CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020181

ADMINISTRATIVE DOCUMENTS

DIV FILE

Division Director's Comments on NDA 20-181

NDA 20-181 **Review date:** 11/29/91

Sponsor: Abbott Laboratories, Inc.

Drug: Liposyn III 30% (an intravenous fat emulsion), Pharmacy Bulk Package

Proposed Indication: Liposyn III 30% in the Pharmacy Bulk Package is indicated for use with automated compounding devices for preparing intravenous nutritional admixtures in the pharmacy.

Liposyn III (intravenous fat emulsion) is indicated as a source of calories for patients requiring parenteral nutrition. Where such nutrition is required for extended periods of time (more than 5 days), Liposyn III is also indicated as a source of essential fatty acids to prevent or reverse biochemical changes in fatty acid composition of plasma (elevated triene/tetraene ratio) and the clinical manifestations of EFAD.

Related Reviews: Medical Officer's Review dated 6/27/91

Review Comments:

NDA Summary Statement:

Reference is made to the clinic information contained in the following for intravenous fat emulsion products which utilize similar bulk drug components in their formulations.

Solution
Liposyn

Liposyn II

Reviewer's Comments:

1. *The references listed above as not the same as the drug product which is the subject of this application. The sponsor has failed to provide substantial evidence consisting of adequate and well-controlled investigations, as defined in § 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.*

2. *The sponsor has not provided any safety updates or information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.*

3. *In addition to the clinical use studies noted above, I concur with Dr. Kenealy's recommendations that adequate data to demonstrate that direct infusion of a 30% lipid emulsion is safe should be presented or that the container be so designed that direct infusion cannot be accomplished.*

4. *I concur with Dr. Kenealy's recommendation that the package insert undergo major revisions due to the numerous inconsistencies.*

APPEARS THIS WAY
ON ORIGINAL

Recommendation:

The application as submitted is **not recommended** for approval.

APPEARS THIS WAY
ON ORIGINAL

/S/

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

cc: Orig NDA 20-181
HFD-160
HFD-161/CSO/Joyce
HFD-160/CHEM/Koch
HFD-160/PHARM/Wilson
HFD-160/MO/Kenealy

APPEARS THIS WAY
ON ORIGINAL

JOYCE

JUN 27 1991

NDA 20-181

MOR of Original NDA

Completed 6/27/91

Sponsor: Abbott Laboratories Inc.

Drug: Liposyn III 30% (an intravenous fat emulsion), Pharmacy Bulk Package

Category: Nutritional Supplement

Classification: 3CP

Dosage Form: Sterile, non-pyrogenic emulsion

Route of Administration: Peripheral or central venous infusion following appropriate admixture

Submitted: 4/10/91
Received: 4/25/91
Assigned: 4/25/91

Type of Submission: Original NDA in accord with 21 CFR 314.50

Background and Clinical Comment: The drug product that is the subject of this application has been previously approved in 10% and 20% concentrations under NDA 18-970, original approval date 9/25/84. This is a Pharmacy Bulk Package of 30% emulsion of identical composition intended for dilution to 20% or less prior to administration as part of a TPN admixture.

Prior to this time there have been no lipid emulsions more concentrated than 20% approved, although one other application for a 30% concentration in a Pharmacy Bulk Package is presently under review. (The sponsor of that application has been required to present Phase I clinical data to demonstrate safety in the event of an inadvertent episode of direct administration.) It should be noted that the container proposed for that emulsion is easily capable of being used for a direct infusion in spite of the fact that it is to be clearly labeled "Not For Direct Infusion".
The sponsor of that application has submitted Phase I data to support claims of clinical safety of direct infusion into healthy, adult male volunteers of a 30% fat emulsion as compared with direct infusion of 20% fat emulsion.
The primary response variable in these studies was fractional elimination rate. There were no clinically or statistically significant differences noted. Serial hematologic parameters, serum chemistries and liver function studies remained well within the normal limits. There were no significant or unanticipated adverse reactions observed during the course of these studies.

This application does not address the possibility of direct infusion by error. There are no clinical studies reported inasmuch

as the 10% and 20% emulsions have been approved and marketed widely in this country since 1984. However, the reviewing Microbiologist reports that the container is not significantly different from that in which the 10% and 20% emulsions are marketed, suggesting that erroneous direct infusion of the 30% emulsion is a distinct possibility. Therefore, it is the opinion of this reviewer that Phase I studies to demonstrate the safety of direct infusion of a 30% lipid emulsion must be submitted prior to consideration of approval of this application. If such data are not presented, the sponsor must design a container from which direct infusion cannot be accomplished.

Chemistry: As with all lipid emulsions, the most immediate safety concern is with stability of admixtures. The data presented in support of stability of recommended admixtures of this product will be considered in the Chemist's review.

Pharmacology: See Pharmacologist's review for preclinical data. From the standpoint of clinical pharmacology, data concerning clearance rate and data describing hematological and hepatic functional changes, if any, associated with inadvertent direct infusion of the 30% emulsion should be submitted.

Conclusion and Recommendation: Because of the significant possibility of inadvertent administration of this 30% fat emulsion as a direct infusion, it is the opinion of this reviewer that this application is not clinically approvable for reasons of safety. There are numerous records of this type of error with drugs formulations intended for dilution prior to administration having been given directly, often with disastrous outcome. In spite of the fact that the drug is clearly labeled "NOT FOR DIRECT INFUSION", there should be some clinical data concerning the outcome should inadvertent direct administration occur. As noted above, another sponsor of a similar product has been required to submit safety data consisting of Phase I studies of clearance rates and hepatic function estimation following direct administration of 30% lipid emulsion.

