CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-064

Chemistry Review(s)

DIVISION OF NEW DRUG CHEMISTRY-II (DMIRDP, HFD-160)
Review of Chemistry, Manufacturing, and Controls

NDA #: **21-064** CHEM.REVIEW #: 4 REVIEW DATE: 15-Feb-01
Revised: 02-Mar-01

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment (AC)	30-Jan-01	31-Jan-01	31-Jan-01

NAME & ADDRESS OF APPLICANT: DuPont Pharmaceutical Company
331 Treble Cove Road
North Billerica, MA 01862
Contact : Robert A. Morgan, MS, JD [(978) 671-8495]

DRUG PRODUCT NAME

Proprietary: **DEFINITY™**
Nonproprietary/USAN: Perflutren Lipid Microsphere
Code Names/#'s: DMP-115
Chemical Type/Therapeutic Class: **1S**

PATENT STATUS:

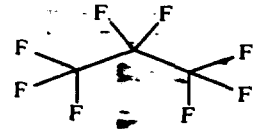
U.S. Patent 5,527,521: ImaRx Pharmaceutical Corp., Compound & method of use, Expires 05-Apr-2011.
U.S. Patent 5,547,656: ImaRx Pharmaceutical Corp., Compound & method of use, Expires 05-Apr-2011.
U.S. Patent 5,769,080: DuPont Merck Pharmaceutical Company, Compound, July 20, 2010.

PHARMACOLOGICAL CATEGORY/INDICATION: Echopharmaceutical / Contrast enhancement during the indicated ultrasound procedures.

DOSAGE FORM: Sterile injectable suspension
STRENGTHS: ≥ 5.5 mg / mL octafluoropropane
ROUTE OF ADMINISTRATION: Intravenous injection
DISPENSED: X Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

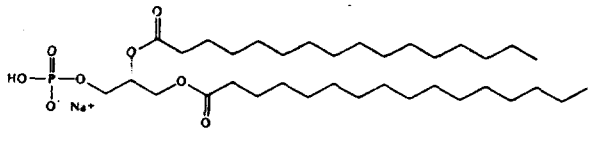
GAS COMPONENT:



1,1,1,2,2,3,3,3-Octafluoropropane

C_3F_3 ; 188.02

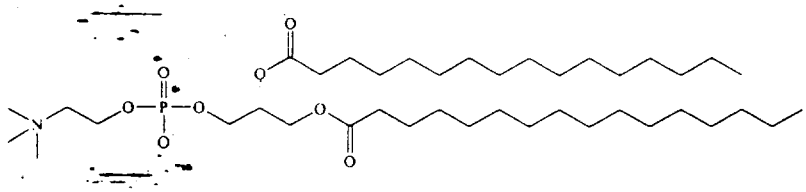
LIPID COMPONENTS:



(R)-Hexadecanoic acid-[phosphonooxy)methyl]-1,2-ethanediyl ester, monosodium salt.
1,2-Dipalmitoyl-sn-glycero-3-phosphatidic acid

$C_{35}H_{68}O_8PNa$.

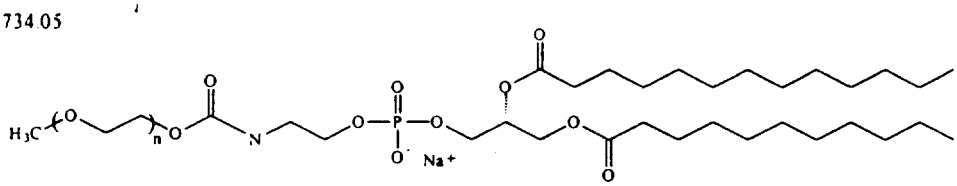
670.89



(R)-4-Hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,5,9-trioxa-4-phosphapentacosan-1-aminium,4-oxide, inner salt; 1,2 Dipalmitoyl-*sn*-glycero-3-phosphatidylcholine

$C_{40}H_{80}NO_8P$

734.05



N-(Methoxyploye thylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine, monosodium salt.

Approximate Formula: $C_{265}H_{527}NO_{123}Pna$

Approximate Mol. Wt.: 5,750 g/mol

SUPPORTING DOCUMENTS: None for this submission.

RELATED DOCUMENTS (if applicable): IND DuPont Pharmaceutical Company

CONSULTS: OPADRA for Trademark. OPADRA does not have objections to the use of the proprietary name, Definity.

REMARKS/COMMENTS: See review notes.

CONCLUSIONS & RECOMMENDATIONS: I have reviewed the labeling and have some comments, which should be faxed to the sponsor, requesting the response within 10 days so that the review can continue. The review of other submitted material is continuing, but since these issues have been identified they should be faxed to the sponsor.

/S/ 3/2/01

Review Chemist, DNDC-II, HFD-160

cc: Orig. NDA 21-064
HFD-160/Division File NDA 21-064
HFD-160/Kasliwal/15-Feb-01
HFD-160/Zelman
HFD-160/Laniyonau
HFD-160/Nguyen
R/D Init by: Leutzinger

/S/ 6/9/2001

7 pages redacted from this section of the approval package consisted of draft labeling

DIVISION OF NEW DRUG CHEMISTRY-II (DMIRDP, HFD-160)

Review of Chemistry, Manufacturing, and Controls

FINAL COMPREHENSIVE REVIEW

NDA #: **21-064** CHEM.REVIEW #: 5 REVIEW DATE: 16-May-01

Revised: 06-Jun-01

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	09-Dec-98	10-Dec-98	10-Dec-98
Amendment (BC)	19-Jan-99	20-Jan-99	26-Jan-99
Amendment (BC)	26-Mar-99	29-Mar-99	05-Apr-99
Amendment (BC)	29-Mar-99	31-Mar-99	05-Apr-99
Amendment (BC)	28-May-99	01-Jun-99	03-Jun-99
Amendment (BC)	24-Jun-99	25-Jun-99	13-Jul-99
Amendment (BC)	12-Jul-99	13-Jul-99	13-Jul-99
Amendment (BC)	27-July-99	28-July-99	09-Aug-99
Amendment (BC)	06-Aug-99	09-Aug-99	10-Aug-99
Amendment (BC)	11-Aug-99	08-Sep-99	10-Sep-99
Amendment (AZ)	07-Feb-00	08-Feb-00	09-Feb-00
Amendment (NC)	19-Jun-00	20-Jun-00	03-Jul-00
Amendment (BC)	05-Jul-00	06-Jul-00	10-Jul-00
Amendment (NC)	17-Jul-00	18-Jul-00	20-Jul-00
Amendment (BC)	20-Jul-00	21-Jul-00	27-Jul-00
Amendment (AC)	30-Jan-01	31-Jan-01	31-Jan-01
Amendment (BC)	04-Apr-01	05-Apr-01	05-Apr-01
Amendment (BC)	11-Apr-01	12-Apr-01	18-Apr-01
Amendment (BC)	19-Apr-01	20-Apr-01	24-Apr-01
Amendment (BC)	02-May-01	03-May-01	04-May-01
Amendment (BL)	02-May-01	03-May-01	11-May-01
Amendment (BL)	11-May-01	14-May-01	15-May-01
Amendment (BC)	15-May-01	16-May-01	16-May-01
Amendment (BC)	18-May-01	21-May-01	22-May-01
Amendment (BC)	22-May-01	23-May-01	24-May-01
Amendment (BC)	31-May-01	01-Jun-01	04-Jun-01

NAME & ADDRESS OF APPLICANT: DuPont Pharmaceutical Company
331 Treble Cove Road
North Billerica, MA 01862

Contact : James M. Adie [(978) 671-8069]

DRUG PRODUCT NAME

Proprietary:	**DEFINITY™**
Nonproprietary/USAN:	Perflutren Lipid Microsphere
Code Names/#'s:	DMP-115
Chemical Type/Therapeutic Class:	3S

PATENT STATUS:

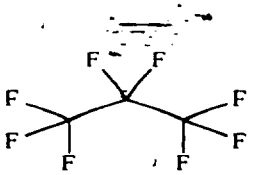
U.S. Patent 5,527,521: ImaRx Pharmaceutical Corp., Compound & method of use, Expires 05-Apr-2011.
U.S. Patent 5,547,656: ImaRx Pharmaceutical Corp., Compound & method of use, Expires 05-Apr-2011.
U.S. Patent 5,769,080: DuPont Merck Pharmaceutical Company, Compound, July 20, 2010.

PHARMACOLOGICAL CATEGORY/INDICATION: Echopharmaceutical / Contrast enhancement during the indicated ultrasound procedures.

