFD-160/Cooney/Joyce/Koch/Kenealy/Wilson

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology- 19-942
Review #2

2.1

JAN 3 1991

Division of Medical Imaging, Surgical and Dental Drug Products
Microbiologist's Review No. 1
January 3, 1991

A. 1. **Application Number:** NDA 19-942

Applicant: Kabi Vitrum, Inc.
P.O. Box 597
U.S Route 70 East
Clayton, NC 27520

2. **Product Name:** Intralipid 30% (30% I.V. Fat Emulsion)

3. **Dosage Form:** Sterile emulsion in 250 and 500 ml Pharmacy Bulk Package.

4. **Method of Sterilization:**

5. **Pharmacological Category and/or Principle Indication:** Source of calories and essential fatty acids.

6. **Drug Priority Classification:** 5C

B. 1. **Initial Submission:** June 29, 1990 (Resubmission)

2. **Amendments:** N/A

3. **Supporting Documents:** NDA 17-643 Intralipid 10%
NDA 18-449 Intralipid 20%

C. **Remarks:**

The subject drug product is a 30% fat emulsion to be marketed as a Pharmacy Bulk Package. As such it is intended to be used in the preparation of total nutrient admixtures and is not intended for direct infusion. The composition of the product is similar to Intralipid 10% and 20% except that the soybean oil concentration is increased to 30% and the glycerin content is decreased from 2.25% to 1.7%.

The product is to be manufactured by KabiVitrum at the Clayton, NC facility. According to the applicant, "The facilities, equipment, containers and closures, and packaging procedures to be used in the production of Intralipid 30% are the same as those currently used (and approved) for KabiVitrum's Intralipid 10% (NDA 17-643) and Intralipid 20% (NDA 18-449)." It is further stated that the sterilization process is the same as that currently used for Intralipid 10% and 20%. For specific comments, see "E. Review Notes" below.

D. **Conclusions:** The application is not approvable from the standpoint of microbiology. See "E. Review Notes" and "Draft of Letter to Applicant" below.

Peter H Cooney 1/3/91

Peter H. Cooney, PhD
Supervisory Microbiologist

J Palmer 2-2-91

cc: NDA 19-~~627~~ 942
HFD-160/Div File
HFD-160/Cooney/Joyce

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology- 19-942 Renew #1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-942

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # 19-942 SUPPL # /

Trade Name Intralipid 30% Pharmacy Bulk Package Generic Name I.V. Fat Emulsion

Applicant Name _____ HFD # 160

Approval Date If Known Dec 1993

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /✓/ NO /___/

If yes, NDA # 17-643 18-449 Drug Name Intralipid 10% Intralipid 20%.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 17-643 Intralipid 10%

NDA# 18-449 Intralipid 20%

NDA# ~~18-951~~ 19-531 Nutrilipid 10%&20%

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

① Clinical Tolerance of Intralipid 30% #85 04200

② Tolerance and Elimination of Fat Emulsion in Healthy Volunteers

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

None _____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(These were European trials)

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /✓/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /✓/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Anna Marie H. Weibel 12.16.93
Signature Date
Title: CSO

_____ _____
Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-85 Mary Ann Ward

SEP 26 1994

NDA 19-942

Kabi Pharmacia Inc.
Hospital Care
P.O. Box 597
8484 US 70 West
Clayton, NC 27520-0597

Attention: Thomas L. Pituk
Director, Regulatory Affairs

Dear Mr. Pituk:

Reference is made to your approved new drug application (NDA) for Intralipid™ 30% I.V. Fat Emulsion, Pharmacy Bulk Package.

We acknowledge receipt of your submission dated February 1, 1994, containing the final printed labeling (FPL) which includes the package insert and the container labeling for the 500 mL fill size. We remind you of your commitment to submit the FPL for the 250 mL fill size s soon as it is available.

We have reviewed this FPL in accordance with our approval letter dated December 30, 1993, and we find it acceptable.

Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

As evidenced by the recent FDA TPN Safety Alert, we are concerned about the formation of calcium phosphate precipitates in total parenteral nutrition admixtures. Please note that we are presently re-evaluating the recently requested stability data. When our evalution has been completed, we will provide you with new labeling recommendations to address these concerns. Changes may require the submission of a labeling supplement.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Patricia Y. Love, M.D., M.B.A.
Director
Division of Medical Imaging,
Surgical, and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Orig NDA
Div File
HFC-130/DO *
HFD-80 *
HFD-100
HFD-735 *
HFD-161/Weikel * lmw 9.16.94
Acknowledgements: Cheever, 9.14.94; Koch/Sheinin, 9.15.94
F/T by: Wilson, 9.15.94

ACKNOWLEDGE AND RETAIN

9/9/94

9/22/94

CSO REVIEW OF FPL

NDA: 19-942

Submission Date: February 1, 1994

Sponsor: Kabi Pharmacia

Review date: 9/15/94

This FPL was submitted for the package insert and the container for the 500 mL size as was requested in our December 30, 1993, approval letter. The labeling for the 250 mL size will follow as soon as it is available.

I have reviewed the FPL and it is acceptable.

Anna Marie H. Weikel
Consumer Safety Officer

cc: Orig NDA
Div File

Pharmacia

Date

February 1, 1994 Federal Express

Reference

ORIGINAL

ORIG AMENDMENT
FPL

FA

Patricia Y. Love, M.D., M.B.A.
Acting Director
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
HFD-160, Document Room 18B04
5600 Fishers Lane
Rockville, MD 20857

NDA 19-942
Intralipid® 30% I.V. Fat Emulsion
(Pharmacy Bulk Package)

SUBJECT: Final Printed Labeling for Approved NDA 19-942

Dear Dr. Love:

Reference is made to your "approval" letter of December 30, 1993 for Intralipid® 30% I.V. Fat Emulsion (Pharmacy Bulk Package), NDA 19-942.

At this time we are submitting twelve copies each of the final printed labeling for Intralipid® 30%, 500 mL fill size only, including the immediate label and the package insert. This labeling is identical in text to the draft labeling submitted December 13, 1993 and includes the changes requested by you in your December 30, 1993 approval letter. The final printed labeling for Intralipid® 30% 250 mL fill size will be submitted to FDA at a later date since the labeling has not yet been printed.