The sponsor of this application has two possible courses to follow.

1. Offer this 30% emulsion in a container so designed that direct infusion cannot be accomplished, rather than in the container presently proposed.

2. Present data adequate to demonstrate that direct infusion of a 30% lipid emulsion is safe. This can be accomplished by Phase I studies to demonstrate adequate clearance and lack of hematological, hepatic or other adverse response to this highly concentrated emulsion. The safety and efficacy of this product in the concentrations proposed, if used as it should be labeled, i.e. as a 20% or lower concentration in TPN admixtures) has been adequately

demonstrated. Need for further studies to demonstrate efficacy are not anticipated.

The following should be conveyed to the sponsor:

"NDA 20-181 is not approvable clinically due to lack of data to demonstrate safety in the event of inadvertent direct infusion of a 30% lipid emulsion.
One of the following is offered as a possible route to follow in order for ultimate approval of this product to be considered:

1. Offer this 30% emulsion in a container so designed that direct infusion cannot be accomplished, rather than in the container presently proposed.

2. Present data adequate to demonstrate that direct infusion of a 30% lipid emulsion is safe. This can be accomplished by Phase I studies to demonstrate adequate clearance and lack of hematological, hepatic or other adverse response to this highly concentrated emulsion. The safety and efficacy of this product in the concentrations proposed, if used as it should be labeled, (i.e. as a 20% or lower concentration in TPN admixtures) has been adequately demonstrated. Need for further studies to demonstrate efficacy are not anticipated.

The package insert for this product as proposed in this application contains numerous inconsistencies. (e.g. The Dosage and Administration section discusses direct administration via a Y-connector, clearly suggesting use by direct infusion, while the initial boxed warning under the title contraindicates direct infusion.) Detailed review will be delayed until the application is otherwise approvable. However it should be noted that major revisions will be required and should be considered prior to re-submission."

BEST POSSIBLE COPY

John C.Kenealy, M.D.

cc:NDA 20-181
HFD-160/Div File
HFD-160/Kenealy
HFD-160/Koch
HFD-169/Wilson
HFD-161/Joyce/Jenkins
HFD-340
F/T:Kenealy-6/27/91

Div Director's Comments

See Division Director Memo

HFD-160

No Statistical review was required. The response to the not approvable letter included utility data based upon use of the Liposyn III 30% in a clinical setting to demonstrate the safety of the drug. Due to the small number of patients and the type of data submitted no statistical analysis of the data was required.

/S/ ESO 2-21-97

/S/ 2-25-97

APPEARS THIS WAY
ON ORIGINAL

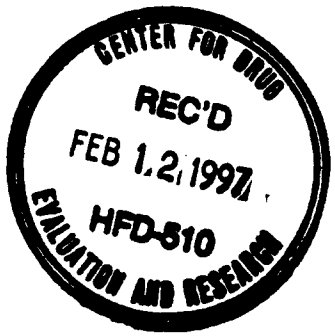
APPEARS THIS WAY
ON ORIGINAL

ABBOTT

spital Products Division
ott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

APPEARS THIS WAY
ON ORIGINAL

February 7, 1997



CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS, HFD #510
Attn: DOCUMENT CONTROL ROOM #14B-19
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Solomon Sobel, M.D.
Director

RE: NDA 20-181, Liposyn III 30% (an intravenous fat emulsion), Pharmacy Bulk Package

Abbott Laboratories hereby submits additional information as requested in a teleconference between Mr. Steve McCord of FDA and Mr. Thomas P. Sampogna of Abbott Laboratories on February 7, 1997.

e following additional information was requested:

Request 1: Please submit to NDA 20-181, the necessary Debarrement Certification.

Response: As requested, Debarrement Certification is enclosed.

We trust that this information is complete.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Thomas P. Sampogna
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 935-3715
Fax: (847) 938-7867
enc.

ABBOTT

CERTIFICATION REQUIREMENT FOR ALL APPLICATIONS

FOR APPROVAL OF A DRUG PRODUCT

CONCERNING USING SERVICES OF DEBARRED PERSONS

Under the new law, any application for approval of a drug product submitted on or after June 1, 1992, must include:

> "a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with such application."

Abbott Laboratories certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with this application.

Generic Drug Enforcement Act of 1992
Section 306(k) (1) of the act (21 USC 335a(k) (1)).

APPEARS THIS WAY
ON ORIGINAL

Thomas P. Sampogna — February 7, 1997

Thomas P. Sampogna
Manager, Regulatory Affairs
Hospital Products Division
D-389. AP30
Abbott Laboratories
200 Abbott Road
Abbott Park, Illinois 60064-3537

Date

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

LIST OF RELEVANT CONVICTIONS FOR

PERSONS DEBARRED OR NOT DEBARRED

Per letter from the Office of Generic Drugs dated January 15, 1993, abbreviated applications must contain a list of relevant convictions, as described in section 306(a) and (b) of the GDEA*, of the applicant and affiliated persons (i.e., contractors, et. al.) responsible for the development or submission of the application, which have occurred within five years before the date of the application. Firms with no convictions to list should submit a statement to that effect.

Abbott Laboratories states that it has no such convictions to list.

* Generic Drug Enforcement Act of 1992
Section 306(k) (1) of the act (21 USC 335a(k) (1)).