DOSAGE FORM:	Sterile injectable suspension
STRENGTHS:	6.52 mg / mL perflutren (octafluoropropane) in headspace
ROUTE OF ADMINISTRATION:	Intravenous injection
DISPENSED:	X Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

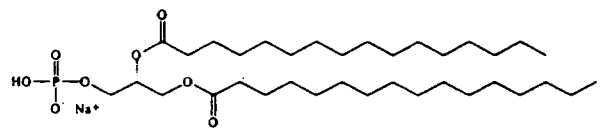
GAS COMPONENT:



1,1,1,2,2,3,3,3-Octafluoropropane

C_3F_3 ; 188.02

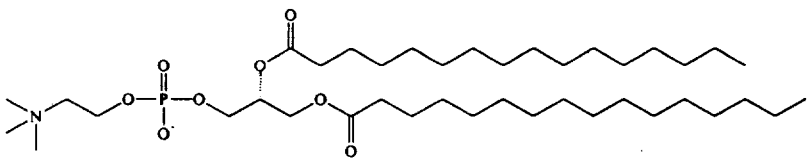
LIPID COMPONENTS:



(R)-Hexadecanoic acid,-[phosphonooxy)methyl]-1,2-ethanediyl ester, monosodium salt; 1,2-Dipalmitoyl-sn-glycero-3-phosphatidic acid

$C_{35}H_{68}O_8PNa$;

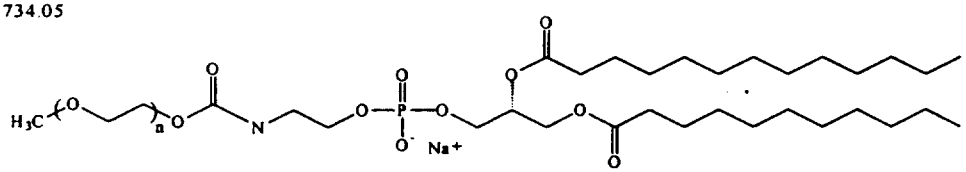
670.89



(R)-4-Hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,5,9-trioxa-4-phosphapentacosan-1-aminium,4-oxide, inner salt; 1,2 Dipalmitoyl-*sn*-glycero-3-phosphatidylcholine

$C_{40}H_{80}NO_8P$

734.05



N-(Methoxyploye thylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine, monosodium salt.

Approximate Formula: $C_{265}H_{527}NO_{123}Pna$

Approximate Mol. Wt.: 5,750 g/mol

SUPPORTING DOCUMENTS:

TYPE/ NUMBER	SUBJECT	HOLDER	STATUS	REVIEW DATE	LETTER DATE
	Perfluoropropane Manufacturer		Acceptable	7/00	N/A
	Closure (Stopper)		Acceptable	9-99	NA
	Container (Glass vial)		Acceptable	9-99	NA

RELATED DOCUMENTS (if applicable): IND DuPont Pharmaceutical Company

CONSULTS: OPADRA for Trademark. OPADRA does not have objections to the use of the proprietary name, DEFINITY™.

REMARKS/COMMENTS: This is the final review for this New Drug Application. The reviews performed for the original submission and the resubmission have been considered for the final recommendation made here. The only outstanding issue will be validation of the methods by the FDA laboratories. The packages have been received from the company and are in the process of being sent to the FDA laboratories.

CONCLUSIONS & RECOMMENDATIONS:

The sponsor has provided data to demonstrate that they have necessary control over the manufacture of the proposed drug product and can reproducibly manufacture the drug product of defined identity, strength, quality and purity, which has been studied for safety and efficacy. The proposed manufacturing facilities are in acceptable cGMP compliance. OPADRA and LNC have reviewed the trademark "DEFINITY" and they do not object to its use. The trademark is acceptable. The vial and the carton labels as well as product labeling, as amended is acceptable. The new drug application contains sufficient information, as required under section 505 of the FD& C act from a chemistry, manufacturing and controls point of view.

Recommended action from a CMC point of view: APPROVAL.

The approval letter should remind the sponsor of all their chemistry agreements (commitments) made in the NDA. There are no phase 4 commitment in the chemistry section of the NDA.

The approval letter should also state that the established name "Perflutren Lipid Microsphere" is conditional pending acceptance of this name by the USP. The name may have to be revised if USP establishes a different name.

/S/ 3/6/01

Ravindra K. Kasliwal, Ph.D.,
Review Chemist
DNDC-II, HFD-160

cc: Orig. NDA 21-064
HFD-160/Division File NDA 21-064
HFD-160/Kasliwal/30-APR-01
HFD-160/Nguyen
HFD-160/Zolman
HFD-160/Laniyonau
HFD-800/Hoiberg
HFD-820/Koepke

R/D Init by: Leutzinger

Concur. /S/ 6/07/2001

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commercial

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(p. 4- 78)

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DIVISION OF NEW DRUG CHEMISTRY-II (DMIRDP, HFD-160)
Review of Chemistry, Manufacturing, and Controls

NDA #: **21-064** CHEM.REVIEW #: 2 REVIEW DATE: 18-July-00
Revised: 27-July-00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment (AZ)	07-Feb-00	08-Feb-00	09-Feb-00
Amendment (NC)	19-Jun-00	20-Jun-00	03-Jul-00
Amendment (BC)	05-Jul-00	06-Jul-00	10-Jul-00
Amendment (NC)	17-Jul-00	18-Jul-00	20-Jul-00

NAME & ADDRESS OF APPLICANT: DuPont Pharmaceutical Company
331 Treble Cove Road
North Billerica, MA 01862
Contact : Robert A. Morgan, MS, JD [(978) 671-8495]

DRUG PRODUCT NAME

Proprietary:	**DEFINITY™**
Nonproprietary/USAN:	Perflutren Lipid Microsphere
Code Names/#'s:	DMP-115
Chemical Type/Therapeutic Class:	**1S**

PATENT STATUS:

U.S. Patent 5,527,521: ImaRx Pharmaceutical Corp., Compound & method of use, Expires 05-Apr-2011.
U.S. Patent 5,547,656: ImaRx Pharmaceutical Corp., Compound & method of use, Expires 05-Apr-2011.
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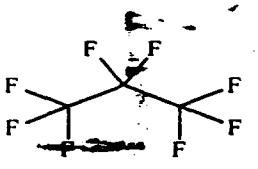
PHARMACOLOGICAL CATEGORY/INDICATION: Echopharmaceutical / Contrast enhancement during the indicated ultrasound procedures.

DOSAGE FORM:	Sterile injectable suspension
STRENGTHS:	≥ 5.5 mg / mL octafluoropropane
ROUTE OF ADMINISTRATION:	Intravenous injection
DISPENSED:	X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

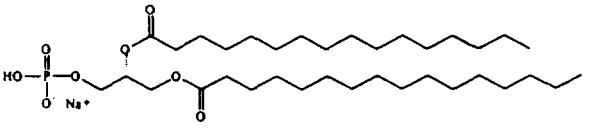
GAS COMPONENT:



1,1,1,2,2,3,3,3-Octafluoropropane

C_3F_3 ; 188.02

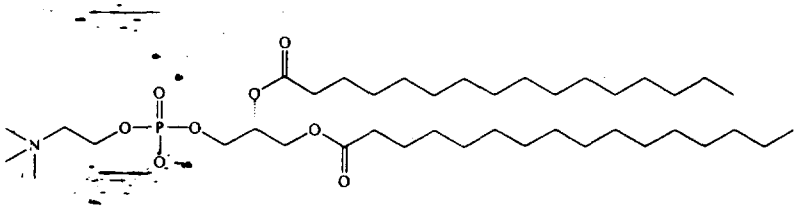
LIPID COMPONENTS:



(R)-Hexadecanoic acid,-[phosphonooxy)methyl]-1,2-ethanediyl ester, monosodium salt: 1,2-Dipalmitoyl-sn-glycero-3-phosphatidic acid

$C_{35}H_{68}O_8PNa$.

670 89



(R)-4-Hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,5,9-trioxa-4-phosphapentacosan-1-aminium,4-oxide, inner salt, 1,2 Dipalmitoyl-*sn*-glycero-3-phosphatidylcholine

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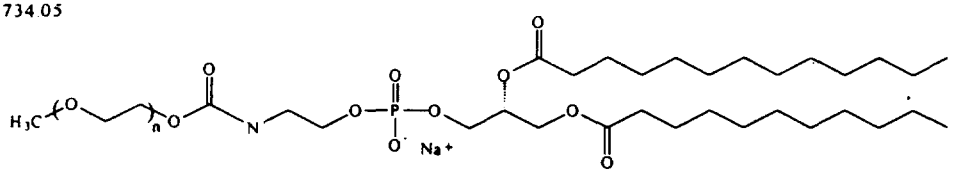
734.05



N-(Methoxyploye thylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine, monosodium salt.