Should there be any questions, please do not hesitate to call me at (919) 553-1419.

Sincerely,
KABI PHARMACIA INC.
Hospital Care

Thomas L. Pituk

Thomas L. Pituk
Director, Regulatory Affairs

TLP/jp

Enclosure

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

Kabi Pharmacia Inc.
Hospital Care
P.O. Box 597
8484 US 70 West
Clayton, NC 27520-0597

Telephone (919) 553-3831
DID

Telefax (919) 553-1434 Operations
Telefax (919) 553-3601 Management
Telefax (919) 553-0547 Distribution
Telefax (919) 553-2399 Quality/Research

71-6053-0
(Issued January 1994)

Intralipid® 30%

A 30% I.V. Fat Emulsion

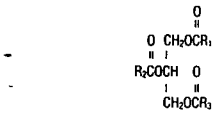
Pharmacy Bulk Package
Not For Direct Infusion

DESCRIPTION

Intralipid® 30% (30% I.V. Fat Emulsion) Pharmacy Bulk Package is a sterile, non-pyrogenic fat emulsion intended as a source of calories and essential fatty acids for use in a pharmacy admixture program. It is made up of 30% Soybean Oil, 1.2% Egg Yolk Phospholipids, 1.7% Glycerin and Water for Injection. In addition, sodium hydroxide has been added to adjust the pH so that the final product pH is 8.0; pH range is 6.0 - 8.9.

Intralipid® 30% Pharmacy Bulk Package is not for direct infusion. It is a sterile dosage form which contains several single doses for use in the preparation of three-in-one or total nutrient admixtures (TNAs) in a pharmacy admixture program.

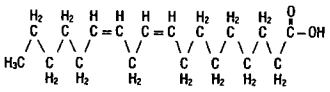
The soybean oil is a refined natural product consisting of a mixture of neutral triglycerides of predominantly unsaturated fatty acids with the following structure:



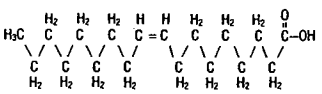
where R_1C-, R_2C- and R_3C- are saturated and unsaturated fatty acid residues.

The major component fatty acids are linoleic (44-62%), oleic (19-30%), palmitic (7-14%), linolenic (4-11%) and stearic (1.4-5.5%).[1] These fatty acids have the following chemical and structural formulas:

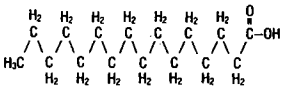
Linoleic acid $C_{18}H_{32}O_2$



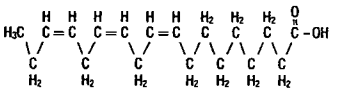
Oleic acid $C_{18}H_{34}O_2$



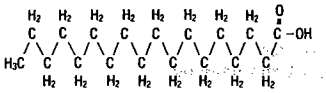
Palmitic acid $C_{16}H_{32}O_2$



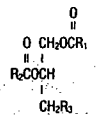
Linolenic acid $C_{18}H_{30}O_2$



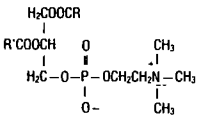
Stearic acid $C_{18}H_{36}O_2$



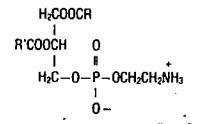
Purified egg phosphatides are a mixture of naturally occurring phospholipids which are isolated from the egg yolk. These phospholipids have the following general structure:



R_1C- and R_2C- contain saturated and unsaturated fatty acids that abound in neutral fats. R_3 is primarily either the choline or the ethanolamine ester of phosphoric acid.



Phosphatidylcholine



Phosphatidylethenolamine

Glycerin is chemically designated $C_3H_8O_3$ and is a clear colorless, hygroscopic syrupy liquid. It has the following structural formula:

Intralipid® 30% (30% I.V. Fat Emulsion) has an osmolality of approximately 310 mOsmol/kg water (which represents 200 mOsmol/liter of emulsion) and contains emulsified fat particles of approximately 0.5 micron size.

The total caloric value, including fat, phospholipid and glycerin, is 3.0 kcal per mL of Intralipid® 30%. The phospholipids present contribute 47 milligrams or approximately 1.5 mmol of phosphorus per 100 mL of the emulsion.

CLINICAL PHARMACOLOGY

Intralipid® is metabolized and utilized as a source of energy causing an increase in heat production, decrease in respiratory quotient and increase in oxygen consumption. The infused fat particles are cleared from the blood stream in a manner thought to be comparable to the clearing of chylomicrons.

Intralipid® will prevent the biochemical lesions of essential fatty acid deficiency (EFAD), and correct the clinical manifestations of the EFAD syndrome.

INDICATIONS AND USAGE

Intralipid® 30% Pharmacy Bulk Package is indicated for use in a pharmacy admixture program for the preparation of three-in-one or total nutrient admixtures (TNAs) to provide a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods of time (usually for more than 5 days) and as a source of essential fatty acids for prevention of EFAD.

CONTRAINDICATIONS

INTRALIPID® 30% PHARMACY BULK PACKAGE IS NOT INTENDED FOR DIRECT INTRAVENOUS ADMINISTRATION. DILUTING INTRALIPID® 30% TO A 10% OR 20% CONCENTRATION WITH AN INTRAVENOUS FLUID SUCH AS NORMAL SALINE OR OTHER DILUENT DOES NOT PRODUCE A DILUTION THAT IS EQUIVALENT IN COMPOSITION TO INTRALIPID® 10% OR 20% I.V. FAT EMULSIONS, AND SUCH A DILUTION SHOULD NOT BE GIVEN BY DIRECT INTRAVENOUS ADMINISTRATION (FOR EXAMPLE, THROUGH A Y-CONNECTOR).

The administration of Intralipid® is contraindicated in patients with disturbances of normal fat metabolism such as pathologic hyperlipemia, lipoid nephrosis or acute pancreatitis if accompanied by hyperlipidemia. Intralipid® 30% is not intended for direct intravenous infusion.