APPEARS THIS WAY
ON ORIGINAL

Thomas P. Sampogna

February 7, 1997
Date

Thomas P. Sampogna
Manager, Regulatory Affairs
Hospital Products Division
D-389, AP30
Abbott Laboratories
200 Abbott Road
Abbott Park, Illinois 60064-3537

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(TITLE 21, Code of Federal Regulations, 314)

Form approved : OMB No. 0910-0001.
Expiration Date: December 31, 1995.
See OMB Statement on Page 3

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT
Abbott Laboratories

DATE OF SUBMISSION
Februray 11, 1997

ADDRESS *(Number, Street, City, State, and Zip Code)*
200 Abbott Park Road, D-389 AP30
Abbott Park, Illinois 60064-3537

TELEPHONE NO. (Include Area Code)
(847) 937-7597

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*
20-181

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)
Liposyn II 30% (an intravenous fat emuulsion)

PROPRIETARY NAME (If any)

CODE NAME (If any)

CHEMICAL NAME
Intravenous fat emulsion

DOSAGE FORM
Abbovac Container

ROUTE OF ADMINISTRATION
Intravenous

STRENGTH(S)2
30%

PROPOSED INDICATIONS FOR USE
Source of essential fatty acids and calories during extended periods of parenteral nutrition.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part314), AND DRUG MASTER FILES (21CFR 314.420) REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG

HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv))

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

LABEL REVIEW 2

Application Number: 20-181

Name of Drug: Liposyn III 30%(an intravenous fat emulsion) Pharmacy Bulk Package

Sponsor: Abbott Laboratories

Material Reviewed

APPEARS THIS WAY
ON ORIGINAL

Submission Date(s): December 23, 1997

Receipt Date(s): December 29, 1997

Background and Summary Description: This submission included revised draft labeling in response to FAX communicated to the firm on December 23, 1997. The labeling revisions included revisions to the WARNINGS, DOSAGE AND ADMINISTRATION, and PRECAUTIONS section of the package insert.

Review

The revised draft labeling dated December 23, 1997, was compared with draft labeling dated October 22, 1997. All revisions requested by the Division in the December 23, 1997 FAX have been made in this submission.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION:

With the concurrence of the reviewing staff, draft labeling for NDA 20-181 NDA 20-181 is recommended for approval.

/S/ 12 30 97
Project Manager

/S/ 1/2/98
Pharmacology Supervisor

/S/ 1/2/98
Medical Officer

/S/ 1/2/98
Chemistry Reviewer

/S/
Deputy Director

/S/ 1/6/97
Chemistry Team Leader

APPEARS THIS WAY
ON ORIGINAL

/S/
1-13-98

cc:

NDA 20-181
HFD-510/Div. Files
HFD-510/SMcCort/SKoch/DWu/EColman/GTroendle/RSteigerwalt
HFD-510/Solomon Sobel, M.D.

LABEL REVIEW

LABEL REVIEW

Application Number: 20-181

Name of Drug: Liposyn III 30%(an intravenous fat emulsion) Pharmacy Bulk Package

Sponsor: Abbott Laboratories

Material Reviewed

Submission Date(s): March 11, 1996

Receipt Date(s): March 13, 1996

Background and Summary Description: This submission included revised draft labeling in response to deficiencies communicated in the November 29, 1991, not approvable letter for NDA 20-181.

Review

The revised draft labeling dated March 11, 1996, was compared with the draft labeling dated April 10, 1991. The following changes were made:

1. The pharmacy bulk package boxed declaration has been changed from:

   "Pharmacy Bulk Package - NOT FOR DIRECT INFUSION
   FOR USE WITH AUTOMATED COMPOUNDING DEVICES"

   To read,

   "Pharmacy Bulk Package - NOT FOR DIRECT INFUSION

2. In the **CONTRAINDICATIONS** section, the following has been added as a first paragraph:

   "LYPOSYN III 30% PHARMACY BULK PACKAGE IS NOT INTENDED FOR DIRECT INTRAVENOUS ADMINISTRATION DILUTING LYPOSYN III 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 LIPOSYN II 10% OR 20% I.V. FAT EMULSIONS, AND SUCH A DILUTION SHOULD NOT BE GIVEN BY DIRECT INTRAVENOUS ADMINISTRATION (E.G. THROUGH A Y-CONNECTOR)."

3. Reference to the use of additives and non-use of filters have been deleted from the **CONTRAINDICATIONS** Section, **DOSAGE AND ADMINISTRATION** section, and **PRECAUTIONS** section of the package insert.

4. The following has been section has been added to the **WARNING** section of the package insert to appear as paragraph 1 (under the boxed warning statement:

"Precipitation occurring in parenteral nutrition admixtures as a result of incorrect admixture practices has been reported . Precipitate formation may occur as result of incompatibility of calcium and phosphate salts. Liposyn III 30%, as a component of these admixtures, will obscure the presence of particulate matter (see DOSAGE AND ADMINISTRATION and MIXING INSTRUCTIONS FOR COMBINED ADMINISTRATION)."

5. Under **PRECAUTIONS** section, the sentence:

"AVOID OVERDOSAGE ABSOLUTELY"

has been deleted as the final sentence after the sentence, "Do not dispense....."