Approximate Formula: $C_{265}H_{527}NO_{123}Pna$

Approximate Mol. Wt.: 5,750 g/mol

SUPPORTING DOCUMENTS:

TYPE/ NUMBER	SUBJECT	HOLDER	STATUS	REVIEW DATE	LETTER DATE
	Perfluoropropane Manufacturer		Acceptable	7/00	N/A
	DPPA Manufacturer		Deficient	1999	9/27/99
	DPPA Manufacturer		Deficient	1999	9/27/99
	DPPC Manufacturer		Deficient	1999	9/27/99
	DPPC Manufacturer		Deficient	1999	11/18/99
	MPEG5000DPPE Manufacturer		Deficient	1999	9/27/00
	Closure (Stopper)		Acceptable	9-99	NA
	Container (Glass vial)		Acceptable	9-99	NA

RELATED DOCUMENTS (if applicable): IND DuPont Pharmaceutical Company

CONSULTS: Trademark "DEFINITY" was consulted to the Labeling and Nomenclature committee, when this drug was in IND phase (IND). The Labeling and Nomenclature Committee found trademark "DEFINITY" to be acceptable.

REMARKS/COMMENTS: A final recommendation on the establishment inspections is pending from the Office of Compliance.

CONCLUSIONS & RECOMMENDATIONS: The sponsor has satisfactorily addressed most of the chemistry concerns except for the acceptability of size distribution of the microspheres. The sponsor has proposed microspheres size distribution acceptance criteria, but the safety of the proposed distribution profile needs to be established and accepted by the safety and clinical reviewers. Since this has not yet been adequately established, we are unable to make a determination on the acceptability of the proposed size distribution acceptance criteria. Because of this reason I recommend an "approvable" action pending satisfactory resolution of this issue. Some modifications, as listed in the deficiency letter, are also required in the vial and carton label prior to an approval action on this drug. The data supports a month expiration dating period. This should be indicated in the final approval letter.

/S/ 7/27/00

Review Chemist, DNDC-II, HFD-160

cc: Orig. NDA 21-064
HFD-160/Division File NDA 21-064
HFD-160/Kasliwal/18-July-00
HFD-160/Zolman
HFD-160/Laniyonau
HFD-160/Nguyen
R/D Init by: Leutzinger

/S/ 7/27/2000

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(pp. 4-43)

JUL 27 2000

DIVISION OF NEW DRUG CHEMISTRY-II (DMIRDP, HFD-160)
Review of Chemistry, Manufacturing, and Controls

NDA #: **21-064** CHEM.REVIEW #: 2 REVIEW DATE: 27-July-00

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment (BC)	20-Jul-00	21-Jul-00	27-Jul-00

NAME & ADDRESS OF APPLICANT: DuPont Pharmaceutical Company
331 Treble Cove Road
North Billerica, MA 01862
Contact : Robert A. Morgan, MS, JD [(978) 671-8495]

DRUG PRODUCT NAME

Proprietary:	**DEFINITY™**
Nonproprietary/USAN:	Perflutren Lipid Microsphere
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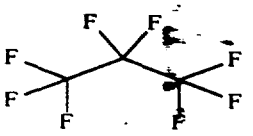
STRENGTHS:	≥ 5.5 mg / mL octafluoropropane
ROUTE OF ADMINISTRATION:	Intravenous injection
DISPENSED:	X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

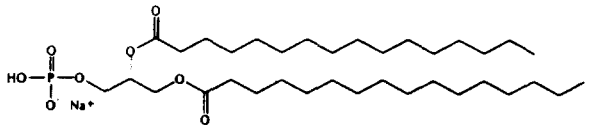
GAS COMPONENT:



1,1,1,2,2,3,3,3-Octafluoropropane

C_3F_3 ; 188.02

LIPID COMPONENTS:



(R)-Hexadecanoic acid,-[phosphonooxy)methyl]-1,2-ethanediyl ester, monosodium salt:
1,2-Dipalmitoyl-sn-glycero-3-phosphatidic acid

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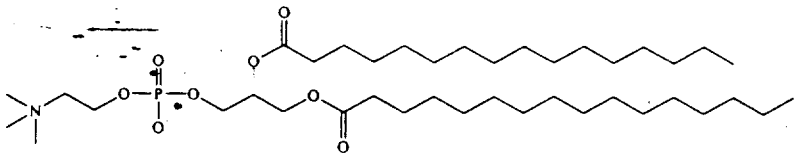
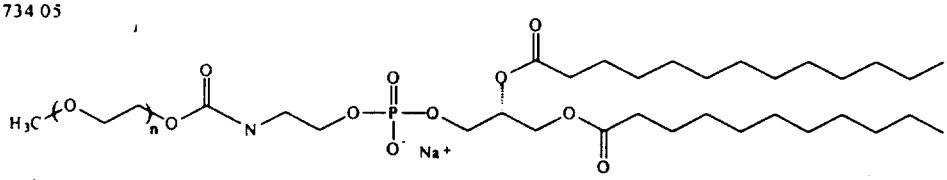
670.89



(R)-4-Hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,5,9-trioxa-4-phosphapentacosan-1-aminium,4-oxide, inner salt; 1,2 Dipalmitoyl-*sn*-glycero-3-phosphatidylcholine

$C_{40}H_{80}NO_8P$

734 05



N-(Methoxyploye thylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine, monosodium salt.

Approximate Formula: $C_{265}H_{527}NO_{123}Pna$

Approximate Mol. Wt.: 5,750 g/mol

SUPPORTING DOCUMENTS: None for this submission.

RELATED DOCUMENTS (if applicable): IND [redacted] DuPont Pharmaceutical Company

CONSULTS: None for this submission.

REMARKS/COMMENTS: See review notes.

CONCLUSIONS & RECOMMENDATIONS: This review does not change the recommendations provided in chemistry review 2. The sponsor should provide us the final printed vial and carton label with actual colors and text size, so that we can make a determination on acceptability on printed overlaid test " Activate Prior to Use".

/S/ 7/27/00

Review Chemist, DNDC-II, HFD-160

cc: Orig. NDA 21-064
HFD-160/Division File NDA 21-064
HFD-160/Kasliwal/18-July-00
HFD-160/Zolman
HFD-160/Laniyonau
HFD-160/Nguyen
R/D Init by: Leutzinger /S/ 7/27/2000

CHEMISTRY REVIEW

The sponsor has submitted the following proposed draft vial label for use in Definity vial:

Vial Label

Note: the proposed final label for the DEFINITY™ vial will have the "Activate Prior to Use" in RED text and will have the "see through" appearance similar to the word "Sample" on the example Quadramet label below.

Reviewer's Comments:

The sponsor has previously indicated that the Definity vial is small (2 mL) and will also contain a small label. I agree with the sponsor that the vial label is small. The information on the vial label will be consistent with the requirements of 21 CFR 201.10 (h)(i) if the carton label contains all the information that is required on the label. The draft carton label has been reviewed in chemistry review # 2 and the sponsor needs to make some changes in that. The sponsor needs to submit the final carton label as well.

Since the Definity vial actually contains the components, which give "perflutren lipid microspheres" upon activation the proposed prefix "Vial for" in the established name, is acceptable provided the overlay "Activate Prior to Use" is such that the printed information underneath is fully visible and readable. From this submitted draft I am unable to make that determination. The sponsor should submit the final vial label with colors and overlay text in actual size for us to make that determination.

COMMENT TO THE SPONSOR:

1. Provide the proposed vial labels in colors and overlay text in actual size for us to make that determination whether the text underneath the overlay is fully visible. Also, provide the proposed carton label.

The comment # 3 of the chemistry review #2 should be modified as follows:

With respect to the vial and carton labels:

- The statement for intravenous administration should be changed to indicate "
- The microspheres are formed after activation; therefore the concentration statement should reflect this fact. The concentration statement should be changed to '
- The statement "NOT EQUIVALENT TO OTHER DRUG PRODUCT CONTAINING PERFLUTREN" should be prominently placed on both sides of the carton label.
- The term " Vial For :" will only be acceptable if the overly text " Activate Prior to Use" is used on the vial label and is found to be acceptable. The name on the carton label will need to be modified.