WARNINGS

Deaths in preterm infants after infusion of intravenous fat emulsion have been reported in the medical literature.[2] Autopsy findings included intravascular fat accumulation in the lungs. Treatment of premature and low birth weight infants with intravenous fat emulsion must be based upon careful benefit-risk assessment. Strict adherence to the recommended total daily dose is mandatory; hourly infusion rate of the admixture should be as slow as possible in each case and the total fat should not in any case exceed 1 g fat/kg in four hours. Premature and small for gestational age infants have poor clearance of intravenous fat emulsion and increased free fatty acid plasma levels following fat emulsion infusion; therefore, serious consideration must be given to administration of less than the maximum recommended doses in these patients in order to decrease the likelihood of intravenous fat overload. The infant's ability to eliminate the infused fat from the circulation must be carefully monitored (such as serum triglycerides and/or plasma free fatty acid levels). The lipemia must clear between daily infusions.

Caution should be exercised in administering Intralipid® to patients with severe liver damage, pulmonary disease, anemia or blood coagulation disorders, or when there is danger of fat embolism.

PRECAUTIONS

When Intralipid® is administered, the patient's capacity to eliminate the infused fat from the circulation must be monitored by use of an appropriate laboratory determination of serum triglycerides. Overdosage must be avoided.

During long term intravenous nutrition with Intralipid®, liver function tests should be performed. If these tests indicate that liver function is impaired, the therapy should be withdrawn.

Frequent (some advise daily) platelet counts should be done in neonatal patients receiving parenteral nutrition with Intralipid®.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies with Intralipid® have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

Pregnancy Category C: Animal reproduction studies have not been conducted with Intralipid®. It is also not known whether Intralipid® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Intralipid® should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Caution should be exercised when Intralipid® is administered to a nursing woman.

Pediatric Use: See DOSAGE AND ADMINISTRATION.

AVOID OVERDOSAGE ABSOLUTELY.

ADVERSE REACTIONS

The adverse reactions observed can be separated into two classes:

1. Those more frequently encountered are due either to a) contamination of the intravenous catheter and result in sepsis, or to b) vein irritation by concurrently infused hypertonic solutions and may result in thrombophlebitis. These adverse reactions are inseparable from the hyperalimentation procedure with or without Intralipid®.
2. Less frequent reactions more directly related to Intralipid® are: a) Immediate or early adverse reactions, each of which has been reported to occur in clinical trials, in an incidence of less than 1%: dyspnea, cyanosis, allergic reactions, hyperlipemia, hypercoagulability, nausea, vomiting, headache, flushing, increase in temperature, sweating, sleepiness, pain in the chest and back, slight pressure over the eyes, dizziness, irritation at the site of infusion and, rarely, thrombocytopenia in neonates. b) Delayed adverse reactions such as hepatomegaly, jaundice due to central lobular cholestasis, splenomegaly, thrombocytopenia, leucopenia, transient increases in liver function tests and overloading syndrome (focal seizures, fever, leukocytosis, hepatomegaly, splenomegaly and shock).

The deposition of a brown pigmentation in the reticuloendothelial system, the so-called "intravenous fat pigment," has been reported in patients infused with Intralipid®. The causes and significance of this phenomenon are unknown.

OVERDOSAGE

In the event of fat overload during therapy, stop the infusion containing Intralipid® 30% until visual inspection of the plasma, determination of triglyceride concentrations, or measurement of plasma light-scattering activity by nephelometry indicates the lipid has cleared. Re-evaluate the patient and institute appropriate corrective measures. See WARNINGS and PRECAUTIONS.

DOSAGE AND ADMINISTRATION

Intralipid® 30% Pharmacy Bulk Package should be administered only as a part of a three-in-one or total nutrient admixture via peripheral vein or by central venous infusion.

Directions For Proper Use Of Pharmacy Bulk Package

INTRALIPID® 30% PHARMACY BULK PACKAGE IS NOT INTENDED FOR DIRECT INFUSION. The container closure may be penetrated only once using a suitable sterile transfer device or dispensing set which allows measured dispensing of the contents. The Pharmacy Bulk Package is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area). Once the closure is penetrated, the contents should be dispensed as soon as possible; the transfer of contents to suitable TPN admixture containers must be completed within 4 hours of closure penetration. The bottle should be stored below 25°C (77°F) after the closure has been entered. Date and time of container entry should be noted in the area designated on the container label.

Manufactured for
Clintec Nutrition Company
Affiliated with
Baxter Healthcare Corporati
Deerfield, IL 60015 USA

Manufactured by
Kabi Pharmacia Inc.
Clayton, NC 27520 USA

Kabi Pharmacia

Admixtures made using Intralipid® 30% should be used promptly. See MIXING GUIDELINES AND LIMITATIONS section for admixture storage recommendations.

Adult Patients

The initial infusion rate of the nutrient admixture in adults should be the equivalent of 0.1 g fat/minute for the first 15 to 30 minutes of infusion. If no untoward reactions occur (see ADVERSE REACTIONS section), the infusion rate of the nutrient admixture can be increased to be equivalent to 0.2 g fat/minute. For adults, the admixture should not contain more than 330 mL of Intralipid® 30% on the first day of therapy. If the patient has no untoward reactions, the dose can be increased on the following day. The daily dosage should not exceed 2.5 g of fat/kg of body weight (8.3 mL of Intralipid® 30% per kg). Intralipid® should make up no more than 60% of the total caloric input to the patient. Carbohydrate and a source of amino acids should comprise the remaining caloric input.

Pediatric Patients

The dosage for premature infants starts at 0.5 g fat/kg body weight/24 hours (1.7 mL Intralipid® 30%) and may be increased in relation to the infant's ability to eliminate fat. The maximum dosage recommended by the American Academy of Pediatrics is 3 g fat/kg/24 hours.[3]

The initial rate of infusion of the nutrient admixture in older pediatric patients should be no more than 0.01g fat/minute for the first 10 to 15 minutes. If no untoward reactions occur, the rate can be changed to permit infusion of 0.1 g of fat/kg/hour. The daily dosage should not exceed 3 g of fat/kg of body weight.[3] Intralipid® should make up no more than 60% of the total caloric input to the patient. Carbohydrate and a source of amino acids should comprise the remaining caloric input.

Essential Fatty Acid Deficiency

When Intralipid® is administered to correct essential fatty acid deficiency, eight to ten percent of the caloric input should be supplied by Intralipid® in order to provide adequate amounts of linoleic and linolenic acids. When EFAD occurs together with stress, the amount of Intralipid® needed to correct the deficiency may be increased.