6. Under **ADVERSE REACTIONS**, the paragraph was added as the 4th paragraph to this section:

If symptoms and signs of acute respiratory distress develop, appropriate medical intervention should be instituted immediately and the cause of the distress investigated. The parenteral nutrition infusion should be replaced with a dextrose infusion (to prevent rebound hypoglycemia) and checked for the presence of particulate matter and oiling out of the emulsion (see MIXING INSTRUCTIONS FOR COMBINED ADMINISTRATION).

7. In the **DOSAGE AND ADMINISTRATION** section of the package insert under **Adult patients**, the following paragraphs has been deleted:

"Lyposyn III can provide up to 60% of daily calories at a dose not to exceed 3 g/kg of body weight per day. The other 40% should be provided by carbohydrate and amino acids.

For the prevention of essential amino acid deficiency, the recommended daily requirement is approximately 4% of the caloric intake as linoleate. In most adult patients, this can be supplied as 153 mL of Liposyn III 30% administered three times weekly."

The original paragraph in the **DOSAGE AND ADMINISTRATION** section April 11, 1991 package insert and included as the last paragraph, has been rewritten as follows,

"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 that 330 mL of Liposyn III 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 Liposyn III 30% per kg). Liposyn III 30% 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."

8. In the **DOSAGE AND ADMINISTRATION** section under **pediatric patients**, the following paragraphs replace the original three paragraphs as follows:

"The dosage for premature infants starts at 0.5 g fat/kg body weight/24 hours (1.7 mL Liposyn III 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.

The initial rate of infusion of the nutrient admixture in older pediatric patients should be no more than 0.01 g 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. Liposyn III 30% 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."

9. The following section has been added to the **DOSAGE AND ADMINISTRATION** section:

Essential Fatty Acid Deficiency

"When Liposyn III 30% is administered to correct essential fatty acid deficiency, eight, to ten percent of the caloric input should be supplied by Liposyn III 30% in order to provide adequate amounts of linoleic acids.. When EFAD occurs together with stress, the amount of Liposyn III 30% needed to correct the deficiency may be increased."

10. Under **DOSAGE AND ADMINISTRATION, Administration** section the following changes were noted:

The first paragraph has been revised. It now reads,

See CONTRAINDICATIONS regarding mixing this emulsion with other I.V. fluids or additives.

The following paragraphs have been added:

"Studies have documented the stability of Liposyn III 30% necessary Abbott electrolytes. Abbott trace metals, and Dextrose Injection, 0 USP and Abbott Aminosyn II amino acid solution.

It is recommended that a 1.2 micron air-eliminating filter be used during administration of admixtures containing Liposyn II 30%."

The following sentence has been deleted from the the Adminstration section:

"Filters should not be used for administration of the emulsion."

11. The following paragraphs have been added to the **MIXING AND INSTRUCTIONS FOR COMBINED ADMINISTRATION** section:

Because warming parenteral nutrition admixtrues may contribute to the formation of precipitates, once adminstrartion begins, care should be taken to avoid excessive warming of the admixture.

Caution should be taken to ensure that precipitates do not form in any parenteral nutrition admixture. Precipitates can develop because of a number of factors such as: the concentration, pH and phosphate content of the amino acid solution, the calcium and phosphate additives or the order of mixing. The presence of a lipid emulsion in the TPN admixture will obscure the presence of any precipitate.

Admixtures must be made using specific mixing protocols for 2 in 1 and 3 in 1 admixtures. Each pharmacy mixing protocol should be verified for compatiability of the resulting admixture. Admixtures should be verified at the final concentration used for amino acids, dextrose, lipid emulsion, the specific additives and the specific order of addition. Different manufacturers' components should not be substituted in a tested pharmacy admixture protocol without prior verification of compatability.

When adding calcium and/or phosphate to parenteral nutrition solution, the pharmacist must assess the impact of the following factors on the formation of a precipitate: 19 order of mixing. @0 salt form and concentration of electrolytes 30 concetration of

amino acids, 40 concetration of extrose, 50 concentration of lipid emulsion, 60 temperature and pH and 7) presence of other addtitives.

The amounts of phosphate and of calcium added to the admixture are critical. The solubility of the added calcium should be calculated from the voume at the time the calcium should be calculated from the volume at the time the calcium is added. It should not be based upon the final volume. Any phosphate ions present in other constituents and the volume at the time the phosphate is added should be considered when calculating the amount of phosphate additives. Also, when adding calcium and phosphate to an admixture, the phosphate should be added first. The calcium should not be added consecutively or in dose sequence to the phosphate addition."

3. *In the storage statement, paragraph three under the **HOW SUPPLIED** section of the package insert, the sentence "Do not store above 30°C (86°F).", has been deleted.*

CONCLUSIONS:

The following recommendations in the March 11, 1997, labeling have been made have been made as follows:

Chemistry:(Stan Koch)

1. In both the **WARNINGS** and **DOSAGE & ADMINISTRATION** sections the statement "compounded admixtures may be stored under refrigeration for up to 24 hours" should be qualified to indicate the stability of these admixtures when so stored has bee demonstrated in the studies conducted by Abbott, rather than leaving the implication that all compounded admixtures are stable under these conditions. In addition, the recommended use of admixtures within 24 hours after removal from refrigerated storage should indicate room temperature (25C) storage during this period.

2. In the **DOSAGE & ADMINISTRATION** section. Under **MIXING INSTRUCTIONS FOR COMBINED ADMINISTRATION** subsection, 8th paragraph, last line, change to "..... added consecutively or in close sequence to the phosphate addition."

