CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020181

CORRESPONDENCE

ABBOTT

Hospital Products Division
Abbott Laboratories
200 Abbott Park Road
Abbott Park, Illinois 60064-3500

December 23, 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

Facsimile Amendment

On December 23, 1997, Abbott Laboratories received a request for additional information regarding the package insert and label for NDA 20-181 Liposyn III 30%. We hereby submit additional information as requested by the Agency regarding the above named NDA.

Request 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."*

Request 2: Under WARNINGS section, paragraph 4, page 2, line 2, which reads, *"Studies have documented the stability of Liposyn III 30% with necessary. Abbott electrolytes, Abbott trace metals and Abbott Dextrose Injection USP and Abbott Aminosyn II amino acid solution in a TPN admixture 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."*

Request 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."*

Request 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."*

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

Response: Abbott Laboratories acknowledges the request by the Agency and has incorporated the changes into the package insert which is appended in Exhibit I.

The Agency also requested in the comment section a copy of the latest container label. Please find appended in Exhibit II a copy of the most current container label.

We trust this information is correct.

Sincerely,

Abbott Laboratories

Thomas P. Sampogna
Manager, Regulatory Affairs
Hospital Products Division
Phone: (8470 935-3715
Fax: (847) 938-7867

APPEARS THIS WAY
ON ORIGINAL

g:\tps\12-97fda

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Abbott Laboratories	**12/23/97**
TELEPHONE NO. *(Include Area Code)* **(847)935-3715**	FACSIMILE (FAX) Number *(Include Area Code)* **(847)938-7867**
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: **200 Abbott Park rd., D-389, AP30 Abbott Park, IL 60064-3537**	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE **N/A**

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-181

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Liposyn II 30%(an intravenous fat emulsion)	**N/A**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Intravenous fat emulsion	**N/A**

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
(b)(4)	**30%**	**Intravenous**

(PROPOSED) INDICATION(S) FOR USE:
Source of essential fatty acids and calories during extended periods of parenteral nutrition.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
Telephone Amendment

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

1

NDA 20-181

MAR 24 1997

Abbott Laboratories
Hospital Products Division
Attention: Mr. Thomas P. Sampogna
Manager, Regulatory Affairs
D-389 Bldg. AP30
200 Abbott Park Road
ABBOTT PARK, ILLINOIS 60061-3537

Dear Mr. Sampogna:

Please refer to your new drug application dated April 10, 1991, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liposyn III 30% (an intravenous fat emulsion), Pharmacy Bulk Package.

We acknowledge receipt of your major amendment dated September 24 and received on September 26, 1996, in response to our not approvable letter dated November 29, 1991. We also acknowledge receipt of your submissions dated March 11, May 21, and November 7, 1996, and February 7, 1997.

The regulatory due date for this application is March 25, 1997.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Manufacturing Establishment Evaluations:

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

Chemistry:

Required chemistry, manufacturing, and controls information is missing.

1. With reference to the raw material controls for egg yolk phospholipid, the following information is requested:

   a. ; should be in place that establish the presence as well as the contribution of phosphatidylcholine and phosphotidylethanolamine

as the constituents in this This information provides added assurance that specific and sufficient emulsification potential is available to perform the intended function.

b. We request that limit tests be included as performed by the egg phosphatide supplier or by Abbott for . Levels of these contaminants found to be present over time may influence the frequency with which these test are conducted.

c. Describe the specification and test procedure used by Abbott to determine fat content , and indicate whether this test encompasses to serve as a replacement for the

2. We request that you respond to the following inquiries regarding the finished drug product controls:

a. With reference to the in the finished drug product. and based on data presented in the March 11, 1996 amendment, , please comment on the following considerations:

(1) Data appear to support some in the specification from the proposed

(2) controls should include the selection of a percentile corresponding to a which the It is recommended that this choice

b. Please verify that the is no longer included as a candidate process for . in the finished drug product.