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF NEW DRUG CHEMISTRY-II (DMIRDP, HFD-160)
Review of Chemistry, Manufacturing, and Controls

NDA #: 21,064 CHEM.REVIEW #: 1 REVIEW DATE: 20-Sep-99

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	09-Dec-98	10-Dec-98	10-Dec-98
Amendment (BC)	19-Jan-99	20-Jan-99	26-Jan-99
Amendment (BC)	26-Mar-99	29-Mar-99	05-Apr-99
Amendment (C)	29-Mar-99	31-Mar-99	05-Apr-99
Amendment (BC)	28-May-99	01-Jun-99	03-Jun-99
Amendment (BC)	24-Jun-99	25-Jun-99	13-Jul-99
Amendment (BC)	12-Jul-99	13-Jul-99	13-Jul-99
Amendment (BC)	27-July-99	28-July-99	09-Aug-99
Amendment (BC)	06-Aug-99	09-Aug-99	10-Aug-99
Amendment (BC)	11-Aug-99	08-Sep-99	10-Sep-99

NAME & ADDRESS OF APPLICANT: DuPont Pharmaceutical Company
331 Treble Cove Road
North Billerica, MA 01862
Contact : Robert A. Morgan, MS, JD [(978) 671-8495]

DRUG PRODUCT NAME

Proprietary:	**DEFINITY™**
Nonproprietary/USAN:	Perflutren Lipid Microspheres
Code Names/#'s:	DMP-115
Chemical Type/Therapeutic Class:	**1S**

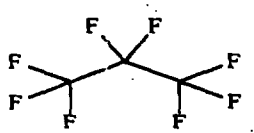
PATENT STATUS:

U.S. Patent 5,527,521: ImaRx Pharmaceutical Corp., Compound & method of use, Expires 05-Apr-2011.
U.S. Patent 5,547,656: ImaRx Pharmaceutical Corp., Compound & method of use, Expires 05-Apr-2011.
U.S. Patent 5,769,080: DuPont Merck Pharmaceutical Company, Compound, July 20, 2010.

PHARMACOLOGICAL CATEGORY/INDICATION: Echopharmaceutical / Contrast enhancement during the indicated ultrasound procedures.

DOSAGE FORM: Sterile injectable suspension
STRENGTHS:
ROUTE OF ADMINISTRATION: Intravenous injection
DISPENSED: X Rx __ OTC

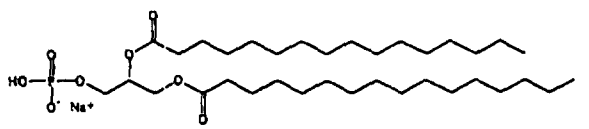
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
GAS COMPONENT:



1,1,1,2,2,3,3,3-Octafluoropropane

C_3F_3 ; 188.02

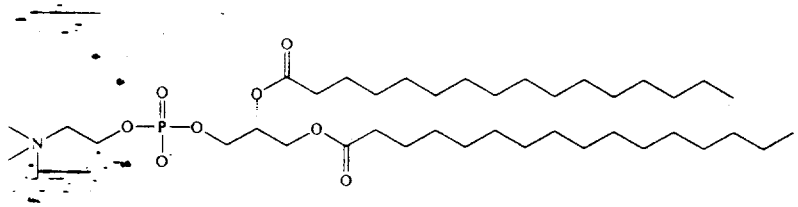
LIPID COMPONENTS:



(R)-Hexadecanoic acid,-[phosphonooxy)methyl]-1,2-ethanediyl ester, monosodium salt; 1,2-Dipalmitoyl-sn-glycero-3-phosphatidic acid

$C_{35}H_{68}O_8PNa$;

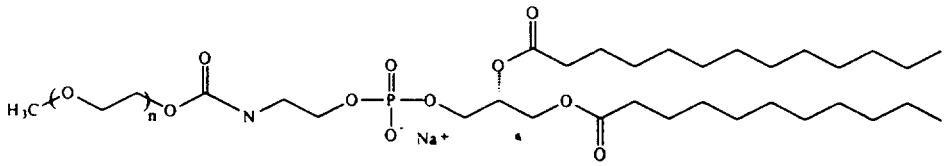
670.89



(R)-4-Hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,5,9-trioxa-4-phosphapentacosan-1-aminium,4-oxide, inner salt; 1,2 Dipalmitoyl-*sn*-glycero-3-phosphatidylcholine

$C_{40}H_{80}NO_8P$

734 05



N-(Methoxyploye thylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine, monosodium salt.

Approximate Formula: $C_{265}H_{527}NO_{123}PNa$

Approximate Mol. Wt.: 5,750 g/mol

SUPPORTING DOCUMENTS:

TYPE/ NUMBER	SUBJECT	HOLDER	STATUS	REVIEW DATE	LETTER DATE
	Perfluoropropane Manufacturer		Deficient	9-99	Pending
	Perfluoropropane Manufacturer		Deficient	9-99	Pending
	DPPA Manufacturer		Deficient	9-99	Pending
	DPPA Manufacturer		Deficient	9-99	Pending
	DPPA Manufacturer		Deficient	9-99	Pending
	DPPC Manufacturer		Deficient	9-99	Pending
	DPPC Manufacturer		Deficient	9-99	Pending
	DPPC Manufacturer		Deficient	9-99	Pending

	DPPC Manufacturer		Deficient	9-99	Pending
	MPEG5000DPPE Mnaufacturer		Deficient	9-99	Pending
	Closure (Stopper)		Acceptable	9-99	NA
	Container (Glass vial)		Acceptable	9-99	NA

RELATED DOCUMENTS (if applicable): IND DuPont Pharmaceutical Company

CONSULTS: Trademark "DEFINITY" was consulted to the Labeling and Nomenclature committee, when this drug was in IND phase (IND). The Labeling and Nomenclature Committee found trademark "DEFINITY" to be acceptable. A copy of the recommendation is attached with this review.

REMARKS/COMMENTS: See chemistry review.

CONCLUSIONS & RECOMMENDATIONS: The application is deficient in the chemistry, manufacturing, and controls for the drug substance and drug product. However, because of the nature of the deficiencies, an approvable action pending satisfactory resolution of all the deficiencies is recommended.

/S/ 9/20/99

Review Chemist, DNDC-II, HFD-160

cc: Orig. NDA 21,064
HFD-160/Division File NDA 21,064
HFD-160/Reviewing Chemist/20-May-99
HFD-160/Reviewing Medical Officer
HFD-160/Reviewing Pharmacologist
HFD-160/Project Manager
R/D Init by: HFD-160 Chemistry Team Leader

/S/ 9/20/99

Redacted 120

pages of trade

secret and/or

confidential

commercial

information

(P.P.4 - 123)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21064/000**
Priority: **S**
Org Code: **160**
Stamp: **09-DEC-1998** Regulatory Due: **09-OCT-1999**
Action Goal:
District Goal: **10-AUG-1999**
Applicant: **DUPONT PHARMS**
331 TREBLE COVE RD
NORTH BILLERICA, MA 01862
Brand Name: **DEFINITY (PERFLUTREN) 10UL/KG IV**
Established Name:
Generic Name: **PERFLUTREN**
Dosage Form: **INJ (INJECTION)**
Strength: **10MCL/KG**

FDA Contacts: **K. CHO (HFD-160) 301-827-7510 , Project Manager**
R. KASLIWAL (HFD-160) 301-827-7510 , Review Chemist

Overall Recommendation:

WITHHOLD on 17-SEP-1999 by B. HARTMAN (HFD-324) 301-827-0067

Establishment:
DMF No:
AADA No:

Profile: **SVT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-MAR-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:
DUPONT MERCK PHARMA
STATE RD 686 KM 2.3
MANATI, PR 00701
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **20-JAN-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: **SVT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **20-APR-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:
DUPONT MERCK PHARMACEUTIC
331 TREBLE COVE RD
NORTH BILLERICA, MA 01862
DMF No:
AADA No:

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **20-JAN-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Profile: **SVT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **19-JAN-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE PACKAGER**
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
INTERMEDIATE MANUFACTURER

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **19-JAN-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **20-JAN-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Profile: **GAS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **05-APR-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE STABILITY TESTER

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **17-SEP-1999**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRIC**
Profile: **GAS** OAI Status: **NONE**
Last Milestone: **QC RECOMMENDATION**
Milestone Date **17-SEP-1999**
Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRIC**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **QC RECOMMENDATION**
Milestone Date **22-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**
DRUG SUBSTANCE STABILITY TESTER

APPEARS THIS WAY
ON ORIGINAL

DATE: July 23, 2001

FROM: Eldon E. Leutzinger, Ph.D.
Chemistry Team Leader, DNDC2

SUMMARY OF DMF ACTIVITY FOR DEFINITY:

DMF	Reviewed	Deficient	Withdrawn	Acceptable
[redacted]	X			X
[redacted]			X	
[redacted]	X	X*	X	
[redacted]	X	X*		
[redacted]	X	X*		
[redacted]		X	X**	
[redacted]	X	X*		
[redacted]	X	X*		
[redacted]	X	X	X	
[redacted]	X	X*		
[redacted]	X			X
[redacted]				X
[redacted]				

1. All of the DMF's that were "reviewed" are as listed in the above table, and the reviews are included in the package.
2. There were 6 DMF's (marked with an asterisk) that were all determined to have no consequence on the NDA for its approval. Accept for #[redacted] those determinations were made by formal review, and those reviews are included in the package. DMF #[redacted] (marked by a double asterisk) was withdrawn and needed no review.
3. DMF #[redacted] #[redacted] and #[redacted] were also withdrawn. DMF #[redacted] and #[redacted] were reviewed before notice was obtained of their withdrawl; their reviews are included.
4. DMF #[redacted] was determined to be acceptable for the NDA, but did not need a formal review; so there is no review for #[redacted] in the package. DMF's #[redacted] and #[redacted] were also found acceptable by formal review; their reviews are in the package.