3. Dialogue pointing our the Abbott studies demonstrating stable admixtures prepared with Liposyn III 30% and Abbott additives has been entered into the package insert in three locations - the **WARNINGS** section, the **DOSAGE AND ADMINISTRATION** section, and again under **MIXING INSTRUCTIONS FOR COMBINED ADMINISTRATION**. As this latter section is considered a subsection of the **DOSAGE AND ADMINISTRATION** section, it is recommended that reference to these Abbott studies in the insert be reduced from three locations to two locations, once in the WARNINGS section and once in the DOSAGE AND ADMINISTRATION section.

Medical: (Eric Colman)

1. In the **WARNINGS** section, the statement which reads, "..... to the dosage levels of the divalent cations (Ca and Mg) administered....."

   should be revised to read,

   "..... to the dosage levels of the divalent cations (Ca and Mg) and phosphates administered .....".

2. In the **MIXING INSTRUCTIONS FOR COMBINED ADMINISTRATION** section

   the following should be added at the beginning of the first sentence of the fifth paragraph,

   "Because of the potential for life thretening events caution should be taken....."

Pharmacology: (Ron Steigerwalt)

1. Please add the following sections to the package insert:

   Carcinogenesis, mutagenesis, impairment of fertility

   Long term studies in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility of Liposyn® III 30% have not been conducted.

2. **Nursing Mothers**

   It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be excercised when Liposyn® III 30% is administered to a nursing mother.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION:

The above comments/recommentations to the March 11, 1996, draft labeling should be communicated to the sponsor in the Action letter.

/S/
Project Manager

/S/
Pharmacology Supervisor

/S/
Medical Officer

/S/
Chemistry Reviewer

/S/
Deputy Director

/S/
Chemistry Team Leader

APPEARS THIS WAY
ON ORIGINAL

cc:

/S/

NDA 20-181
HFD-510/Div. Files
HFD-510/SMcCortSKoch/DWu/EColman/GTroendle/RSteigerwalt
HFD-510/Solomon Sobel, M.D.

draft: /February 19, 1997/n20181.lab
r/d Initials:
final:

APPEARS THIS WAY
ON ORIGINAL

CSO REVIEW

PATENT AND EXCLUSIVITY INFORMATION

1. Active Ingredient(s): Egg Phosphatide
   Soybean Oil

2. Strength(s): 30%

3. Trade Name: Liposyn^{R} III 30% (an intravenous fat emulsion)

4. Dosage Form: 500mL & 1000 mL Glass Abbovac Bottles

5. Route of Administration: Intravenous

6. Applicant Firm Name: Abbott Laboratories

7. NDA Number: To be determined

8. Approval Date: To be determined

9. Exclusivity: Date first ANDA could be approved and length of exclusivity period: None

10. Applicable patent numbers and expiration date of each:

Applicant has no applicable patents at this time. Applicant certifies that to its knowledge there is no patent claiming the drug or the method of use for which approval is sought.

Frederick A. Gustafson Date

EXCLUSIVITY SUMMARY for NDA # 20-181 SUPPL # _____

Trade Name Liposyn III 30% Generic Name Intravenous Fat Emulsion, PBP___

Applicant Name Abbott Laboratories HFD- 510

Approval Date 1-13-98

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 questions about the submission.

   a) Is it an original NDA?
   YES /_x__/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_x__/

   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 /_x__/ 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.

   The sponsor submitted only safety studies (Study # 92008 &92010) to support the safety of the drug product. This is a higher concentration of the active moieties contained in the "fat emulsion than previously approved NDA's 18-969 and 18-970 contained 10% and 20% fat emulsion.

   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 /_x__/

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 /_x__/

If yes, NDA # _____ Drug Name _____

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 /_x__/

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).

APPEARS THIS WAY
ON ORIGINAL

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 # _____ _____

NDA # _____ _____

NDA # _____ _____

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 /_x__/ NO /___/

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

NDA # 18-969 Liposyn III 10% (an intravenous fat emulsion)

NDA # 18-970 Lyposyn III 20% (an intravenous fat emulsion)

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 /_x__/ NO /___/

Note that the sponsor submitted no new clinical studies other than a safety study to support their NDA. They referenced previously approved NDA 18-969 Liposyn III 10% and NDA 18-970, Liposyn III 20% in their application that contain the same qualitative lineup of active ingredients.

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.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (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 /_x__/ 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 /_x__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_x__/

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 /_x__/

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:

Investigation #1, Study # 92008 - Safety study of Liposyn III 30% by direct infusion to 8 adult TPN patients

Investigation #2, Study # 92010 - Safety Clearance Study in 12 healthy males

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 92008 YES /___/ NO /_x__/

Investigation #2 92010 YES /___/ NO /_x__/

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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 92008 YES /___/ NO /_x__/

Investigation #2 92010 YES /___/ NO /_x__/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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"):

Investigation #1, Study# 92008 - Safety Study by direct infusion in 8 TPN patients

Investigation #2, Study # 92010- Safety Clearance Study in 12 healthy males

Investigation #_, Study # _____

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.