3. We request that the following additional information be provided concerning the stability of the finished drug product:

a. has been withdrawn from this application due to unexplained developments found to be

present. Please update the data submitted to this file with regard to the probable source of the , the slow development/detection of this , and the extent to which assurances can be provided that this problem will not recur.

b. Clarify the cause for (August 7, 1992) on June 1, 1993 from a controlled environment of

4. Please verify our understanding that future requests to extend the expiration dating period beyond that approved in this application will be submitted to this file in the form of a supplemental application requiring Agency approval prior to implementation.

5. Four copies of updated Methods Validation packages should be submitted to this file. Please contact this Office should questions remain concerning the specific methods to be included in this package. Where alternate methods are provided, the primary regulatory procedure should be designated.

Biopharmaceutics:

An acceptable assay validation is needed for the methods used to quantify triglycerides, cholesterol, and free fatty acids in plasma.

Labeling:

Regarding the draft labeling submitted in the March 11, 1996, amendment we have the following comments:

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 that the stability of these stored admixtures has been 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 (25°C) storage during this period.

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

3. Test describing the Abbott studies demonstrating stable admixtures prepared with Liposyn III 30% and Abbott additives has been stated in 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.

4. In the **WARNINGS** section, the statement in the last paragraph 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 . . ."

5. 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 threatening events caution should be taken....."

6. Please add the following subsections to the Precautions section of 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.

   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 exercised when Liposyn® III 30% is administered to a nursing mother.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under

21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, please contact Steve McCort, Consumer Safety Officer, at (301) 443-3510.

Sincerely yours,

/S/ 3/11/97

APPEARS THIS WAY
ON ORIGINAL

Sólomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

HFD-180

NDA 20-181

NOV 29 1991

Abbott Laboratories
Hospital Products Division
One Abbott Park Road
Abbott Park, Illinois 60064-3500

Attention: Frederick A. Gustafson
Director, Regulatory Affairs

Dear Mr. Gustafson:

Please refer to your new drug application dated April 10, 1991, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Liposyn III 30% (an intravenous fat emulsion), Pharmacy Bulk Package.

We have reviewed your application and find that the information presented is inadequate and the application is not approvable under section 505(b) of the Act and 21 CFR 314.125(b) of the implementing regulations. The deficiencies may be summarized as follows:

The application fails to provide substantial evidence of safety and effectiveness consisting of adequate and well-controlled studies as defined in 314.126. For this we request that you submit utility data based upon use in the actual clinical setting. Also data must be supplied to demonstrate safety in the event of inadvertent direct infusion of the 30% lipid emulsion.

The application ~~fails to include adequate chemistry, manufacturing~~ and control information 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 (see enclosure).

The submission fails to include adequate evidence for the granting of a waiver of *in-vivo* bioavailability testing of the product in humans.

Upon completion of the review process, any additional comments and/or deficiencies will be communicated under separate cover. We also 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 regulations, 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 Mr. Stephen McCort, Consumer Safety Officer at (301) 443-1560.

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. Any amendment should respond to all deficiencies. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

/S/ 11/25/91

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

ENCLOSURE

cc: Orig. NDA
HFD-160
HFD-80
HFD-100
HFC-130
HFD-160/DivDir/Chambers
HFD-160/MO/Rodriguez
HFD-160/CHEM/Koch/Sheinin
HFD-160/PHARM/Wilson
HFD-160/MICRO/Greenman
HFD-160/CSO/McCort
Non-Approvable 11/29/91
Huntley

APPEARS THIS WAY
ON ORIGINAL

NDA 20-181

Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

Attention: Frederick A. Gustafson
Director, Regulatory Affairs

Dear Mr. Gustafson:

We have received your new drug application submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the following:

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

Date of Application: April 10, 1991

Date of Receipt: April 22, 1991

Our Reference Number: NDA 20-181

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 June 21, 1991 in accordance with 21 CFR 314.101(a).

If the application is filed, the due date is October 19, 1991.