The final outcome is that out of the 12 DMF's, 4 of the DMF's were withdrawn, not being consequential to approval of the NDA. Of the 8 remaining DMF's, 5 were determined to be inconsequential to the approval of the NDA, leaving 3 DMF's supporting the NDA. All 3 of those remaining DMF's were found acceptable.

DMF Number: [redacted] DMF Type:
TITLE:
Manufactured in

1. CHEM REVIEW No. 1 2. REVIEW DATE: 11/16/99

3. ITEM REVIEWED
   A. IDENTIFICATION
      Name :
   B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Original	01-Sep-1998	Vol. 1.1

4. PREVIOUS DOCUMENTS None

Type of Document	Date of Document	Location Description

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
ADDRESS:

FDA Contact:

6. DMF REFERENCED FOR:

NDA\ANDA\IND:	NDA 21,064
PRIMARY DMF (as needed)	
APPLICANT NAME:	DuPont Pharmaceutical Company
LOA DATE:	16-Sep-1998
DRUG PRODUCT NAME:	Definity
DOSAGE FORM:	Suspension
STRENGTH:	% Octafluoropropane in headspace.
ROUTE OF ADMINISTRATION:	Intravenous

7. SUPPORTING DOCUMENTS: None

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF:	16-Sep-1998
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED:	16-Sep-1998

9. CONSULTS: None.

10. **COMMENTS:** The DMF holder should be told that for the purpose of DuPont Pharmaceutical's application, the DMF will be considered to be a Type DMF and that the facilities and the methods used for the manufacture of ' must be in compliance with the current Good Manufacturing Practices.

11. **CONCLUSION:**

The Drug Master File does not contain adequate information and is deficient for the support of NDA 21064. The deficiencies 1 through 8, listed in the deficiency letter will need to be adequately addressed prior to an approval action on the NDA 21064. The DMF holder should also be asked to address the deficiencies 9, and10 in the letter. However, since DuPont has addressed the issues listed in the deficiencies 9 and 10 and approval action on NDA 21064 should not be contingent on satisfactory resolution of these later deficiencies.

/S/ 11/16/99

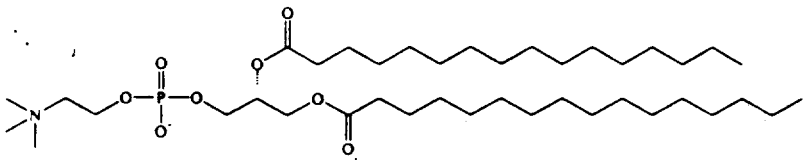
Review Chemist, HFD-160

CC: DMF [redacted] (2 copies)
HFD-160/ Division File for NDA 21064
HFD-160/ Review Chemist for NDA 21064
Rd. Init. By: HFD-160 Chemistry Team Leader

/S/ 11/23/99

CHEMISTRY REVIEW

1. DESCRIPTION:



Molecular Formula: $C_{40}H_{80}NPO_8$

Molecular Weight: 734.1
CAS No. 63-89-8

2. MANUFACTURER

Est. #

Est. #

Est. #

Comments: It is not clear what is done at what address. The DMF holder should be asked to clarify which operation is performed at what address.

DEFICIENCIES:

There are three addresses listed as the manufacturing sites for which specific manufacturing operation is performed at each of the address. ***Clarify***

3. SYNTHESIS / METHOD OF MANUFACTURE

a. Control of Components: The controls for the raw materials are described on pages 38-45 of the DMF. Following raw materials are used in synthesis:

Redacted 6

pages of trade

secret and/or

confidential

commercial

information

(pp. 4-9)

DMF Number[ ] DMF Type:

TITLE: as manufactured in[ ]

1. CHEM REVIEW No. 1 2. REVIEW DATE: 11/15/99

3. ITEM REVIEWED

A. IDENTIFICATION

Name :

B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Original	27-Jan-90	Vol. 1.1
Amendment	24-Mar-93	Vol. 1.1
Amendment	06-Jan-99	Vol. 1.1

4. PREVIOUS DOCUMENTS None

Type of Document	Date of Document	Location Description

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

[

6. DMF REFERENCED FOR:

NDA\ANDA\IND:	NDA 21,064
PRIMARY DMF (as needed)	
APPLICANT NAME:	DuPont Pharmaceutical Company
LOA DATE:	09-Sep-98
DRUG PRODUCT NAME:	Definity
DOSAGE FORM:	Suspension
STRENGTH:	[redacted]% Octafluoropropane in headspace.
ROUTE OF ADMINISTRATION:	Intravenous

7. SUPPORTING DOCUMENTS: None

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: 06-Jan-99

DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: 06-Jan-99

9. CONSULTS: None.

10. **COMMENTS:** The DMF holder sh ·ld be told that for the purpose of DuPont Pharmaceutical's application, the DMF will be considered to be a Type DMF and that the facilities and the methods used for the manufacture of [redacted] must be in compliance with the current Good Manufacturing Practices.

11. **CONCLUSION:**

The Drug Master File does not contain adequate information and is deficient for the support of NDA 21064. The deficiencies 1 through 5, listed in the deficiency letter will need to be adequately addressed prior to an approval action on the NDA 21064. The DMF holder should also be asked to address the deficiencies 6, and 7 listed in the letter. However, since DuPont has addressed the issues listed in the deficiencies 6 and 7, an approval action on NDA 21064 should not be contingent on satisfactory resolution of these later deficiencies.

/S/ 11/15/99

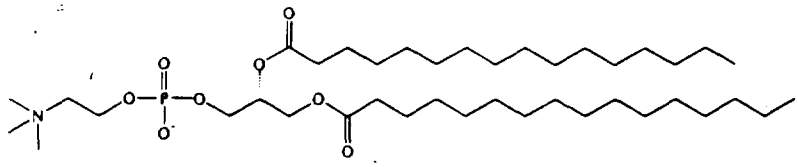
Review Chemist, HFD-160

CC: DMF [redacted] (2 copies)
HFD-160/ Division File for NDA 21064
HFD-160/ Review Chemist for NDA 21064
Rd. Init. By: HFD-160 Chemistry Team Leader

/S/ 11/16/99

CHEMISTRY REVIEW

1. DESCRIPTION:



Molecular Formula: $C_{40}H_{80}NPO_8$

Molecular Weight: 734.1

2. MANUFACTURER

3. SYNTHESIS / METHOD OF MANUFACTURER

a. Control of Components: The controls for the raw materials are described on pages 15-23 of the DMF. Following raw materials are used in synthesis:

Redacted 7

pages of trade

secret and/or

confidential

commercial

information

(pp. 4- 10)

DMF Number:( ) DMF Type:

TITLE:

Manufactured in :

1. CHEM REVIEW No. 1 2. REVIEW DATE: 11/16/99

3. ITEM REVIEWED
   A. IDENTIFICATION
      Name :
   B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Original	19-May1998	Vol. 1.1

4. PREVIOUS DOCUMENTS None

Type of Document	Date of Document	Location Description

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

   NAME:
   ADDRESS:

   FDA Contact:

6. DMF REFERENCED FOR:

NDA\ANDA\IND:	NDA 21,064
PRIMARY DMF (as needed)	
APPLICANT NAME:	DuPont Pharmaceutical Company
LOA DATE:	01-Jul-1998
DRUG PRODUCT NAME:	Definity
DOSAGE FORM:	Suspension
STRENGTH:	% Octafluoropropane in headspace.
ROUTE OF ADMINISTRATION:	Intravenous

7. SUPPORTING DOCUMENTS: None

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF:	19-Feb-1999
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED:	01-Jul-1998

9. CONSULTS: None.

10. COMMENTS: The DMF holder should be told that for the purpose of DuPont Pharmaceutical's application, the DMF will be considered to be a Type DMF and that the facilities and the methods used for the manufacture of , must be in compliance with the current Good Manufacturing Practices.