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 (#92008)

IND YES /_x__/ NO /___/ Explain: _____

Investigation #2 (92010)

IND YES /_x__/ 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 _____

_____ _____

_____ _____

APPEARS THIS WAY
ON ORIGINAL

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: _____

_____

_____

_____

/S/ 1-13-98

Signature Date

Title: Project Manager

APPEARS THIS WAY
ON ORIGINAL

/S/ 1-13-98

Signature of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

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

McCORT

DEC 19 1997

MEMORANDUM OF A MEETING
DIVISION OF METABOLISM AND
ENDOCRINE DRUG PRODUCTS (HFD-510)

MEETING DATE: December 3, 1997 TIME: 2:30 pm PLACE: Parklawn Rm 14B-56

DRUG: Liposyn III 30% (an intravenous fat emulsion) Pharmacy Bulk Package

NDA: 20-181

TYPE OF MEETING: Labeling meeting

MEETING CHAIR: Gloria Troendle, M.D., Deputy Director

MEETING RECORDER: Steve McCort, Project Manager

FDA STAFF:

Gloria Troendle, M.D., Deputy Director (HFD-510)
Eric Colman, M.D., Medical Reviewer
Ron Steigerwalt, Pharmacology Team Leader
Stan Koch, Chemistry Reviewer
Steve McCort, Project Manager

Meeting Objective:

To review the October 22, 1997 revised draft package insert and the container draft label.

CONCLUSIONS AND DECISIONS REACHED:

The following changes were requested by the reviewing staff in the package insert dated October 22, 1997.

1. Under **WARNINGS**, section, paragraph 4, page 2, line 7, insert the word "These in place of "Such" at the beginning of the sentence to now read, *"These compounded admixtures may be stored under refrigeration for up to 24 hours."*

2. Under **WARNINGS**, section,paragraph 4, page 2, line 2, which reads,

   "Studies have documented the stability of Liposyn III 30% with necessary Abbott electolytes, Abbott trace metals and Abbott Dextrose Injection, USP and Abbott Aminosyn II amino acid solution in a TPN admixtrue container ..."

   should now read,

   "Studies have documented the stability of Liposyn III 30%, when admixed with Abbott electrolytes, Abbott trace metals, Abbott Dextrose Injection, USP and Abbott Aminosyn II (amino acid) Injection."

3. Under the **DOSAGE AND ADMINISTRATION** section, the following revisions were requested:

   a. Under **Administration** subsection, paragraph 2 which reads,

   "Studies have documented the stability of Liposyn III 30%, necessary Abbott electrolytes, Abbott trace metals, and Abbott Dextrose Injection, USP and Abbott Aminosyn II amino acid solution."

   should be revised to read,

   "Studies have documented the stability of Liposyn III 30%, when admixed with Abbott electrolytes, Abbott trace metals, Abbott Dextrose Injection, USP and Abbott Aminosyn II (amino acid) Injection."

   and should be moved to paragraph 4, line 4, before the sentence that reads,

   "These compounded admixtures may be stored under refrigeration for up to 24 hours."

   b. Under **Administration** subsection, line 4, first sentence, insert the word "These" in place of "such"at the beginning of the sentence to now read, *"These compounded admixtures may be stored under refrigeration for up to 24 hours."*

4. In the **MIXING INSTRUCTIONS FOR COMBINED ADMINISTRATION** section, paragraph 3, first sentence, insert the word "These in place of "Such" at the beginning of the sentence to now read, *"These compounded admixtures may be stored under refrigeration for up to 24 hours."*

5. The **Carcinogenesis, Mutagenesis, Impairment of fertility** section should be moved to precede the **Pregnancy** section.

CONCLUSIONS:

The draft labeling revisions for the draft package insert dated October 22, 1997, will be communicated to the Sponsor.

APPEARS THIS WAY
ON ORIGINAL

ACTION ITEMS:

Item	Responsible person	Due Date
1. Revised Labeling will be FAXed To the sponsor	Steve McCort	December 20, 1997

Signature of Minutes preparer: /S/ 12-18-97

Signature of the Chair: /S/ 12-19-97

APPEARS THIS WAY
ON ORIGINAL

Concurrence:GTroendle 12-16-97/EColman 12-12-97/RSteigerwalt 12-17-97/SKoch 12-18-97
DWu 12-18-97

Attachment/Handouts: Copy of October 22,1997, revised draft labeling

cc: NDA 20-181
HFD-510/DivFile
HFD-510/SSobel/GTroendle/EColman/RSteigerwalt/DWu/SKoch/SMcCort

APPEARS THIS WAY
ON ORIGINAL

MFCORT

OCT 20 1997

MEMORANDUM OF A MEETING
DIVISION OF METABOLISM AND
ENDOCRINE DRUG PRODUCTS (HFD-510)

MEETING DATE: October 1, 1997 TIME: 11:00 a.m. PLACE: Parklawn Rm 14B-56

DRUG: Lyposyn III 30%

NDA: 20-181

TYPE OF MEETING: Status/Planning Meeting

MEETING CHAIR: Steve McCort, Project Manager

MEETING RECORDER: Steve McCort, Project Manager

PARTICIPANTS:

Eric Colman, M..D., Medical Team Leader (HFD-510)
Stan Koch, Chemistry Reviewer (HFD-510)
Steve McCort, Project Manager (HFD-510)

Meeting Objective:

Planning meeting.

Background: The firm responded, in a major amendment dated July 24, 1997, to a March 24, 1997, not approvable letter. The NDA was deficient for chemistry and biopharmaceutics, and labeling issues.

Discussion and Planning:

Chemistry: Need to evaluate response to deficiencies sent sponsor with the not approvable letter dated March 24, 1997. **A preliminary target date of December 20, 1997**, for completion of the review including sign off by the supervisor was set. This will be confirmed later by the supervisor and reviewer. The completion date of the review will depend upon the Firm responding adequately to the chemists additional requests.