Administration

See MIXING GUIDELINES AND LIMITATIONS section for information regarding mixing this fat emulsion with other parenteral fluids.

Intralipid® 30% (30% I.V. Fat Emulsion) is not for direct infusion. It must be infused as part of an admixture into a central or peripheral vein. The flow rate of the admixture should be controlled with an infusion pump. Filters of less than 1.2 micron pore size must not be used with admixtures containing Intralipid® 30%.

Conventional administration sets and TPN pooling bags contain polyvinyl chloride (PVC) components that have DEHP (diethyl hexyl phthalate) as a plasticizer. Fat-containing fluids such as Intralipid® extract DEHP from these PVC components. Therefore, it may be advisable to use a non-DEHP administration set for infusing admixtures which contain Intralipid®.

Do not use any bottle in which there appears to be an oiling out on the surface of the emulsion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

MIXING GUIDELINES AND LIMITATIONS

INTRALIPID® 30% PHARMACY BULK PACKAGE IS NOT INTENDED FOR DIRECT INFUSION. It must be combined with total parenteral nutrition (TPN) fluids so that the resulting admixture has a final concentration of not more than 20% fat (0.2 g fat per mL of admixture). The following table may be used as a guide:

Volume of Intralipid® 30%		Required Minimum Volume of Dextrose/ Amino Acid Solutions		Final Volume of Admixture	Final Fat Concentration
1 mL	+	0.5 mL	=	1.5 mL	20%
100 mL	+	50 mL	=	150 mL	20%
250 mL	+	125 mL	=	375 mL	20%
500 mL	+	250 mL	=	750 mL	20%

Investigations have been conducted which demonstrate the compatibility of Intralipid® 30% when properly mixed with either

Novamine® (8.5%, 11.4% or 15%) or 8.5% Travasol® or 10% Travasol® Amino Acid Injections for use in Total Parenteral Nutrition (TPN) therapy.

Perform all manipulation in a suitable work area, such as a laminar flow hood.

Failure to follow the Mixing Guidelines and Limitations below, including recommended storage temperature, storage time, order of mixing, etc., may result in an unstable admixture.

The following proper mixing sequence must be followed to minimize pH related problems by ensuring that typically acidic Dextrose Injections are not mixed with lipid emulsions alone:

1. Transfer Dextrose Injection to the TPN admixture container
2. Transfer Amino Acid Injection
3. Transfer Intralipid® 30%.

Note: Amino Acid Injection, Dextrose Injection and Intralipid® may be simultaneously transferred to the admixture container. Admixing should be accompanied by gentle agitation to avoid localized concentration effects.

These admixtures should be used promptly with storage under refrigeration (2°-8°C) not to exceed 24 hours and must be completely used within 24 hours after removal from refrigeration.

It is essential that the admixture be prepared using strict aseptic technique as this nutrient mixture is a good growth medium for microorganisms.

Additives other than those named above may be incompatible. Complete information is not available. Those additives known to be incompatible should not be used. Consult with pharmacist. If, in the informed judgment of the prescribing physician, it is deemed advisable to introduce additives, use aseptic technique. Mix thoroughly when additives have been introduced. Do not store solutions containing additives (e.g., vitamins and minerals).

Additives must not be added directly to Intralipid® and in no case should Intralipid® be added to the TPN container first. Bags should be shaken gently after each addition to minimize localized concentration.

If evacuated glass containers are used, add the Dextrose and Amino Acid Injections first, followed by Intralipid® and then additives. Bottles should be shaken gently after each addition.

Supplemental electrolytes, trace metals or multivitamins may be required in accordance with the prescription of the attending physician.

The prime destabilizers of emulsions are excessive acidity (low pH) and inappropriate electrolyte content. Careful consideration should be given to additions of divalent cations (Ca^{++} and Mg^{++}) which have been shown to cause emulsion instability. Amino acid solutions exert a buffering effect protecting the emulsion.

The admixture should be inspected carefully for "breaking or oiling out" of the emulsion. "Breaking or oiling out" is described as the separation of the emulsion and can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the admixed emulsion. The admixture should also be examined for particulates. The admixture must be discarded if any of the above is observed.

HOW SUPPLIED

Intralipid® 30% (30% I.V. Fat Emulsion) is supplied as a sterile emulsion in a Pharmacy Bulk Package in the following fill sizes:

250 mL	NDC 0338-0495-02
500 mL	NDC 0338-0495-03

STORAGE

Intralipid® 30% should not be stored above 25°C (77°F). Do not freeze Intralipid® 30%. If accidentally frozen, discard the bottle.

REFERENCES

1. Padley FB: "Major Vegetable Fats," *The Lipid Handbook,* (Gunstone FD, Harwood JL, Padley FB, eds.), Chapman and Hall Ltd, Cambridge, UK (1986), pp. 88-9.
2. Levene MI, Wigglesworth JS, Desai R: Pulmonary fat accumulation after Intralipid® infusion in the preterm infant. *Lancet* 1980; 2(8199):815-8.
3. American Academy of Pediatrics: Use of intravenous fat emulsion in pediatric patients. *Pediatrics* 1981; 68:5(Nov):738-43.

71-6053-0
(Issued January 1994)

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Manufactured for
Clintec Nutrition Company
Affiliated with
Baxter Healthcare Corporation & Nestlé S.A.
Deerfield, IL 60015 USA

Manufactured by
Kabi Pharmacia Inc.
Clayton, NC 27520 USA

Kabi Pharmacia

Immediate Label - 500 mL

Labeling: HF-2

NDA No: 19-942 Rc'd. 2.2.94

Reviewed by: AmWeitzel

NDC 0338-0495-03 **500 mL**

Intralipid® 30%

30% I.V. Fat Emulsion

Pharmacy Bulk Package
Not For Direct Infusion

For Intravenous Use

Once container closure has been penetrated, withdrawal of contents should be completed without delay. Dispense contents within 4 hours after initial entry.

See package insert for proper use of Pharmacy Bulk Package.