11. CONCLUSION:

The Drug Master File does not contain adequate information and is deficient for the support of NDA 21064. The deficiencies 1 through 5, listed in the deficiency letter will need to be adequately addressed prior to an approval action on the NDA 21064. The DMF holder should also be asked to address the deficiencies 6, 7, and 8 listed in the letter. However, since DuPont has addressed the issues listed in the deficiencies 6, 7, and 8 an approval action on NDA 21064 should not be contingent on satisfactory resolution of these later deficiencies.

/S/ 11/16

Review Chemist, HFD-160

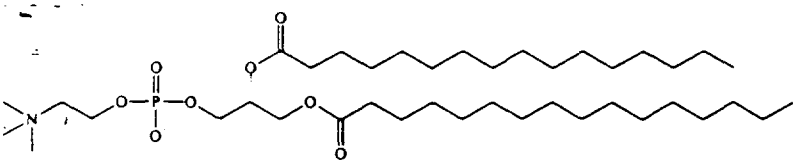
CC: DMF [redacted] (2 copies)
HFD-160/ Division File for NDA 21064
HFD-160/ Review Chemist for NDA 21064
Rd. Init. By: HFD-160 Chemistry Team Leader

/S/ 11/23/99

[redacted]

CHEMISTRY REVIEW

1. DESCRIPTION:



Molecular Formula: $C_{40}H_{80}NPO_8$

Molecular Weight: 734.1
CAS No.

2. MANUFACTURER

3. SYNTHESIS / METHOD OF MANUFACTURER

a. Control of Components: The controls for the raw materials are described on pages 38-45 of the DMF. Following raw materials are used in synthesis:

Redacted 6

pages of trade

secret and/or

confidential

commercial

information

(pp. 4 – 9)

DMF Number:] DMF Type:

TITLE:

manufacture at

1. CHEM REVIEW No. 1

2. REVIEW DATE: 29-Aug-1999
REVISED: 20-Sep-1999

3. ITEM REVIEWED

A. IDENTIFICATION
Name :

B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Original	08-Sep-98	Vol. 1.1

4. PREVIOUS DOCUMENTS None

Type of Document	Date of Document	Location Description

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
ADDRESS:

AGENT:
NAME:
ADDRESS:

TELEPHONE NUMBER:

6. DMF REFERENCED FOR:

NDA\ANDA\IND:	NDA 21,064
PRIMARY DMF (as needed)	
APPLICANT NAME:	DuPont Pharmaceutical Company
LOA DATE:	02-Oct-98
DRUG PRODUCT NAME:	Definity
DOSAGE FORM:	Suspension
STRENGTH:	% Octafluoropropane in headspace.
ROUTE OF ADMINISTRATION:	Intravenous

7. SUPPORTING DOCUMENTS: None

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF:	28-Aug-99
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED:	02-Oct-98

9. CONSULTS: None.

10. COMMENTS: None.

11. CONCLUSION:

The Drug Master File does not contain adequate information and is deficient for the support of NDA 21064. The deficiencies 1 through 6, listed in the deficiency letter will need to be adequately addressed prior to an approval action on the NDA 21064. The DMF holder should also be asked to address the deficiencies 7 through 9, listed in the letter. However, since DuPont has addressed the issues listed in the deficiencies 7-9, an approval action on NDA 21064 should not be contingent on satisfactory resolution of these later deficiencies.

/S/ 9/20/99

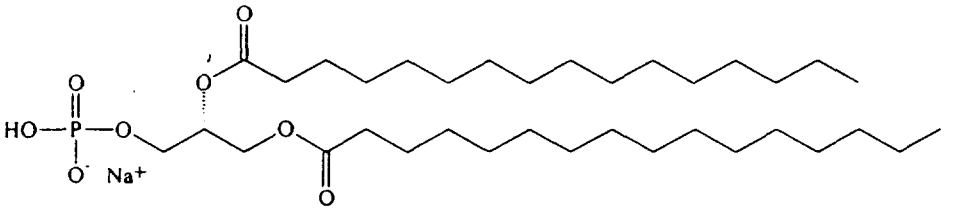
Review Chemist, HFD-160

CC: DMF (2 copies)
HFD-160/ Division File for NDA 21064
HFD-160/ Review Chemist for NDA 21064
Rd. Init. By: HFD-160 Chemistry Team Leader

/S/ 9/20/99

CHEMISTRY REVIEW

1. DESCRIPTION:



(R)-Hexadecanoic acid,-[phosphonooxy)methyl]-1,2-ethanediyl ester, monosodium salt;
1,2-Dipalmitoyl-sn-glycero-3-phosphatidic acid

$C_{35}H_{68}O_8PNa$;

670.89

2. MANUFACTURER

I

3. SYNTHESIS / METHOD OF MANUFACTURER

a. **Control of Components:** Following raw materials are used in synthesis:

Following specifications are provided for

Redacted 8

pages of trade

secret and/or

confidential

commercial

information

(PP. 4-11)

JUL 26 2000

DMF Number [ ] DMF Type:

TITLE: Manufactured in

1. **CHEM REVIEW No.** 1 **2. REVIEW DATE:** 19-July-00

3. **ITEM REVIEWED**
   A. IDENTIFICATION
   Name :
   B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Amendment	12-Jan-00	Vol. 1.1

4. **PREVIOUS DOCUMENTS** None

Type of Document	Date of Document	Location Description

5. **NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):**

NAME:
ADDRESS:

Contact:

TELEPHONE NUMBER

6. **DMF REFERENCED FOR:**

NDA\ANDA\IND:	NDA 21,064
PRIMARY DMF (as needed)	
APPLICANT NAME:	DuPont Pharmaceutical Company
LOA DATE:	05-Aug-98
DRUG PRODUCT NAME:	Definity
DOSAGE FORM:	Suspension
STRENGTH:	_ mg Octafluoropropane in headspace.
ROUTE OF ADMINISTRATION:	Intravenous

7. **SUPPORTING DOCUMENTS:** None

8. **CURRENT STATUS OF DMF:**

DATE OF LAST UPDATE OF DMF:	12-Jan-00
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED:	12-Jan-00

9. **CONSULTS:** None.

10. **COMMENTS:** None

11. CONCLUSION:

The Drug Master File contains adequate information for the manufacture of octafluoropropane for use in the manufacture of ultrasound microbubble drug products.

/S/ 7/19/00

Ravindra K. Kasliwal, Ph.D.
Review Chemist, DNDC-II, HFD-160

CC: DMF (2 copies)
HFD-160/ Division File for NDA 21064
HFD-160/ Kasliwal / Cho
Rd. Init. By: Leutzinger

/S/ 7/26/2000

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(pp. 3-5)

DMF Number[ ] DMF Type:

TITLE:

1. **CHEM REVIEW No.** 1 **2. REVIEW DATE:** 21-Sep-1999

3. **ITEM REVIEWED**
   A. IDENTIFICATION
      Name :
   B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Original	28-Aug-97	Vol. 1.1
Amendment	25-Jan-99	Vol. 1.1

4. **PREVIOUS DOCUMENTS** None

Type of Document	Date of Document	Location Description

5. **NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):**

   NAME:
   ADDRESS:

   Contact:

   TELEPHONE NUMBER:

6. **DMF REFERENCED FOR:**

NDA\ANDA\IND:	NDA 21,064
PRIMARY DMF (as needed)	
APPLICANT NAME:	DuPont Pharmaceutical Company
LOA DATE:	05-Aug-98
DRUG PRODUCT NAME:	Definity
DOSAGE FORM:	Suspension
STRENGTH:	% Octafluoropropane in headspace.
ROUTE OF ADMINISTRATION:	Intravenous

7. **SUPPORTING DOCUMENTS:** None

8. **CURRENT STATUS OF DMF:**

   DATE OF LAST UPDATE OF DMF: 21-Jan-99

   DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: 21-Jan-99

9. **CONSULTS:** None.

10. **COMMENTS:** None

11. CONCLUSION:

The Drug Master File does not contain adequate information and is deficient for the support of NDA 21064. The deficiencies 1 through 6, listed in the deficiency letter will need to be adequately addressed prior to an approval action on the NDA 21064. The DMF holder should also be asked to address the deficiencies 7 through 9, listed in the letter. However, since DuPont has addressed the issues listed in the deficiencies 7-9, an approval action on NDA 21064 is not be contingent on satisfactory resolution of these later deficiencies.