Biopharmaceutics: The reviewer Dr. Carolyn Jones has not yet received a copy of the amendment. The project manager will get a copy of the amendment to the reviewer, but will go through the supervisor, Dr. Hae Young Ahn first. **A preliminary target date of December 20, 1997**, was agreed upon. However the final target date will be set later upon receipt of the amendment and upon consultation with Dr. Ahn.

EA: Not needed. It was determined that an Environmental Assessment would not be needed.

Labeling: A separate review of the labeling will be needed by all disciplines.

Pharm: Review of Labeling completed August 7, 1997. Acceptable.

Clinical: Label Review needed. Review of labeling completed. Needs concurrence of supervisor.

EER Inspection: Pending. Ordered August 15, 1997 for three facilities.

ACTION ITEMS:

Item	Responsible person	Due Date
1. Reviews to be completed	All reviewers	December 20, 1997 (Preliminary)
2. Package to Dr. Sobel	Steve McCort	January 7, 1997
3. Action letter signed and sent	Dr. Solomon Sobel	January 21, 1997

Signature of Minutes preparer: /S/ Oct 20, 1997

cc: NDA 20-181
HFD-510/DivFile
HFD-510/CSO/SMcCort
HFD-510/GTroendle/EColman/SSobel
HFD-510/DWu/SKoch
HFD-510/RSteigerwalt
HFD-870/CJones/HAhn
HFD-805/NSweeney

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF A MEETING
DIVISION OF METABOLISM AND
ENDOCRINE DRUG PRODUCTS (HAD-510)

MEETING DATE: November 8, 1996 TIME: 11:00 a.m. PLACE: Parklawn Rm 14B-56

DRUG: Lyposyn III 30%

NDA: 20-181

TYPE OF MEETING: Internal Planning meeting

MEETING CHAIR: Solomon Sobel, M.D. Division Director

MEETING RECORDER: Steve McCort, Project Manager

PARTICIPANTS:

Solomon Sobel, M.D., Division Director (HFD-510)
Gloria Troendle, M.D., Deputy Director (HFD-510)
Eric Colman, M..D., Medical Team Leader (HFD-510)
Hae Young Ahn, Ph.D., Biopharmaceutics Team Leader (HFD-510)
Stephen Moore, Ph.D., Chemistry Team Leader (HFD-510)
Stan Koch, Chemistry Reviewer (HFD-510)
Ron Steigerwalt, Ph.D., Pharmacology Team Leader (HFD-510)
Neal Sweeney Ph.D., Microbiology Reviewer (HFD-720)
Steve McCort, Project Manager (HFD-510)

Meeting Objective:

Planning meeting.

Background: The firm responded September 24, 1996, to a not approvable letter dated November 29, 1991. The NDA was deficient for clinical, chemistry and biopharmaceutics issues. In addition the firm submitted amendments dated March 2, May 21 and November 7, 1996.

Discussion and Planning:

Medical: Need to evaluate two studies: (1) a safety clearance study of trygceride and/or cholesterol and free fatty acids from healthy volunteers and (2) a utility study of Liposyn III 30% given to Adult TPN Patients given by direct Intravenous Infusion.

Statistics: Not needed

Microbiology: Not needed. No deficiencies for not approval letter

DSI: Not needed

EER: Needed

Chemistry: Need to evaluate response to deficiencies sent sponsor with the not approvable letter dated April 10, 1991.

Biopharmaceutics: Need to evaluate whether the sponsor qualifies for a request for waiver

EA: Not needed

ACTION ITEMS:

Item	Responsible person	Due Date
1. Reviews to be completed	All reviewers	February 25, 1997
2. Package to Dr. Sobel	Steve McCort	March 15, 1997
3. Action letter signed and sent	Dr. Solomon Sobel	March 25, 1997

Signature of Minutes preparer: /S/

Concurrence Chair: _____

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 20-181
HFD-510/DivFile
HFD-510/CSO/SMcCort
HFD-510/GTroendle/EColman/SSobel
HFD-510/DWu/SKoch
HFD-510/RSteigerwalt
HFD-870/CJones/HAhn
HFD-805/NSweeney

APPEARS THIS WAY
ON ORIGINAL

The problem of the NDA not qualifying for a biopharmaceutics review waiver was discussed.

Dr. Kenealy was concerned that the proposed container is capable of being used for a direct infusion despite that it is labeled "Not For Direct Infusion". He suggested that the it be modified.

Next the agency status

/S/

Anna Marie H. Weikel
Consumer Safety Officer

APPEARS THIS WAY
ON ORIGINAL

cc:

NDA 20-181

HFD-160/DivDir/Chambers
HFD-160/SMO/Kenealy
HFD-161/CSO/Weikel

Concurrences:
HFD-160/DivDir/Chambers
HFD-160/SCSO/Rumble

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF MEDICAL IMAGING, SURGICAL
AND DENTAL DRUG PRODUCTS

MEETING SUMMARY

DATE: February 21, 1992 TIME: 1:00 p.m. PLACE: 18B CR

PARTICIPANTS:
From FDA Div. of MISDDP:

Wiley Chambers, M.D., Acting Director
John Kenealy, M.D., Senior Medical Officer
Anna Marie Weikel, R.Ph., CSO

From FDA Div. of Biometrics:

Dr. Ponnapalli

From Abbott Laboratories:

Fred Gustafson, Director, Regulatory Affairs
Laurence Shaw, M.D., Vice President, Medical and Regulatory Affairs
Clair Callan, M.D.
David Thompson, Ph.D.