Manufactured for
Clintec Nutrition Company
Affiliated with
Baxter Healthcare Corporation & Nestlé S.A.
Deerfield, IL 60015 USA

Manufactured by
Kabi Pharmacia Inc.
Clayton, NC 27520 USA
Intralipid is a trademark of
Kabi Pharmacia Inc.

Exp.

Lot

Kabi Pharmacia

Each 100 mL contains:

Soybean Oil	30.0 g
Phospholipids (from powdered egg yolk)	1.2 g
Glycerin, USP	1.7 g
Water for Injection	qs
Calories	300 kcal

pH 8.0 (6.0-8.9), adjusted with sodium hydroxide.
Osmolarity: 200 mOsmol/L (Actual)
Use only if bottle and seal are undamaged.
Administer intravenously.

Sterile-Nonpyrogenic
See Directions Before Using.
Do not store above 25°C (77°F).
Do not freeze Intralipid® 30%; if accidentally frozen, discard the bottle.
Do not use if there appears to be an oiling out of the emulsion.
Caution: U.S. Federal law prohibits dispensing without prescription.

04-9055-0

Intralipid® 30%
500 mL

Time of entry: _____

Date entered: _____

Administrative Review of NDA 19-942

MAR - 3 1993

Intralipid 30% I.V. Fat Emulsion (Pharmacy Bulk Package)

Background Information: This NDA was originally submitted on December 29, 1988 and was withdrawn by the company on February 2, 1989. It was resubmitted on June 29, 1990.

On December 16, 1988, Kabi sent FDA a letter which outlined a stability problem involving "cracking" of the currently marketed 10% and 20% Intralipid I.V. fat emulsions in All-In-One-Admixtures. Since the proposed 30% emulsion will be used in pharmacies for compounding these types of admixtures rather than for direct patient infusion, this incompatibility problem may of greater concern.

Dr. Kenealy indicated that further investigation of the December 16, 1988 report was needed. Kabi's letter of September 20, 1991 further addressing the issue could not be located in FDA files.

Upon my request, Kabi provided additional copies of the correspondence dated September 20, 1991 which has now been added to the respective NDA files for NDA 17-643 and 18-449 (Intralipid 10% and 20%).

Reviews:

Microbiology
Dr. Cooney: Remains approvable for sterility assurance (January 22, 1992)

Pharmacology
Dr. Wilson: Approvable with labeling recommendations (June 2, 1992)

Chemistry
Stan Koch: Approvable with comments except for EER and methods validation (December 15, 1992)

Medical
Dr. Kenealy: Clinically approvable (January 3, 1991)

Dr. Chambers: Not approvable (November 28, 1992)

Action to Be Taken: Further review of the incompatibility reports relating to the use of 10% and 20% I.V. Fat Emulsions in pharmacy admixtures, specifically the one dated September 20, 1991, may be needed.

cc: Original NDA 19-942
Div File

Anna Marie H. Weikel 2/10/93
Anna Marie H. Weikel
Consumer Safety Officer

The 9/20/91 letter contains no new clinical information and provides no information about events after 1988. We should write the company to ask for (1) a safety update in the NDA, which should include ~~all~~ evaluation of adverse reactions ~~submitted~~ received by the company since the NDA was submitted.

(2) reports of any cracking after 1988 and evaluation of those reports

(3) clinical outcome in any patients who have received cracked product

(4) steps to be taken in labeling to prevent cracking caused by misuse of the product.

NA letter.

Paula Botstein MD 3/3/93

6-1

GROUP LEADER'S COMMENTS
NDA 19-942

DEC 17 1993

AGENT: Intralipid 30%, I.V. Fat Emulsion

SPONSOR: Kabi Pharmacia

SUBMITTED: June 30, 1993

MOR DATE: September 23, 1993

I agree with Dr. Woodbury's conclusion that this NDA is approvable. I have only the following concerns which should not change the recommendation to approve this product. The article by Brown, Quercia and Sigman published in Journal of Parenteral and Enteral Nutrition, volume 10, page 650, 1986 and titled Total Nutrient Admixture: A Review comments on "long term consequences of infusing droplets larger than 0.4 um is not definitely known." Also, "contamination of extemporaneously compounded TNA systems becomes a major concern."

RECOMMENDATIONS:

A. Labeling:

1. The second paragraph of Precautions should be changed. It states that liver function tests (LFT's) should be assessed "During long term intravenous nutrition with Intralipid." times, i.e.

   The second paragraph should be worded as follows:

   Intralipid "contains emulsified fat particles of approximately 0.5 micron size."

2. The following sentences in the labeling should be in bolded letters:

   a. The entire second paragraph under **"Description"**

b. [redacted]

c. Under **"Dosage and Administration:"** the first sentence of the **"Directions for Proper Use of Pharmacy Bulk Package."**

3. Under Precautions, to comply with 21CFR 201.57 (f)(g), this subsection of the [redacted]

4. The "Overdosage" sections of the labeling is missing: 21CFR 201.57(i). The sponsor should be asked to propose labeling or justify why it is not needed.

5. [redacted]

6. [redacted]

Recommend change of words [redacted]

This change should be made in all TPN fat package inserts; [redacted]
include:

[redacted]

B. This NDA should be considered approvable and with the above labeling changes an approval is recommended.

Alfred Eric Jones M.D. 11/30/93

Alfred Eric Jones, M.D.
Group Leader, Medical Imaging
November 29, 1993

P Mus
see my comments
12/17/93

DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
LABELING REVIEW

NDA: 19-942

JAN 29 1993

SPONSOR: Kabi Pharmacia

DRUG: Intralipid® 30% I.V. Fat Emulsion Pharmacy Bulk Package

SUBMISSION: December 19, 1991

REVIEWER: Anna Marie H. Weikel, CSO

REVIEW DATE: 01/08/93

BACKGROUND:

This submission provides for specific labeling changes permitting the addition of a Kabi Pharmacia sterile vitamin preparation, KabiVite Ped F + W (Pediatric Multivitamins for Infusion), to Intralipid® I.V. Fat Emulsions.

LABELING REVIEW:

1. The labeling revisions requested by the chemist as part of Chemistry Review #1 have been accomplished as indicated in Chemistry Review #2, page 15; and Chemistry Review #3, pages 2 and 11.

2. The PRECAUTIONS section should be revised as required by 21 CFR 201.57 (f) according to the pharmacology review dated June 2, 1992.

