CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-632
NDA 21-948

Chemistry Review(s)

NDA 21-632
NDA 21-948

ERAXIS™
(anidulafungin)
For Injection

Pfizer Pharmaceuticals Inc.

Mark R. Seggel
Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch IV

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-632 (Re-submission)
   NDA 21-948

2. REVIEW #: 2

See Chemistry Review #1 (NDA 21-632 Drug Substance) prepared by Dr. Balajee Shanmugam for drug substance CMC and Chemistry Review #1 (NDA 21-632 Drug Product) prepared by M. Seggel.

3. REVIEW DATE: 17-FEB-2006

4. REVIEWER: Mark R. Seggel, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N21-632 Original NDA	25-APR-2003
BC (info for Methods Validation Package)	25-NOV-2003
BC (product quality microbiology update)	14-JAN-2004
BC (drug substance update)	30-JAN-2004
BC (stability update)	13-FEB-2004
BC (drug substance and drug product updates)	24-FEB-2004
BC (drug substance and drug product updates)	03-MAR-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N21-948 Original NDA	18-AUG-2005
N21-632 1st Resubmission	27-MAY-2005
N21-632 2nd Resubmission	24-JAN-2006
N21-948 (EA – claim for cat. exclusion)	16-FEB-2006
N21-632/N21-948 (labeling)	16-FEB-2006

7. NAME & ADDRESS OF APPLICANT:

On September 14, 2005, Vicuron Pharmaceuticals, the original owner of these New Drug Applications, was acquired by Pfizer. At that time, Pfizer was authorized to act as agents on behalf of Vicuron.

Name:	Pfizer Inc.
Address:	East 42nd Street 605/5 New York, NY 10017
Representative:	Maureen H. Garvey, PhD Senior Director, Worldwide Regulatory Strategy Worldwide Regulatory Affairs and Quality Assurance
Telephone:	212-733-5688

Name:	Vicuron Pharmaceuticals Inc.
Address:	455 South Gulph Road King of Prussia, PA 19406
Representative:	Harriette L. Nadler, PhD Senior Director, Regulatory Affairs
Telephone:	610-491-2211

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ERAXIS™ (originally proposed [redacted])
b) Non-Proprietary Name (USAN): anidulafungin
c) Code Name/# (ONDC only): VER002; LY303366;
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: N21-632 Type 1
  N21-948 Type 6
- Submission Priority: N21-632 S
  N21-948 P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Systemic antifungal

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 50 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

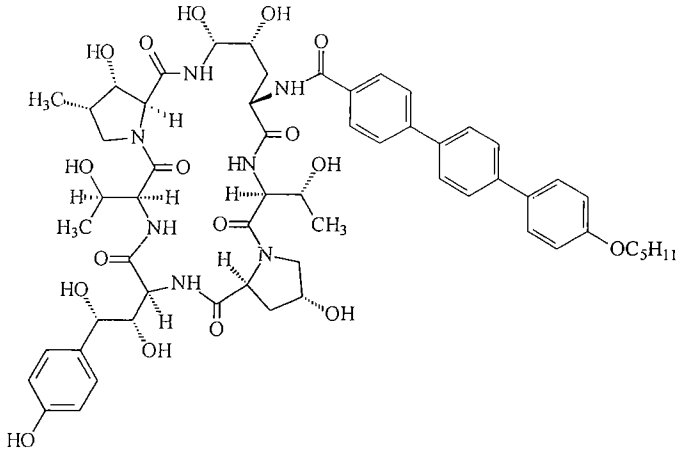
___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Echinocandin B, 1-[(4R,5R)-4,5-dihydroxy-N^2-[[4"-(pentyloxy)[1,1',:4',1"-terphenyl]-4-yl]carbonyl]-L-ornithine]-

(4R,5R)-4,5-Dihydroxy-N^2-[[4"-(pentyloxy)-p-terphenyl-4-yl]carbonyl]-L-ornithyl-L-threonyl-*trans*-4-hydroxy-L-prolyl-(S)-4-hydroxy-(p-hydroxyphenyl)-L-threonyl-L-threonyl-(3S,4S)-3-hydroxy-4-methyl-L-proline cyclic (6→1)-peptide

Molecular formula: $C_{58}H_{73}N_7O_{17}$
Molecular weight: 1140.27
CAS: 166663-25-8



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	3, 4	Adequate	12-FEB-2003	-
[redacted]	III	[redacted]	[redacted]	3, 4	Adequate	06-AUG-2003	-

*The [redacted]