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:

Mr. Stephen McCort
Consumer Safety Officer
(301) 443-3500

Sincerely yours,

/S/ for 5/2/91

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 20-181
HFD-160
HFD-161/CSO/JRhee
HFD-160/DJenkins
R/D by: COeur 04-25-91 /S/ 5-2-91
R/D Init. by: WRumble 05-01-91
F/T by: AChapman 05-02-91
Wang # 5191Y

ACKNOWLEDGEMENT OF ORIG NDA

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

Hospital Products Division
Abbott Laboratories
200 Abbott Park Road
Abbott Park, Illinois 60064-3500

November 11, 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 specifications and test methods to the Agency for the above named NDA. This information was inadvertently omitted from a correspondence package sent to the Agency on November 4, 1997.

The following finished drug product specifications and test methods were requested: C-1029, C-1225, C-1050, C-0755 and C-1591.

The specifications have been included for your review and can be inserted directly into the 4 copies of the test methods which were submitted on November 4, 1997

We trust this information is correct.

Sincerely,

Abbott Laboratories

Thomas P. Sampogna

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

G:/tps 11-97FDA

ORIGINAL

NDA ORIG AMENDMENT

B2

ABBOTT

Hospital Products Division
Abbott Laboratories
39, Bldg. AP30
J Abbott Park Road
Abbott Park, Illinois 60064-3537

November 7, 1996

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

NAI.
/S/ 12/5/96

ATTENTION: Solomon Sobel, M.D.
Director

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

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 November 04, 1996.

The following additional information was requested:

Request 1: Please submit to NDA 20-181, The Liposyn III 30% Safety Clearance Study Number 92010 which has already been submitted to the Administration

Response: As requested, appended in **Exhibit I** (Protocol 92010) is the Liposyn III 30% Phase I Safety Clearance Study.

noted 11/25/96
/S/

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 12 1996
HFD-510

Noted
/S/ 12/3/96

We trust that this information is complete.

Sincerely,

Thomas P. Sampogna

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☒ MEMO

/S/ 12-2-96
CSO INITIALS DATE

reviews for
Amendment
not completed.
/S/
12-2-96

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	DATE OF SUBMISSION
Abbott Laboratories	**November 7, 1996**
ADDRESS *(Number, Street, City, State, and Zip Code)*	TELEPHONE NO. (Include Area Code)
200 Abbott Park Road, D-389 AP30 **Abbott Park, Illinois 60064-3537**	**(847) 937-7597**
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)* **20-181**

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)	PROPRIETARY NAME (If any)	
Liposyn II 30% (an intravenous fat emuulsion)		
CODE NAME (If any)	CHEMICAL NAME	
	Intravenous fat emulsion	
DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)2
Glass Abbovac Container	**Intravenous**	**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)

NDA ORIG AMENDMENT
AM
ORIGINAL

ABBOTT

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

September 24, 1996

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

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
/S/ 11-26-96
CSO INITIALS DATE

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 the Administration's letter of November 29, 1991. The following additional information was requested:

Request 1: "The application fails to provide substantial evidence of safety and effectiveness consisting of adequate and well-controlled studies as defined in 314.126. For this we request that you submit utility data based upon use in the actual clinical setting. Also data must be supplied to demonstrate safety in the event of inadvertent direct infusion of the 30% lipid emulsion."

Request 2: "The submission fails to include adequate evidence for the granting of a waiver of *in-vivo* bioavailability testing of the product in humans."

Response: Please refer to our responses dated March 11, 1996. At that time we stated we would notify the Administration upon completion of the for Liposyn III 30% Phase III clinical studies. As requested, appended in **Exhibit I** (Protocol 92008) and **Exhibit II** (Protocol 95017) are the utility data results providing well-controlled studies and utility data based upon use in actual clinical settings. The studies conclude that Liposyn III 30% was safe when administered by direct intravenous injection to medical/surgical patients on total parenteral nutritional. The intended use for Liposyn III 30% will be for the mixing of multiple 3 in 1 parenteral nutritional admixtures via manual or automated methods.

We trust that this information is complete.