   Carcinogenesis, mutagenesis, impairment of fertility: Studies with Intralipid® have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

   Nursing Mothers: Caution should be exercised when Intralipid® is administered to a nursing woman.

   Pediatric use: See DOSAGE AND ADMINISTRATION.

3. As indicated in the Medical Review dated January 3, 1991, the Mixing Guidelines and Limitations section has been revised to include a table of fluid volumes that will produce a final admixture containing no more than 20% fat emulsion.

4. The OVERDOSAGE section should be revised as required by 21 CFR 201.57(i).

JAN 29 1993

CONCLUSION:

If these proposed labeling additions are acceptable to the reviewers, the sponsor should be requested to incorporate these labeling changes.

Anna Marie H. Weikel 1/29/93
Anna Marie H. Weikel, R.Ph.
Consumer Safety Officer

Linda M. DeWitt 1/29/93
Linda DeWitt, Ph.D.
Supervisory Pharmacologist

Stan Koch 1/29/93
Stan Koch
Reviewing Chemist

cc:
NDA ~~19-843 & 19-449~~
HFD-160/DivFiles
HFD-160/Sheinin/Koch/DeWitt
HFD-161/Weikel

DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
FINAL LABELING REVIEW

NDA: 19-942

DEC 30 1993

SPONSOR: Kabi Pharmacia

DRUG: Intralipid® 30% I.V. Fat Emulsion Pharmacy Bulk Package

SUBMISSION: December 13, 1993

REVIEWER: Anna Marie H. Weikel, CSO

REVIEW DATE: 12/15/93

BACKGROUND:

The Agency's labeling recommendations were faxed to the company on December 10, 1993. These recommendations consisted of stronger labeling restricting the use of this product to a pharmacy admixture system for the preparation of All-in-One TPN admixtures.

LABELING REVIEW:

DESCRIPTION

The first and second paragraphs have been modified as requested to reflect the use of this product for the preparation of All-in-One admixtures in the pharmacy.

INDICATIONS AND USAGE

The indications statement has been modified as requested to distinguish this product from the other Intralipid® I.V. Fat Emulsions that are also being marketed.

CONTRAINDICATIONS

The addition to this section is acceptable.

COMMENT:

PRECAUTIONS

This section has been satisfactorily revised (as requested in the Not Approvable letter dated March 19, 1993) to include the required subsections that were previously lacking.

OVERDOSAGE

This required section has been added to the package insert as requested.

FEB 26 1991

ADMINISTRATIVE REVIEW OF NDA 19-942

Intralipid 30% I.V. Fat Emulsion (Pharmacy Bulk Package)

BACKGROUND INFORMATION: This NDA was originally submitted December 29, 1988 and then withdrawn February 2, 1989 at our request. We had requested this withdrawal after an inhouse meeting held January 24, 1989 for the following reasons: 1) There is no other 30% I.V. Fat Emulsion on the market for comparison, [redacted] 3) there is no other I.V. Fat Emulsion on the market labeled for pharmacy bulk package.

A meeting was held March 22, 1989 with the company addressing the above. The company was informed that clinicals would have to be conducted on adults and pediatric patients if it was to be used in pediatrics. It was stated that the drug product must be studied as it is going to be stated in the labeling. There were also microbiology concerns about the container/closure that would have to be addressed. For details see the minutes which are in Vol. 1.1.

This NDA was resubmitted June 29, 1990 which we received July 2, 1990. The NDA does not contain the necessary patent information either in the original submission or in the resubmission as required by 505(b)(1) of the Act. This will be noted in the letter to the company.

A consult was sent to the Division of Biometrics July 6, 1990.

REVIEWS:

Mr. Koch: Not Approvable for manufacturing and controls. Deficiencies are in the areas of both the active and inactive drug substances, container and components, particle size, finished drug product controls, stability, information on the enviromental assessment and labeling - completed November 15, 1990

Dr. Cooney: Not Approvable for sterility assurance - completed January 3, 1991

Dr. Kenealy: Approvable - completed December 21, 1990

To date, January 29, 1991, reviews have not been completed by the pharmacologist, the Division of Biometrics.

In doing this administrative review, it was discovered that the Division of Biopharmaceutics never received the information for this NDA. In talking to Dr. Gordon they never recieved anything from the original submission that he could find, but this may have been shredded since the NDA was withdrawn. I will send the resubmission over to them and ask for an expidated review.

ACTION TO BE TAKEN: A Not approvable letter will be drafted conveying the chemistry and microbiology deficiencies. There will also be a statement requesting the patent information and a statement if there are any deficiencies from the pharmacology, Division of Biometrics or Division of Biopharmaceutics they will be conveyed at a later date.

cc: NDA 19-942
HFD-160
HFD-160/Kenealy/Cooney/Koch/Wilson/Joyce
RDJoyce 1/29/91 (0878J/D-0017)

noted
J Palmer
2-26-91
Regarding addition deficiencies, along the ltr. includes only Biometrics but not Pharmacology nor Biopharmaceut

Correction, I see that all but Biometrics are accounted for.
JPP
2-26-91

DOSAGE AND ADMINISTRATION

The statement, "Intralipid® 30% Pharmacy Bulk Package is not intended for direct infusion.", has been added as requested in the latest fax.

The warning, "Failure to follow the above Mixing Guidelines and Limitations, including recommended storage temperature, storage time, order of mixing, etc., may result in an unstable mixture.", has been added by Kabi to prevent the cracking of admixtures by misuse of the product. This change in the labeling was requested in our previous Not Approvable letter dated March 19, 1993.

COMMENT:

Anna Marie H. Weikel

Anna Marie H. Weikel, R.Ph.
Consumer Safety Officer

cc:
NDA 19-942
HFD-160/DivFile
HFD-161/Weikel

fwe 12/30/93

6.1

Final Administrative Review of NDA 19-942

Intralipid® 30% Pharmacy Bulk Package

DEC 15 1993

Reviews:

Medical Dr. Woodbury:	Approvable with labeling comments - completed 10/14/93.
Chemistry Stan Koch:	Approvable - completed 10/13/93
Pharmacology Dr. Wilson:	Remains approvable.
Microbiology Dr. Cooney:	Remains approvable.
Action to Be Taken:	An approval letter will be drafted based on the draft labeling dated December 13, 1993, which contains stronger wording restricting the use of this product to a pharmacy admixture system for the preparation of All-in-One TPN admixtures.