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

See Chemistry Review #1, Drug Product CMC

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Acceptable	25-JUL-2003 26-AUG-2005	S. Ferguson, HFD-322
Pharm/Tox	n/a		
Biopharm	n/a		
LNC	n/a		
Methods Validation	n/a		
DMETS	Trademark acceptable; other labeling recommendations conveyed to applicant	02-DEC-2003 13-FEB-2006	C. Hoppes, HFD-420
EA	Categorical exclusion acceptable	16-MAY-2003 16-FEB-2006	M. Seggel
Microbiology	Acceptable	25-FEB-2004	J. McVey, HFD-805

The Chemistry Review for NDA 21-632 and NDA 21-948

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applications, as amended, are recommended for approval from the chemistry, manufacturing and controls perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no recommendations for Phase 4 CMC commitments. The applicant will continue to monitor the stability of the drug substance and drug product. The applicant will also re-evaluate the drug substance and drug product specifications after the manufacture of ten commercial batches of each.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

See Chemistry Review #1, Drug Substance CMC for NDA 21-632 and Chemistry Review #1, Drug Product CMC for NDA 21-632.

The drug product is a lyophilized sterile solid containing 50 mg of the antifungal agent anidulafungin. The product is reconstituted and diluted prior to intravenous infusion. A 20% (w/w) ethanol diluent is provided for reconstituting the lyophilized product. The commercial package will contain two 15 mL vials. One vial contains 50 mg of anidulafungin and the second contains the diluent used for reconstituting the drug product. The manufacture of the drug product is straightforward. Common, compendial-grade excipients are used and include fructose, mannitol, tartaric acid, polysorbate 80, and sodium hydroxide and/or hydrochloric acid to adjust the pH. The formulation is [ ] and lyophilized. The identity, strength, quality and purity of the drug product are assured by release testing appropriate for a product for intravenous administration. The drug product exhibits good stability at 25°C/60% RH. The diluent is simply a 20% aqueous ethanol solution that has been [ ]

Anidulafungin is a semisynthetic antifungal lipopeptide (cyclic hexapeptide with lipophilic acyl side chain) derived from echinocandin B. It has activity against pathogenic fungi including *Candida* spp. The echinocandins, and structurally related pneumocandins, inhibit the enzyme β-1,3-D-glucan synthetase. β-(1,3)-D-Glucan, a polymer of glucose, is an integral component of the fungal cell wall. The drug substance is insoluble in water and slightly soluble in ethanol. It has good chemical stability, but the recommended storage condition is [ ] The identity, strength, quality and purity of the drug substance are assured by appropriate stability-indicating tests.

B. Description of How the Drug Product is Intended to be Used

Anidulafungin for injection is indicated for the treatment of esophageal candidiasis (NDA 21-632) and Candidemia and other forms of *Candida* infections (NDA 21-948). The intended dosing regimen for the treatment of esophageal candidiasis is a 100-mg loading dose followed by a 50-mg daily maintenance dose for the duration of treatment. For invasive candidiasis, a 200-mg loading dose will be followed by 100 mg daily dosing. The lyophilized drug product requires two dilutions prior to infusion: dilution with the 20% (w/w) dehydrated alcohol/water for injection diluent and subsequent dilution with either 5% Dextrose Injection USP (D5W) or 0.9% Sodium Chloride Injection USP. The final concentration of the infusion solution is 0.5 mg/mL.

The stability studies support an expiration dating period of 30 months for product stored at 25°C/60% RH. The reconstituted solution is stable for up to [ ] while the infusion solution is stable for up to [ ] s. However, the reconstituted solution should be used within 24 hours of preparation to insure microbiological quality.

C. Basis for Approvability or Not-Approval Recommendation

The physicochemical properties of the drug substance have been adequately characterized. The manufacturing process is adequately described. Suitable controls for the drug substance have been established. The stability of the drug substance has also been adequately characterized and appropriate storage conditions established.

The components and composition of the drug product have been adequately specified. The inactive ingredients are commonly used in this dosage form and are of suitable quality. The manufacturing process has been adequately described.

Additional details regarding the manufacture of the drug substance have been provided by the applicant as requested. All issues regarding the drug substance and drug product specifications have been adequately negotiated with the applicant. The applicant will continue to monitor the stability of the drug substance and drug product. The applicant

will also re-evaluate the drug substance and drug product specifications after the manufacture of – commercial batches of each.

The manufacturing and testing facilities have acceptable cGMP status and the Office of Compliance has issued an Overall Recommendation of Acceptable for the NDA.

The relevant sections of the Package Insert and the container/carton labels have been revised as requested by the chemistry reviewer and DMETS. As revised, the labeling is acceptable.