Sincerely,

Thomas P. Sampogna

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 26 1996
HFD-510

M.CFC

ABBOTT

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

May 21, 1996

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 the Administration's Fax of December 3, 1991 regarding microbiological comments: "Draft of Letter to Application". The following additional information was requested:

Request: The application is not approvable on the basis that insufficient information and data have been supplied in support of sterility assurance of the subject drug products. Please respond to the following specific comments:

(1) Concerning the described batch/shaker autoclave process for the 500 mL and 1000 mL sizes, are containers-of-convenience (pilot bottles) used to monitor

Response: Containers-of-convenience are actual product containers from each load that is
They are located in the

We had previously responded to the Administration's letter of November 29, 1991 which requested information for the Chemistry, Manufacturing and Control Section of this NDA. The Microbiological Comments were received as a separate Fax.

We trust that our response to your requests for information on the chemistry, manufacturing and control section of this submission is complete.

Sincerely,

ABBOTT LABORATORIES

APPEARS THIS WAY
ON ORIGINAL

Donald Mowles
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-7597
Fax: (847) 938-7867
5-96fda.dlm/

ABBOTT

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

March 11, 1996

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

noted
/S/ 4/8/96

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 the Administration's letter of November 29, 1991. The following additional information was requested:

Request: "The application fails to provide substantial evidence of safety and effectiveness consisting of adequate and well-controlled studies as defined in 314.126. For this we request that you submit utility data based upon use in the actual clinical setting. Also data must be supplied to demonstrate safety in the event of inadvertent direct infusion of the 30% lipid emulsion."

Response: for Liposyn III 30% is in Phase 3 clinical studies. A supplement to the NDA referring to the completed IND studies will be made when the studies are complete.

Request: "The application fails to include adequate chemistry, manufacturing and control information as requested 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 (see enclosure)."

Response: Response to the deficiency questions for "adequate chemistry, manufacturing and control information" in the Administration's deficiency letter of November 29, 1991 is appended.

Request: "The submission fails to include adequate evidence for the granting of a waiver of *in-vivo* bioavailability testing of the product in humans."

Response: for Liposyn III 30% is in Phase 3 clinical studies. A supplement to the NDA referring to the completed IND studies will be made when the studies are complete.

We will notify the Administration when the Phase 3 clinical studies are completed. We trust that our response to your requests for information on the chemistry, manufacturing and control section of this submission is complete.

Sincerely,

ABBOTT LABORATORIES

APPEARS THIS WAY
ON ORIGINAL

Donald Mowles
Manager, Regulatory Affairs
Hospital Products Division
Phone: (708) 937-7597
Fax: (708) 938-7867

6-95fda.dlm/

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

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

ORIGINAL

January 25, 1995

NEW CORRESP

NC

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF MEDICAL IMAGING, SURGICAL
AND DENTAL DRUG PRODUCTS, HFD #160
Attn: DOCUMENT CONTROL ROOM # 18B-08
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☑ N.A.I.

/s/ 5-25-95

CSO INITIALS DATE

ATTENTION: Patricia Love, M.D.
Director

Re: GENERAL CORRESPONDENCE
REQUEST FOR MEETING

Abbott Laboratories is requesting a meeting with you and appropriate staff to review the status of the clinical data for NDA 20-181 } Liposyn III 30% (an intravenous fat emulsion), Pharmacy Bulk Package.

Background Information

The NDA for Liposyn III 30%, Pharmacy Bulk Package was filed on October 10, 1991. A **Not Approvable** letter was received from the Agency on November 29, 1991 stating that the application fails to provide substantial evidence of safety and effectiveness. In a subsequent meeting between Dr. Wiley Chambers of the Division and Dr. Shaw and Mr. Gustafson of Abbott Laboratories it was agreed that we would conduct Phase 1 and Phase 3 clinical studies.
administration of the Liposyn III 30% fat emulsion without admixture, and evaluate parameters (Phase 3) associated with Liposyn III 30% when given as an admixture as part of a total parenteral nutrition regimen in post-surgical patients.

