

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-629

CHEMISTRY REVIEW(S)



NDA 21-629

ApridaTM
[insulin glulisine (rDNA origin) injection]

Aventis, Inc.

CMC Review # 2

Xavier Ysern, PhD
HFD-510



Table of Contents

Table of Contents.....2

Chemistry Review Data Sheet3

The Executive Summary.....5

I. Recommendations5

 A. Recommendation and Conclusion on Approvability.....5

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....5

II. Summary of Chemistry Assessments5

 A. Description of the Drug Product(s) and Drug Substance(s).....5

 B. Description of How the Drug Product is Intended to be Used.....5

 C. Basis for Approvability or Not-Approval Recommendation.....5

III. Administrative5

 A. Reviewer's Signature.....5

 B. Endorsement Block.....5

 C. CC Block5

Chemistry Assessment

I. Review of Amendment dated 25-MAR-2004 (Applicant's response to the Information Request Letter).....6

Attached

Updated EER Summary Report dated 30-MAR-20049



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-629
2. REVIEW #: 2
3. REVIEW DATE: 30-MAR-2004
4. REVIEWER: Xavier Ysem, PhD

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 61,956 (HMR1964 Aventis Pharmaceuticals Inc.)	02-MAY-2001

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	18-JUN-2003
	10-SEP-2003
	14-JAN-2004
	25-MAR-2004
	26-MAR-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Aventis Pharmaceutical Inc.
Address: 200 Crossing Boulevard
P.O. Box 6890
Bridgewater, NJ 08807-0890
Representative: Steve Caffe, MD
Telephone: 908 304-7000

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Aprida
b) Non-Proprietary Name: Insulin glulisine (rDNA origin) injection
c) Code Name: HMR 1964
d) Chem. Type/Submission Priority:
- Chem. Type: 1 (New Molecular Entity)
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Protein Hormone. Treatment of diabetes mellitus.
11. DOSAGE FORM: Solution for Injection 10 mL Vial
12. STRENGTH/POTENCY: 100 I.U./mL
13. ROUTE OF ADMINISTRATION: Subcutaneous injection
14. Rx/OTC DISPENSED: Rx



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be approved.

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

The applicant has agreed to perform a study of the antimicrobial effectiveness at the observed lowest m-cresol concentration ~~observed~~ at the needle end of the catheter tubing during the pump studies. As stated by the applicant in amendment dated 25-MAR-2004, the results of the study will be submitted to the Agency within a year.

of the m-cresol formulation

II. Summary of Chemistry Assessments

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

See CMC Review # 1.

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

See CMC Review # 1.

C. Basis for Approvability or Not-Approval Recommendation

This application can be approved from a CMC viewpoint. The amendments dated March 25 and 26, 2004, adequately addressed the Agency Information Request letter (see CMC Review # 1). An acceptable recommendation was given by the Office of Compliance for the two remaining contract testing facilities (EER Summary Report dated March 30, 2004, is attached).

III. Administrative

A. Reviewer's Signature

See electronic signature page.

B. Endorsement Block

Chemist Name/Date:
Chemistry Team Leader Name/Date
Project Manager Name/Date

Xavier Ysern, PhD/30-MAR-2004
Stephen Moore, PhD/Date
Julie Rhee/Date

C. CC Block

Eric Duffy, PhD HFD-820
Blair Fraser, PhD HFD-820

3 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

(b4)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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Page 1 of 2

30-MAR-2004

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21629/000 Sponsor: AVENTIS PHARMA
 Org Code : 510 BOX 800202
 Priority : 1S CHARLOTTESVILLE, VA 229080202

Stamp Date : 18-JUN-2003 Brand Name : APIDRA
 PDUFA Date : 18-APR-2004 Estab. Name:
 Action Goal : Generic Name: INSULIN GLULISINE
 District Goal: 18-FEB-2004 Dosage Form: (FOR INJECTION)
 Strength : 3.49 MG/ML (100 IU/ML)

FDA Contacts: H. RHEE Project Manager (HFD-510) 301-827-6424
 X. YSERN Review Chemist (HFD-510) 301-827-6420
 S. MOORE Team Leader (HFD-510) 301-827-6401

 Overall Recommendation: ACCEPTABLE on 30-MAR-2004 by S. ADAMS (HFD-322) 301-827-9051

Establishment : CPN : 9610129 FEI : 3002807197
 AVENTIS BEHRING GMBH
 FRANKFURT AM MAIN, , GM