/S/ 9/21/99

Ravindra K. Kasliwal, Ph.D.
Review Chemist, DNDC-II, HFD-160

CC: DMF (2 copies)
HFD-160/ Division File for NDA 21064
HFD-160/ Kasliwal / Cho
Rd. Init. By: Leutzinger

/S/ 9/21/99

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commercial

information

(PP. 3-11)

DMF Number[ ] DMF Type:

TITLE:

manufacture at

1. **CHEM REVIEW No.** 1 **2. REVIEW DATE:** **29-Aug-1999**
   REVISED: 20-Sep-1999

3. **ITEM REVIEWED**
   A. IDENTIFICATION
   Name :

   B. LOCATION IN DMF

Type of Submission	**Date of Submission**	**Location of Information**
Original	08-Sep-98	Vol. 1.1

4. **PREVIOUS DOCUMENTS** None

Type of Document	**Date of Document**	**Location Description**

5. **NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):**

   NAME:
   ADDRESS:

   U.S. AGENT:
   NAME:
   ADDRESS:

   TELEPHONE NUMBER:

6. **DMF REFERENCED FOR:**

NDA\ANDA\IND:	NDA 21,064
PRIMARY DMF (as needed)	
APPLICANT NAME:	DuPont Pharmaceutical Company
LOA DATE:	02-Oct-98
DRUG PRODUCT NAME:	Definity
DOSAGE FORM:	Suspension
STRENGTH:	% Octafluoropropane in headspace.
ROUTE OF ADMINISTRATION:	Intravenous

7. **SUPPORTING DOCUMENTS:** None

8. **CURRENT STATUS OF DMF:**

   DATE OF LAST UPDATE OF DMF: 28-Aug-99

   DATE OF MOST RECENT LIST OF COMPANIES
   FOR WHICH LOA's HAVE BEEN PROVIDED: 02-Oct-98

9. **CONSULTS:** None.

10. **COMMENTS:** None.

11. CONCLUSION:

The Drug Master File does not contain adequate information and is deficient for the support of NDA 21064. The deficiencies 1 through 6, listed in the deficiency letter will need to be adequately addressed prior to an approval action on the NDA 21064. The DMF holder should also be asked to address the deficiencies 7 through 9, listed in the letter. However, since DuPont has addressed the issues listed in the deficiencies 7-9, an approval action on NDA 21064 should not be contingent on satisfactory resolution of these later deficiencies.

/S/ — 9/20/99

Review Chemist, HFD-160

CC: DMF (2 copies)
HFD-160/ Division File for NDA 21064
HFD-160/ Review Chemist for NDA 21064
Rd. Init. By: HFD-160 Chemistry Team Leader

/S/ 9/20/99

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(pp. 3-11)

DMF Number: [redacted] DMF Type:

TITLE:

1. CHEM REVIEW No: 1 2. REVIEW DATE: 29-Aug-1999
REVISED: 20-Sep-1999

3. ITEM REVIEWED
A. IDENTIFICATION
Name :

B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Original	28-Aug-98	Vol. 1.1

4. PREVIOUS DOCUMENTS None

Type of Document	Date of Document	Location Description

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
ADDRESS:

TELEPHONE NUMBER:

6. DMF REFERENCED FOR:

NDA\ANDA\IND:	NDA 21,064
PRIMARY DMF (as needed)	
APPLICANT NAME:	DuPont Pharmaceutical Company
LOA DATE:	21-Sep-98
DRUG PRODUCT NAME:	Definity
DOSAGE FORM:	Suspension
STRENGTH:	% Octafluoropropane in headspace.
ROUTE OF ADMINISTRATION:	Intravenous

7. SUPPORTING DOCUMENTS: None

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: 19-Feb-99

DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: 19-Feb-99

9. CONSULTS: None.

10. COMMENTS: The DMF holder should be told that for the purpose of DuPont Pharmaceutical's application, the DMF will be considered to be a Type)MF and that the facilities and the methods used for the manufacture of) must be in compliance with the current Good Manufacturing Practices.

11. CONCLUSION:

The Drug Master File does not contain adequate information and is deficient for the support of NDA 21064. The deficiencies 1 through 8, listed in the deficiency letter will need to be adequately addressed prior to an approval action on the NDA 21064. The DMF holder should also be asked to address the deficiencies 9 through 13, listed in the letter. However, since DuPont has addressed the issues listed in the deficiencies 9-13, an approval action on NDA 21064 should not be contingent on satisfactory resolution of these later deficiencies.

/S/ 9/20/99

Review Chemist, HFD-160

CC: DMF [redacted] (2 copies)
HFD-160/ Division File for NDA 21064
HFD-160/ Review Chemist for NDA 21064
Rd. Init. By: HFD-160 Chemistry Team Leader

/S/ 9/20/99

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(pp. 3-11)

DMF Number: [redacted] DMF Type:

TITLE:

Manufactured in

1. **CHEM REVIEW NO.** 1

2. **REVIEW DATE:** 29-Aug-1999
Revised: 20-Sep-99

3. **ITEM REVIEWED**
   A. IDENTIFICATION
      Name :

   B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Original	25-Sep-98	Vol. 1.1

4. **PREVIOUS DOCUMENTS** None

Type of Document	Date of Document	Location Description

5. **NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):**

   NAME:
   ADDRESS:

   U.S. AGENT:

6. **DMF REFERENCED FOR:**

NDA\ANDA\IND:	NDA 21,064
PRIMARY DMF (as needed)	
APPLICANT NAME:	DuPont Pharmaceutical Company
LOA DATE:	02-Oct-98
DRUG PRODUCT NAME:	Definity
DOSAGE FORM:	Suspension
STRENGTH:	% Octafluoropropane in headspace.
ROUTE OF ADMINISTRATION:	Intravenous

7. **SUPPORTING DOCUMENTS:** None

8. **CURRENT STATUS OF DMF:**

DATE OF LAST UPDATE OF DMF:	25-Sep-98
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED:	25-Sep-98

9. **CONSULTS:** None.

10. **COMMENTS:** The DMF holder should be told that for the purpose of DuPont Pharmaceutical's application, the DMF will be considered to be a Type DMF and that the facilities and the methods used for the manufacture of . must be in compliance with the current Good Manufacturing Practices.

11. **CONCLUSION:**

11. CONCLUSION:

The Drug Master File does not contain adequate information and is deficient for the support of NDA 21064. The deficiencies 1 through 6, listed in the deficiency letter will need to be adequately addressed prior to an approval action on the NDA 21064. The DMF holder should also be asked to address the deficiencies 7 through 9, listed in the letter. However, since DuPont has addressed the issues listed in the deficiencies 7-9, an approval action on NDA 21064 should not be contingent on satisfactory resolution of these later deficiencies.

S

Review Chemist, HFD-160

9/20/99

CC: DMF (2 copies)
HFD-160/ Division File for NDA 21064
HFD-160/ Review Chemist for NDA 21064
Rd. Init. By: HFD-160 Chemistry Team Leader

S

9/20/99

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(pp. 3-10)

DMF Number: [redacted] DMF Type:

TITLE:

Manufactured in :

1. **CHEM REVIEW No:** 1

2. **REVIEW DATE:** 31-Aug-1999
REVISED: 20-Sep-99

3. **ITEM REVIEWED**
   A. IDENTIFICATION
      Name :

   B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Original	23-Sep-98	Vol. 1.1

4. **PREVIOUS DOCUMENTS** None

Type of Document	Date of Document	Location Description

5. **NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):**

   NAME:
   ADDRESS:

   CONTACT:

6. **DMF REFERENCED FOR:**

NDA\ANDA\IND:	NDA 21,064
PRIMARY DMF (as needed)	
APPLICANT NAME:	DuPont Pharmaceutical Company
LOA DATE:	06-Oct-98
DRUG PRODUCT NAME:	Definity
DOSAGE FORM:	Suspension
STRENGTH:	% Octafluoropropane in headspace.
ROUTE OF ADMINISTRATION:	Intravenous

7. **SUPPORTING DOCUMENTS:** None

8. **CURRENT STATUS OF DMF:**

DATE OF LAST UPDATE OF DMF:	22-Sep-98
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED:	06-Oct-98

9. **CONSULTS:** None.

10. **COMMENTS:** The DMF holder should be told that for the purpose of DuPont Pharmaceutical's application, the DMF will be considered to be a Type DMF and that the facilities and the methods used for the manufacture of

must be in compliance with the current Good Manufacturing Practices.