Anna Marie H. Weikel

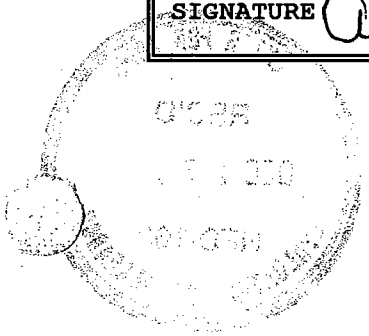
Anna Marie H. Weikel 12.15.93
Consumer Safety Officer

cc: NDA 19-942
Div File

NV 12/20/93

6.1

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE December 15, 1993
I spoke with Mr. Pituk of Kabi Pharmacia regarding the revised draft labeling that was submitted on December 13, 1993. I told him that it was acceptable to us except for two minor changes to the CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION sections which can be made post approval. I told him we will issue an approval letter detailing these slight revisions as terms of the approval. He agreed with our recommendations and will include them on the FPL when it is submitted. CC: NDA 19-942 Div File	NDA NUMBER 19-942 IND NUMBER TELECON/MEETING INITIATED BY ☐ APPLICANT/ SPONSOR ☑ FDA MADE ☑ BY TELEPHONE ☐ IN PERSON PRODUCT NAME Intralipid® 30% Pharmacy Bulk Package I.V. Fat Emulsion FIRM NAME Kabi Pharmacia NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Mr. Tom Pituk Director of Regulatory Affairs TELEPHONE (919) 553-1419
SIGNATURE Anne Marie H. Wentel	DIVISION HFD-160



61

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: July 16, 1993

BETWEEN: Tom Pituk, Director, Regulatory Affairs
Eric Weichert, PhD, Director, Special Projects
Rosemary Davis, Senior Regulatory Associate
Kabi Pharmacia, Inc., Clayton, N.C.
and
Stan Koch, Chemist, HFD-160

Initiated by: Kabi Pharmacia

SUBJECT: NDA 19-942 Methods Validation

TO: Eric Sheinin, PhD, Supervisory Chemist, HFD-160
NDA 19-942 File

Tom Pituk called to request a few minutes for Eric Weichert and Rosemary Davis to discuss the comments from the FDA analyst concerning the NDA 19-942 methods validation procedures. These comments were previously forwarded to Kabi for resolution.

Eric spent a few minutes going over parts of the first two questions before I asked when Kabi intends to submit their response to these comments. Tom said they hope to respond in a few days. I suggested that, rather than take the time to fully explain all the details via this telecon, without full information in front of me for reference, the upcoming amendment contain a full explanation of their method changes and comments for each inquiry addressed. This will afford me the chance to then communicate with field laboratory personnel if need be, and determine if the issues are properly resolved. If not, I will call Kabi, Eric Weichert in particular, and explain the remaining problems, if any. We will then determine our next step to a satisfactory Methods Validation package. I recommended that their submission in this regard be as complete as possible.

Eric and Tom were in complete agreement with this request. I await their response.

Sincerely,

Stanley Koch

cc:
NDA Div File
Orig NDA 19-942
HFD-160/ESheinin
HFD-160/SKoch
HFD-161/AMWeikel
HFD-160/PLove
F/T SKoch 7-18-93

7-28-93

6.1

MEMORANDUM OF TELECON

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 30, 1993

Between: Stan Koch, Division of Medical Imaging, Surgical & Dental Drug Products, HFD-160, and

Eric Weichert, PhD, Director, Special Projects
Kabi Pharmacia, Inc., Clayton, N.C.
919-553-1413

Subject: Intralipid 30% Fat Emulsion, Pharmacy Bulk Package
NDA 19-942

To: Eric Sheinin, PhD, Supervisory Chemist, HFD-160
NDA 19-942 File

Eric Weichert was called this afternoon for the purpose of informing him of our decision after reviewing data in the 6-30-93 original amendment and examining the bottles of fat emulsion and amino acid injection Kabi Pharmacia sent to us regarding excess fill requirements.

In the opinion of Dr. Sheinin and myself, the viscosity of the submitted samples of Intralipid 10%, 20%, and 30% in comparison with amino acid injections and water, and the submitted viscosity studies completed by Kabi, support categorization of Intralipid 30% Fat Emulsion as a mobile liquid. Such a determination will qualify this fat emulsion for a recommended excess fill of 2% labeled volume (refer to USP requirements found in the General Chapter entitled **Injections**).

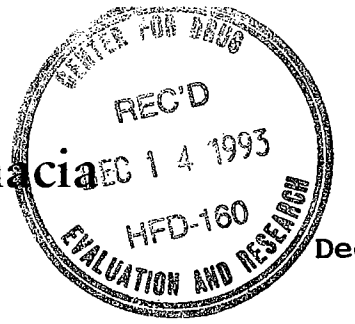
Generally, past actions recalled by this reviewer have resulted in classification of fat emulsions as viscous liquids, resulting in a recommended excess fill of 3% labeled volume. In the case of Intralipid drug products, this position no longer appears warranted.

It was made clear to Dr. Weichert that this is a preliminary opinion, and while unlikely to be changed, does not have the force of Agency approval until the firm is formally so informed. He was very appreciative.

cc:
Orig NDA 19-942
HFD-160/Div File
HFD-160/ESheinin
HFD-161/AMWeikel
HFD-160/SKoch
R/D Init by: ESheinin
F/T SKoch 7/30/93
HFD-160/Love

Stan Koch

E B Sheinin
8-2-93



Kabi Pharmacia

FEDERAL EXPRESS

ORIGINAL

ORIG AMENDMENT

December 13, 1993

BL

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

Patricia Y. Love, M.D., M.B.A.
Acting Director
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
HFD-160, Document Room 18B04
5600 Fishers Lane
Rockville, MD 20857

NDA 19-942
Intralipid® 30% I.V. Fat Emulsion
(Pharmacy Bulk Package)

SUBJECT: Amendment - Revised Draft Labeling - Response to FDA Fax Dated 12/10/93

Dear Dr. Love:

Reference is made to our NDA 19-942 for Intralipid® 30% I.V. Fat Emulsion (Pharmacy Bulk Package).