DMP No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Profile : SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-OCT-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9610806 FEI : 3000222873
AVENTIS BEHRING GMBH
EMIL VON BEHRINGSTRASSE 76
MARBURG, , GM

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 09-DEC-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :



CHEMISTRY REVIEW



Chemistry Review Data Sheet

30-MAR-2004

FDA CDER EES

Page 2 of 2

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

DMF No: AADA:

Responsibilities: _____

Profile : CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 30-MAR-04
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

 Establishment : CPN : FBI :

DMF No: AADA:

Responsibilities: _____

Profile : CTL OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 30-MAR-04
 Decision : ACCEPTABLE
 Reason : DISTRICT RECOMMENDATION

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Xavier Ysern
3/30/04 05:15:24 PM
CHEMIST

Stephen Moore
3/30/04 05:21:33 PM
CHEMIST



NDA 21-629

ApridaTM
[insulin glulisine (rDNA origin) injection]

Aventis, Inc.

Xavier Ysern, PhD
HFD-510



Table of Contents

Table of Contents.....2

Chemistry Review Data Sheet3

The Executive Summary5

I. Recommendations5

 A. Recommendation and Conclusion on Approvability.....5

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....5

II. Summary of Chemistry Assessments5

 A. Description of the Drug Product(s) and Drug Substance(s).....5

 B. Description of How the Drug Product is Intended to be Used.....8

 C. Basis for Approvability or Not-Approval Recommendation9

III. Administrative9

 A. Reviewer’s Signature.....9

 B. Endorsement Block.....9

 C. CC Block9

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....10

 S DRUG SUBSTANCE Insulin Glulisine.....12

 P DRUG PRODUCT Insulin Glulisine Solution for Injection.....67

 A APPENDICES.....107

 R REGIONAL INFORMATION.....111

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1115

 A. Labeling & Package Insert.....115

 B. Environmental Assessment Or Claim Of Categorical Exclusion.....114

 C. Establishment Inspections.....114

III. List Of Deficiencies To Be Communicated.....117



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Chemistry Review Data Sheet

- 1. NDA 21-629
- 2. REVIEW #: 1
- 3. REVIEW DATE: 06-FEB-2003
- 4. REVIEWER: Xavier Ysem, PhD
- 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 61,956 (HMR1964 Aventis Pharmaceuticals Inc.)	02-MAY-2001

- 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	18-JUN-2003
	10-SEP-2003
	14-JAN-2004

- 7. NAME & ADDRESS OF APPLICANT:

Name: Aventis Pharmaceutical Inc.
 Address: 200 Crossing Boulevard
 P.O. Box 6890
 Bridgewater, NJ 08807-0890
 Representative: Steve Caffè, MD
 Telephone: 908 304-7000

- 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Aprida
- b) Non-Proprietary Name: Insulin glulisine (rDNA origin) injection
- c) Code Name: HMR 1964
- d) Chem. Type/Submission Priority:
 - Chem. Type: 1 (New Molecular Entity)
 - Submission Priority: Standard

- 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
- 10. PHARMACOL. CATEGORY: Protein Hormone. Treatment of diabetes mellitus.
- 11. DOSAGE FORM: Solution for Injection 10 mL Vial
- 12. STRENGTH/POTENCY: 100 I.U./mL
- 13. ROUTE OF ADMINISTRATION: Subcutaneous injection
- 14. Rx/OTC DISPENSED: Rx
- 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed



CHEMISTRY REVIEW



Executive Summary Section The Chemistry Review for NDA 21-629

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is APPROVABLE pending (1) submission of additional CMC information described in List of Deficiencies; and (2) Satisfactory cGMP inspection of facilities used to manufacture the drug substance and the drug product.

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

Not Applicable

II. Summary of Chemistry Assessments

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

Drug Substance

The drug substance, insulin glulisine (codename HMR1964), is a rapid-acting insulin analog developed by Aventis Pharma that differs from human insulin by two amino acids. Asparagine and lysine at positions 3 and 29 of the B-chain of human insulin have been substituted by lysine and glutamic acid, respectively, in insulin glulisine.

The drug substance is produced by recombinant DNA technology using the bacterial strain *E. coli* carrying the expression The production strain is *E. coli* K12.