11. CONCLUSION:

The Drug Master File does not contain adequate information and is deficient for the support of NDA 21064. The deficiencies 1 through 9, listed in the deficiency letter will need to be adequately addressed prior to an approval action on the NDA 21064. The DMF holder should also be asked to address the deficiencies 10 and 11, listed in the letter. However, since DuPont has addressed the issues listed in the deficiencies 10 & 11, an approval action on NDA 21064 should not be contingent on satisfactory resolution of these later deficiencies.

/S/ 9/20/99

Review Chemist, HFD-160

CC: DMF (2 copies)
HFD-160/ Division File for NDA 21064
HFD-160/ Review Chemist for NDA 21064
Rd. Init. By: HFD-160 Chemistry Team Leader

/S/ - 9/20/99

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(pp. 3-11)

ENVIRONMENTAL ASSESSMENT INFORMATION

1. **In the Environmental Assessment section, Dr. Kasliwal asks on what basis did we make our claim for exemption? He stated that FDA guidance with regard to environmental assessment should be carefully reviewed by DuPont Pharmaceuticals. He also requested us to provide him with our calculation to support our claim for exemption.**

   In response to the categorical exclusion for the DEFINITY™ NDA, the text of DPC's **"Claim for Categorical Exclusion of Flufosphacele from the Environmental Assessment Requirements of 21 CFR Part 25"** is shown below. The specific regulatory citation and basis for the claim are bolded. The calculations substantiating eligibility for the claim follow on the next page.

   In accordance with **21 CFR 25.31(b)**, The DuPont Merck Pharmaceutical Company claims a categorical exclusion from the environmental assessment requirement of 21 CFR 25.20 for approval of the Flufosphacele NDA, on the basis that:

   1. the estimated concentration of Flufosphacele at the point of entry into the aquatic environment will be below 1 part per billion, and;

   2. **to the applicant's knowledge, no extraordinary circumstances exist that indicate that approval of the NDA will significantly affect the quality of the human environment.**

APPEARS THIS WAY
ON ORIGINAL

The ingredients of Flufosphacele consist of a lipid blend composed of one synthetic and two normally occurring phospholipids and chemically inert, insoluble gas, perfluoropropane. The US annual production volume of Flufosphacele during the fifth-year, post-NDA approval, has been estimated to be This level of production is expected to require ~2.4 kg of lipid blend and ~2.4 kg (~312L) of perfluoropropane gas.

Under the worst-case emission conditions, if the total annual production volume of Flufosphacele was instantaneously emitted into US POTW's, the expected introductory concentration (EIC) of the lipid blend and perfluoropropane at the point of entry into the environment would be much less than 1 ppb as follows (ref., Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications, FDA; July 1998):

$$EIC_{\text{lipid blend}} = (A_{\text{lipid blend}}) \times B \times C \times D$$
$$= 5 \times 10^{-5} \text{ ppb}$$

$$EIC_{\text{perfluoropropane}} = (A_{\text{perfluoropropane}}) \times B \times C \times D$$
$$= 5 \times 10^{-5} \text{ ppb}$$

$$EIC_{\text{total}} = EIC_{\text{lipid blend}} + EIC_{\text{perfluoropropane}}$$
$$= 1 \times 10^{-4} \text{ ppb}$$

where:
- A = production volume of lipid blend or perfluoropropane
- B = 1/liters per day entering POTW (i.e., 1.214×10^{11} liters/day)
- C = year/365 days
- D = 10^9 µg/kg (conversion factor)

This estimate greatly exceeds the likely EIC for Flufosphacele since components of the lipid blend will likely be utilized as an energy source both by the patient and organisms in the sewer system and, due to its inert chemical nature, low aqueous solubility, and low boiling point (~36°C), perfluoropropane will likely be largely emitted to and localize in the atmospheric compartment of the environment.

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

FINISHED DOSAGE STABILITY TESTER
INTERMEDIATE MANUFACTURER

Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**
BASED ON PROFILE
Profile: **SVT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Profile: **GAS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE STABILITY TESTER

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**
DRUG SUBSTANCE STABILITY TESTER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21064/000
Stamp: 09-DEC-1998 Regulatory Due: 31-JUL-2001
Applicant: DUPONT PHARMS
331 TREBLE COVE RD
NORTH BILLERICA, MA 01862

Priority: 1S Org Code: 160
Action Goal: District Goal: 09-JUN-2000
Brand Name: DEFINITY (PERFLUTREN) 10UL/KG IV
Established Name:
Generic Name: PERFLUTREN
Dosage Form: INJ (INJECTION)
Strength: 10MCL/KG

FDA Contacts: [redacted] T Nguyen (HFD-160) 301-827-7510 , Project Manager
R. KASLIWAL (HFD-160) 301-827-7510 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 27-JUL-2000 by M. GARCIA (HFD-322) 301-594-0095
WITHHOLD on 17-SEP-1999 by B. HARTMAN (HFD-324) 301-827-0067

Establishment:
DMF No:
AADA No:

Profile: SVT OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 22-MAY-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment:
DUPONT MERCK PHARMA
HWY 686 KM 2.3
MANATI, PR 00701

DMF No:
AADA No:

Profile: SVT OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 26-JUL-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment:
DUPONT MERCK PHARMACEUTIC
331 TREBLE COVE RD
NORTH BILLERICA, MA 01862

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 15-MAY-2000

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21064/000
Stamp: 09-DEC-1998 Regulatory Due: 08-AUG-2000
Applicant: DUPONT PHARMS
331 TREBLE COVE RD
NORTH BILLERICA, MA 01862

Priority: 1S Org Code: 160
Action Goal: District Goal: 09-JUN-2000
Brand Name: DEFINITY (PERFLUTREN) 10UL/KG IV
Established Name:
Generic Name: PERFLUTREN
Dosage Form: INJ (INJECTION)
Strength: 10MCL/KG

FDA Contacts: T. Nguyen (HFD-160) 301-827-7510 , Project Manager
R. KASLIWAL (HFD-160) 301-827-7510 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 27-JUL-2000 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 17-SEP-1999 by B. HARTMAN (HFD-324) 301-827-0067

Establishment:
DMF No:
AADA No:

Profile: SVT OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 22-MAY-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment:
DUPONT MERCK PHARMA
STATE RD 686 KM 2.3
MANATI, PR 00701
DMF No:
AADA No:

Profile: SVT OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 26-JUL-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment:
DUPONT MERCK PHARMACEUTIC
331 TREBLE COVE RD
NORTH BILLERICA, MA 01862
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 15-MAY-2000
Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

FINISHED DOSAGE STABILITY TESTER
INTERMEDIATE MANUFACTURER

Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**
BASED ON PROFILE
Profile: **SVT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Profile: **GAS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE STABILITY TESTER

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**
DRUG SUBSTANCE STABILITY TESTER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21064/000
Priority: S
Org Code: 160
Stamp: 09-DEC-1998 *Regulatory Due: 09-OCT-1999
Action Goal:
District Goal: 10-AUG-1999
Applicant: DUPONT PHARMS
331 TREBLE COVE RD
NORTH BILLERICA, MA 01862
Brand Name: DEFINITY (PERFLUTREN) 10UL/KG IV
Established Name:
Generic Name: PERFLUTREN
Dosage Form: INJ (INJECTION)
Strength: 10MCL/KG

FDA Contacts: K. CHO (HFD-160) 301-827-7510 , Project Manager
R. KASLIWAL (HFD-160) 301-827-7510 , Review Chemist

Overall Recommendation:

WITHHOLD on 17-SEP-1999 by B. HARTMAN (HFD-324) 301-827-0067

Establishment:
DMF No:
AADA No:

Profile: SVT
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 12-MAR-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment:
DUPONT MERCK PHARMA
STATE RD 686 KM 2.3
MANATI, PR 00701
DMF No:
AADA No:

Profile: CTL
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 20-JAN-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: SVT
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 28-APR-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment:
DUPONT MERCK PHARMACEUTIC
331 TREBLE COVE RD
NORTH BILLERICA, MA 01862
DMF No:
AADA No:

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **20-JAN-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Profile: **SVT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **19-JAN-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE PACKAGER**
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
INTERMEDIATE MANUFACTURER

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **19-JAN-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **20-JAN-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Profile: **GAS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **05-APR-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE STABILITY TESTER

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **17-SEP-1999**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRIC**
Profile: **GAS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **17-SEP-1999**
Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRIC**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **22-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**
DRUG SUBSTANCE STABILITY TESTER

APPEARS THIS WAY
ON ORIGINAL

Method Validation Information: NOT COMPLETED

APPEARS THIS WAY
ON ORIGINAL