In a meeting on January 26, 1994 between Dr. Love of the Division and Drs. Callan, Wilkins and Mr. Gustafson of Abbott Laboratories, the difficulty that we are experiencing in enrolling Phase 3 patients was discussed. Over a two-year period, we screened over 1200 patients for Phase 3. Only 8 patients met the entrance criteria and completed the study . These clinical data were submitted

Based on our past experience in enrolling patients we project that it will take from three to four years to complete the Phase 3, twenty patient study. We are requesting this meeting to discuss discontinuation of the Phase 3 study. We believe the data already obtained in the Phase 1 and Phase 3 studies are adequate to support the safety and efficacy of Lip 30%.

Attending for Abbott Laboratories will be Dr. Clair Callan, M.D., Vice President, Medical and Regulatory Affairs and Mr. Fred Gustafson, Director, Regulatory Affairs. We would like to request a one hour meeting, preferably in the early afternoon, on one of the following dates:

2/8/95
2/10/95
2/13/95
2/17/95

Please contact me or Mr. Donald Mowles at 708.937.7597 directly for making the final arrangements.

Sincerely,

ABBOTT LABORATORIES

APPEARS THIS WAY
ON ORIGINAL

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division
Phone: (708) 937-3213
Fax: (708) 938-7867

1-95fda/3

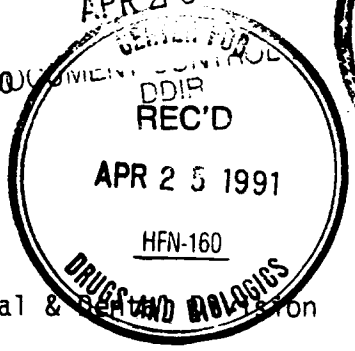
APPEARS THIS WAY
ON ORIGINAL

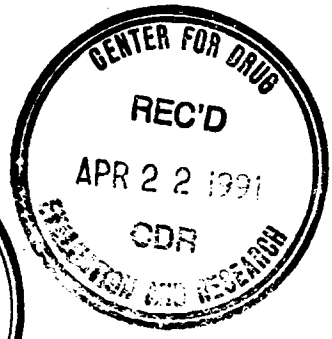
ABBOTT

Hospital Products Division

Abbott Laboratories
One Abbott Park Road
Abbott Park, Illinois 60064-3500

April 10, 1991





CENTER FOR DRUGS AND BIOLOGICS, HFN #160
Attn: DOCUMENT CONTROL ROOM #18B-03
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: John Palmer, M.D.
Acting Director,
Radiopharmaceutical, Surgical & Dental Division

RE: Liposyn^{R} III 30% (an intravenous fat emulsion), Pharmacy Bulk Package
ORIGINAL NEW DRUG APPLICATION

Abbott Laboratories hereby submits an original new drug application in accordance with Section 314.50 of 21 CFR, to provide for Liposyn^{R} III 30% (an intravenous fat emulsion), Pharmacy Bulk Package.

The new drug will be manufactured in our Hospital Products Division's, North Chicago, Illinois facility and be supplied as a 500mL and 1000mL sterile, nonpyrogenic emulsion in a glass Abbovac container and be used as a Pharmacy Bulk Package.

The subject drug is identical in qualitative composition to that of our currently approved Liposyn^{R} III 10% and 20% products included in NDA 18-970 but differs in the fat concentration and its intended use only as a Pharmacy Bulk Package.

Please refer to the accompanying index for the data supporting this submission. We trust that this submission is complete.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson /cs

Frederick A. Gustafson
Director
Regulatory Affairs
Hospital Products Division

DTG/dg
Attachments
lipo-30.nda

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; March 31, 1990.
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
22APR91	
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**
160	20-181

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

NAME OF APPLICANT	DATE OF SUBMISSION
Abbott Laboratories	April 10, 1991
ADDRESS *(Number, Street, City, State and Zip Code)*	TELEPHONE NO *(Include Area Code)*
One Abbott Park Road Abbott Park, Illinois 60064	(708) 937-3216
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Liposyn III 30% (an intravenous fat emulsion)	

CODE NAME *(If any)*	CHEMICAL NAME
	intravenous fat emulsion

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Glass Abbovac Container	Intravenous	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 Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

APR 25 1991

CDR 1991

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

STATUS OF APPLICATION *(Check one)*

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

PROPOSED MARKETING STATUS *(Check one)*

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