BACKGROUND:

The purpose of the meeting was to discuss clinical requirements for large volume parenteral solutions; specifically the following NDAs which are pending in this division:

NDA 20-181 Liposyn III 30% Pharmacy Bulk Package

The meeting was structured so that fifteen minutes could be spent discussing each of the above NDAs.

PRESENTATION/DISCUSSION:

NDA 20-181 for Liposyn III 30% Pharmacy Bulk Package was discussed first. Abbott assumed that since this product is a pharmacy bulk package intended for dilution in a pharmacy prior to patient administration, clinical studies were not required.

Dr. Chambers asked for an agency approved clinical utility study on 20 patients. He also requested a Phase I clearance study on 8-10 normal volunteers to check the rate of clearance of the Liposyn 30%. The purpose of this would be to assess the effects of inadvertent administration of undiluted drug.

MEMORANDUM OF TELECON

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

: December 1, 1997

Between: David Guzek, Director, Regulatory Affairs
Tom Sampogna, Manager, Regulatory Affairs
Martin Van Trieste, Director, Quality Assurance
Dave Williamson, Manager, Methods Development, QA
Hospital Products Division, Abbott Laboratories
North Chicago, IL 60064
847-937-3213

and

Stan Koch, HFD-510

Subject: NDA 20-181 Liposyn III 30% Pharmacy Bulk Package and
Status as Supplier of Soybean Oil

To: NDA 20-181 File

The purpose of this call deals with the likely change in regulatory status of the
I suggested that Abbott begin to consider a scenario that looms large as of this morning, and that is the consideration of by FDA as a food processing facility, , that the final product shipped to Abbott from is ean oil. Should this position be formally adopted by the Agency, I will be seeking yet another amendment to NDA 20-181 in which Abbott will be assuming additional responsibility for control of the incoming raw material. At the present time the needed controls look
I did not mention anything about maintenance of the DMF at this time, but indicated that I will call back with more definite information within a day or two.

Before leaving the phone I raised a question concerning the
; performed by Abbott. Material read on the processed soybean oil state
I asked for what reason this is so, and whether, should

Martin wondered where I read about the storage restrictions or warnings, and at that moment I could not remember. The reference will be found and passed along when I call back. Martin said he will get an answer in the interim.

NDA 20-181 Telecon
December 3, 1997

Another call was placed to David Guzek today to make a specific request for further information as a result of HFD-325 decision to regard
eed as a It was made clear that there will be
cific recommendations issue from the Agency's field operations, and that the topics discussed here are intended to address NDA considerations.

The information now requested is in line with that cited earlier this week, i.e., provisions for testing as received from

an outside laboratory is quite extensive, and I believe includes all candidates for contamination. The other major item raised is retention and maintenance a request that is predicated on the Agency's reconsideration of the facility as a producer of [verified with Barry Rothman HFD-325 on 12/3/97]. We are comfortable requesting that the be kept in a current state due to the importance of the , and the impact of this manufacturing procedure on the The definition of drug substance purity may not be addressed in all respects by the official monograph. will be contacted to verify their understanding that this should continue to be updated, i.e., the deficiency letter coming their way from this review division should be addressed in a timely manner.]

David was requested to provide another amendment containing this information in an expeditious fashion. He indicated a response would be on its way, barring
olications, by early next week. Abbott will get back if a problem arises.

It was also mentioned that the warning against refrigeration of processed soybean oil is in the Abbott controls for I again requested firm's opinion on reason for the warning - and, if so, what the concerns are when subjecting the finished fat emulsion to lower temperatures. This information will be included in the amendment.

/S/

APPEARS THIS WAY
ON ORIGINAL

cc: Orig NDA 20181
HFD-510/Div File
HFD-510 DGWu
HFD-510/SKoch
HFD-510/SMcCort
F/T SKoch 12-3-97

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE August 17, 1994

I spoke with Don Mowles of Abbott regarding the April 22, 1994, submission to the IND which requested permission to use data from only 8 patients from a Phase III study to support an NDA that has already been submitted (NDA 20-181) due to their difficulty in obtaining patients for entry into the study. I told him that first we are currently evaluating safety data that has been recently submitted regarding 3-in-1 admixtures. I told him we are uncomfortable approving anymore NDAs indicated for specific use in 3-in-1 admixtures at this time until we have evaluated this data. Second I told him that our reviewers feel that more patients should be enrolled in the study.

I suggested that they continue on with the study and check back with us sometime in the Fall to request a follow-up meeting or telecon to discuss the study results. At that point we will be better prepared to advise them on the TPN situation. Mr. Mowles said he understood about the TPN situation. He also said that in the meantime, they will continue to try to enroll more patients in the study.

We parted amicably.

cc: Orig IND
Div File
HFD-160/DivDir/Love
HFD-160/PWaymack

APPEARS THIS WAY
ON ORIGINAL

NDA NUMBER 20-181

IND NUMBER

TELECON/MEETING

INITIATED BY
[✓] APPLICANT/ SPONSOR
[ ] FDA

MADE
[✓] BY TELEPHONE
[ ] IN PERSON

PRODUCT NAME

Liposyn III 30% IV Fat Emulsion

FIRM NAME

Abbott Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Don Mowles
Manager, Regulatory Affairs

TELEPHONE

(708) 937-7597

IGNATURE /S/

DIVISION HFD-160