III. Administrative

A. Reviewer's Signature

{see Electronic Signature Page}

B. Endorsement Block

ChemistName/Date: Same date as draft review
ONDQA/DPAII BC/Div.Dir. Name/Date

{see Electronic Signature Page}

C. CC Block

See dfs

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

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/s/

Mark Seggel
2/17/2006 09:13:07 AM
CHEMIST
N21632/N21948

Elaine Morefield
2/17/2006 10:14:04 AM
CHEMIST

NDA 21-632

{ }

(anidulafungin)
For Injection

Vicuron Pharmaceuticals Inc.

Mark R. Seggel
HFD-590
Division of Special Pathogen and
Immunologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-632

2. REVIEW #: 1 (Drug Product)

See Chemistry Review #1 (Drug Substance) prepared by Dr. Balajee Shanmugam for drug substance CMC.

3. REVIEW DATE: 05-MAR-2004

4. REVIEWER: Mark R. Seggel, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	25-APR-2003
BC (info for Methods Validation Package)	25-NOV-2003
BC (product quality microbiology update)	14-JAN-2004
BC (drug substance update)	30-JAN-2004
BC (stability update)	13-FEB-2004
BC (drug substance and drug product updates)	24-FEB-2004
BC (drug substance and drug product updates)	03-MAR-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Vicuron Pharmaceuticals Inc.
Address:	455 South Gulph Road King of Prussia, PA 19406
Representative:	Harriette L. Nadler, PhD Senior Director, Regulatory Affairs
Telephone:	610-491-2211

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: [redacted]™
b) Non-Proprietary Name (USAN): anidulafungin
c) Code Name/# (ONDC only): VER002; LY303366;
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Systemic antifungal

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 50 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note22]:

_____ SPOTS product – Form Completed

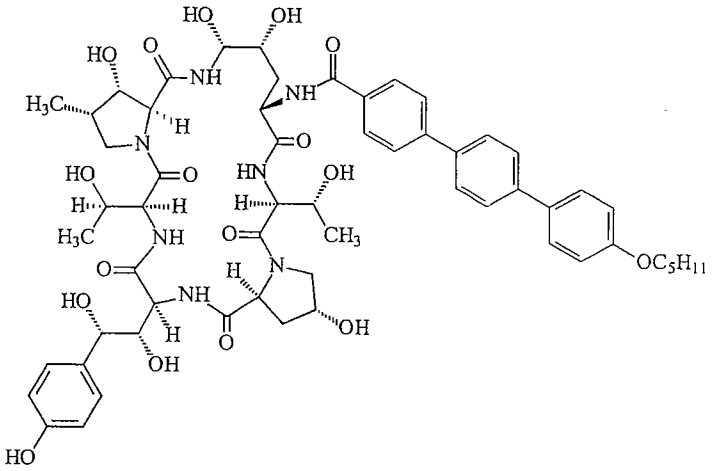
___X___ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Echinocandin B, 1-[(4R,5R)-4,5-dihydroxy-N^2-[[4"-(pentyloxy)[1,1',:4',1"-terphenyl]-4-yl]carbonyl]-L-ornithine]-

(4R,5R)-4,5-Dihydroxy-N^2-[[4"-(pentyloxy)-p-terphenyl-4-yl]carbonyl]-L-ornithyl-L-threonyl-*trans*-4-hydroxy-L-prolyl-(S)-4-hydroxy-(p-hydroxyphenyl)-L-threonyl-L-threonyl-(3S,4S)-3-hydroxy-4-methyl-L-proline cyclic (6→1)-peptide

Molecular formula: $C_{58}H_{73}N_7O_{17}$
Molecular weight: 1140.27
CAS: 166663-25-8



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	3, 4	Adequate	12-FEB-2003	-
[redacted]	III	[redacted]	[redacted]	3, 4	Adequate	06-AUG-2003	-

*The[redacted]

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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original IND application, amendments and reports	IND [ )	[ ]
Original IND application, amendments and reports	IND 54,597	IV anidulafungin
Memoranda of Telephone Conversations	N21-632	18-FEB-2004 01-MAR-2004

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Acceptable	25-JUL-2003	S. Ferguson, HFD-324
Pharm/Tox	n/a		
Biopharm	n/a		
LNC	n/a		
Methods Validation	To Be Determined		
DMETS	Trademark acceptable; other labeling recommendations conveyed to applicant	02-DEC-2003	C. Hoppes, HFD-420
EA	Categorical exclusion acceptable	16-MAY-2003	M. Seggel
Microbiology	Acceptable	25-FEB-2004	J. McVey, HFD-805

The Chemistry Review for NDA 21-632

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application as amended is recommended for approval from the chemistry, manufacturing and controls perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no recommendations for Phase 4 CMC commitments. The applicant will continue to monitor the stability of the drug substance and drug product. The applicant will also re-evaluate the drug substance and drug product specifications after the manufacture of ← commercial batches of each.