Reference is also made to a telefax dated 12/10/93, sent to us by Ms. Anna Marie Weikel, CSO of your Division, which contained revisions in the package insert labeling requested by FDA. Following receipt of that telefax, a telephone conversation was held between Ms. Weikel and Thomas Pituk of Kabi Pharmacia to discuss the revisions covered by the fax and to clarify the procedures to be followed in submitting our response. We were informed that our response should be faxed to FDA by no later than 12/15/93, and the hard copy of that response should be sent via overnight mail by no later than 12/16/93, in order for FDA to review the response and be able to sign an action letter the week of 12/20/93.

During that telephone conversation, certain clarifications were discussed:

1. We noted that the latest draft package insert labeling in the NDA, which had been submitted June 30, 1993, was not the version on which the faxed FDA comments were based. Several of the faxed comments had already been included in the 6/30/93 version. We indicated, therefore, that for our response to the 12/10/93 fax, we would enlarge the 6/30/93 draft labeling to improve readability and annotate that version to comply with the faxed FDA comments.

   That procedure has been followed for the attached revised draft package insert labeling.

A Procordia Company

Kabi Pharmacia Inc.	Telephone	Telefax	Telefax	Telefax
P.O. Box 597	(919) 553-3831	(919) 553-3601	(919) 553-0547	(919) 553-2399
1899 Highway 70 East		Management	Distribution	Quality / Research
Clayton, NC 27520-0597	DID			

2. FDA indicated that "Pharmacy Bulk Package" should be part of the product name in the package insert running text. Consequently, the attached draft package insert has been revised to delete the words ——— every time it appeared before "Pharmacy Bulk Package."

3. The possibility of revising the term "three-in-one" ——— was discussed. However, we agree to use the term "three-in-one" where indicated in the faxed version.

4. For the proposed addition to the CONTRAINDICATIONS section, we understand that the intent of the FDA wording is to restrict practitioners from diluting Intralipid® 30% down to 10% or 20% with some diluent and then administering that dilution by direct infusion. We would like to suggest alternate wording for that section:

   "Intralipid® 30% Pharmacy Bulk Package is not intended for direct intravenous administration. Diluting Intralipid® 30% to a 10% or 20% concentration with an intravenous fluid such as normal saline or other diluent does not produce a dilution that is equivalent in composition to Intralipid® 10% or 20% I.V. Fat Emulsions, and such a dilution should not be given by direct intravenous administration (for example, through a Y-connector)."

5. The proposed additions to the PRECAUTIONS section (included as an attachment following the last page of the draft) had already been added in the 6/30/93 version of the draft package insert.

   In addition, the subheadings in the PRECAUTIONS section have been made bold.

6. Regarding OVERDOSAGE information, the 6/30/93 version of the draft package insert retains the statement "AVOID OVERDOSAGE ABSOLUTELY" immediately before the ADVERSE REACTIONS section and also includes a separate OVERDOSAGE section to be inserted immediately following the ADVERSE REACTIONS section. This appears in the attached revised draft package insert.

7. For the "Required Minimum Volume" heading of the table that appears under MIXING GUIDELINES AND LIMITATIONS, we agreed during the telephone conversation to change ——— to "dextrose/amino acid solutions."

We agree to all other revisions suggested in the 12/10/93 FDA fax. The attached draft package insert has been revised accordingly.

As mentioned previously, the 6/30/93 version of the draft package insert already contained additional revisions as follows:

1. The PRECAUTIONS section was revised to contain the following subsections (wording as proposed by FDA in a letter dated 3/19/93):

   a. Carcinogenesis, Mutagenesis, Impairment of Fertility

   b. Nursing Mothers

   c. Pediatric Use

2. Wording was added to the MIXING GUIDELINES AND LIMITATIONS section (please refer to the last paragraph of this section in the attached draft package insert) which was intended to prevent the cracking of admixtures caused by misuse.

3. In the DESCRIPTION section, in the paragraph describing the R_3 group of purified egg phosphatides, [redacted] was changed to "phosphoric acid," as requested earlier by FDA.

4. An OVERDOSAGE section was inserted immediately following the ADVERSE REACTIONS section, as noted above.

For additional details regarding the revisions contained in the 6/30/93 version of the draft package insert, please see pages 13-14 of the cover letter for that submission.

Enclosed are four (4) copies of the draft package insert labeling that has been revised as indicated above. Upon notification by FDA that the attached draft labeling is acceptable, we commit to prepare final printed package insert labeling that is identical to the draft version. In addition, because these revisions do not appear to affect the text of the immediate label, we also commit to prepare the final printed immediate label that is identical in text to the latest version included in the NDA (submitted 9/4/92). Final printed labeling will be submitted to FDA as soon as available.

Should you have additional questions or comments, please advise. We look forward to rapid approval of this NDA.

Sincerely,

Thomas L. Pituk

Thomas L. Pituk
Director of Regulatory Affairs

TLP/jp
Enclosures

21

JUL 11 1990

NDA 19-942

KabiVitrum, Inc.
Attention: Mr. Thomas L. Pituk
P.O. Box 597
Clayton, North Carolina 27520

Dear Mr. Pituk:

We have received your new drug application resubmitted under section 505(b)(1) of the Federal Food, Drug and Cosemetic Act for the following:

Name of Drug Product: Intralipid 30% I.V. Fat Emulsion (Pharmacy Bulk Package)

Date of Application: June 29, 1990

Date of Receipt: July 2, 1990

Our Reference Number: NDA 19-942

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b)(1) of the Act on August 1, 1990 in accordance with 21 CFR 314.101(a).

If the application is filed, the new date is December 29, 1990.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Should you have any questions concerning this NDA, please contact:

Regina Joyce
Consumer Safety Officer
(301) 443-3500

Sincerely yours,

Warren Rumble 7/11/90

Warren F. Rumble
Chief, Project Management Staff
Division of Medical Imaging
Surgical and Dental Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Orig. NDA 19-942
HFD-160
HFD-160/CSO
HFD-160/WRumble/7.11.90
F/T AChapman/7.11.90
Wang 4749Y

ACKNOWLEDGEMENT