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Anidulafungin is a semisynthetic antifungal lipopeptide (cyclic hexapeptide with lipophilic acyl side chain) derived from echinocandin B (see Attachment 1 for the structure of echinocandin B and related compounds). It has activity against pathogenic fungi including *Candida* spp. The echinocandins, and structurally related pneumocandins, inhibit the enzyme β-1,3-D-glucan synthetase. β-(1,3)-D-Glucan, a

polymer of glucose, is an integral component of the fungal cell wall. The drug substance is insoluble in water and slightly soluble in ethanol. It has good chemical stability, but the recommended storage condition is [ ] The identity, strength, quality and purity of the drug substance as assured by appropriate stability-indicating tests.

B. Description of How the Drug Product is Intended to be Used

Anidulafungin for injection is indicated for the treatment of esophageal candidiasis. The intended dosing regimen is a 100-mg loading dose followed by a 50-mg daily maintenance dose for the duration of treatment. The lyophilized drug product requires two dilutions prior to infusion: dilution with the 20% (w/w) ethanol/water diluent and subsequent dilution with either 5% Dextrose Injection USP (D5W) or 0.9% Sodium Chloride Injection USP. The final concentration of the infusion solution is 0.5 mg/mL.

The stability studies support an expiration dating period of 30 months for product stored at 25°C/60% RH. The reconstituted solution is stable for up to [ ] while the infusion solution is stable for up to [ ]s. However, the reconstituted solution should be used within 24 hours of preparation to insure microbiological quality.

C. Basis for Approvability or Not-Approval Recommendation

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The manufacturing and testing facilities have acceptable cGMP status and the Office of Compliance has issued an Overall Recommendation of Acceptable for the NDA.

III. Administrative

A. Reviewer's Signature

{see Electronic Signature Page}

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

34 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

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/s/

Mark Seggel
5/3/04 12:54:20 PM
CHEMIST
N21-632

Norman Schmuff
5/4/04 06:13:04 AM
CHEMIST

NDA 21-632

Anidulafungin Infusion

Vicuron Pharmaceuticals Inc

Balajee Shanmugam
HFD-590
Division of Special Pathogens and Immunologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-632

2. REVIEW # 1 DS (drug substance, for drug product see Dr. Mark Seggel's review # 1 DP)

3. REVIEW DATE:

4. REVIEWER: Balajee Shanmugam

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	04-25-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Vicuron Pharmaceuticals

Address: 455 South Gulph Road, King of Prussia, PA 19406

Representative: Harriette L. Nadler, Ph.D.

Telephone: 610-491-2211

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN): Anidulafungin
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Infusion

12. STRENGTH/POTENCY: 50 mg

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

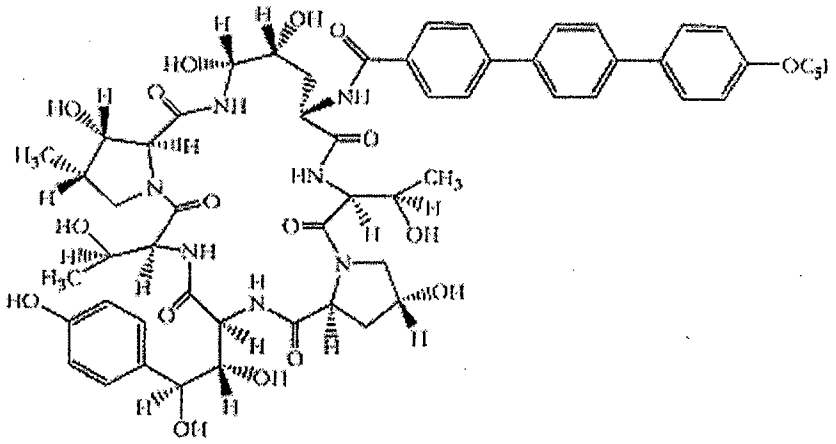
__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 1-[(4R,5R)-4,5-Dihydroxy-N(2)-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]carbonyl]-L-ornithine]echinocandin B

Executive Summary Section

Structure of Anidulafungin



Molecular Formula: $C_{58}H_{73}N_7O_{17}$

Molecular Weight:1140.3

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

For DP DMF's see review #1 DP.

[1] Action codes for DMF Table:
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7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Executive Summary Section

18. STATUS:

ONDC: See DP review # 1 DP

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES			
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology			

The Executive Summary

See Dr. Mark Seggel's review # 1 DP

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/s/

Balajee Shanmugam
4/28/04 04:24:03 PM
CHEMIST

Norman Schmuff
4/29/04 01:13:26 PM
CHEMIST