[Redacted section with four horizontal lines]

The rapid-acting property of insulin glulisine relative to human insulin is due to both destabilization of the hexamer and stabilization of the monomer as a result of the amino acid substitutions. Hexameric insulin itself exists as trimer of dimers. According to structural evidence (3D structure by X-ray diffraction) the 3B-Lys from three dimers of insulin glulisine point to the trigonal axes of the hexamer thereby increasing the electrostatic repulsion between dimers which in turn may lead to the destabilization of the hexamer. The newly introduced 29B-Glu forms a salt bridge with the N-terminus of the corresponding A chain and thus increases the monomer stabilization compared to human [native] insulin. In solution, Insulin and Insulin analogs, are found as an equilibrium between monomeric, dimeric and hexameric forms. As monomeric insulin is the biologically active form, stabilizing the monomer and destabilizing the hexamer, both effects contribute to the glulisine insulin analog rapid-acting properties when compared to native insulin.

The structure of insulin glulisine was determined using the insulin glulisine primary reference standard, batch no. by well established analytical techniques. Results obtained using Mass spectrometry,



CHEMISTRY REVIEW



Executive Summary Section

— spectrometry, Infrared absorption spectrophotometry (IR) and Ultraviolet absorption spectrophotometry (UV) are consistent with the proposed structure. Insulin glulisine primary structure (amino acid sequence) was determined

Manufacture of the drug substance is described as a — step process: _____

Stability studies (six production scale batches and data from early development batches) have shown that no relevant changes are found after _____

_____ made from the same material as is used for storage of the drug substance or packaged in injection vials with injection stoppers and _____

condition). Due to the photosensitivity observed, the drug substance must be protected from light. Under stressed conditions (25 °C), in addition to an increase in the high molecular weight proteins (HMWP), a major degradation product _____ was identified. It is well documented for all kind of insulins that HMWP increase when subjected to higher temperatures than recommended. Also, the _____ like impurity is the major degradation product reported for all insulins. The stability data supports the storage of the drug substance for 24 month at the recommended storage temperature, -20 °C.



CHEMISTRY REVIEW



Executive Summary Section

Drug substance specifications have conventional insulin acceptance criteria. However, two tests (_____) intended by the applicant to be discontinued are requested to be kept as part of the drug substance specifications. The _____ is still required by USP for human insulin. The _____ test is requested because the _____ used in insulin glulisine differs from the human (see fusion protein description) therefore may be immunogenic. Routine testing should be performed to insure that _____ insulin glulisine remains at levels below the limit of detection.

Drug Product

Insulin glulisine drug product, APRIDA™ (insulin glulisine [rDNA origin] injection), is an aqueous, sterile, buffered, clear solution for injection. It contains 3.49 mg of insulin glulisine per milliliter, equimolar to 100 international units of insulin per milliliter. The drug product, insulin glulisine solution for injection, will be supplied in 10 mL vials. The excipients of insulin glulisine for injection, metacresol (*m*-cresol), tromethamine, sodium chloride, polysorbate 20, sodium hydroxide, hydrochloric acid and water for injection, all meet compendial requirements. For the manufacture of the drug product, no excipients of human or animal origin are used. Therefore, no contamination risk can be expected with regard to transmissible spongiform encephalopathy (TSE) or other adventitious agents from excipients. Pharmacopeial requirements on injectable insulin preparations were taken into account for the selection of these components. Metacresol is the antimicrobial preservative. Tromethamine is the buffering agent, using sodium hydroxide and hydrochloric acid as alkalizing and acidifying agents, respectively, the pH of the drug product is adjusted to 7.3, where at this physiological condition, buffering capacity and insulin glulisine solubility are assured. Sodium chloride, added to adjust the osmolarity of the solution, is the tonicity agent. Polysorbate 20, a stability agent, supports the use of the drug product in the continuous insulin pump therapy for insulin glulisine taking into account the accelerated mechanical stress that the solution for injection is exposed to in insulin pumps.

_____ The qualitative and quantitative composition of the batches used in later phase I and in phase III studies represents the final formulation intended for commercialization. The main formulation changes during development are as follows:

Executive Summary Section

[Redacted text]

The solution for injection is filled into 10 mL vials made of colorless tubular glass complying with all pertinent Ph. Eur., USP and JP requirements for Type I glass containers ("Glass Containers for Pharmaceutical Use"- Ph. Eur. Chapter 3.2.1, "Containers" - USP <661> and "Test for Glass Containers for Injections" - JP Chapter 57). The vials are closed with a _____ is the only closure component having a direct contact with the drug product. [Redacted]

[Redacted]

addition to the long term and accelerated stability studies previously mentioned, in-use and adverse shipping stability studies showed the adequacy of the container-closure packaging to assure the quality of the product. The provided stability data fully supports the requested 24 months shelf-life for the product at the recommended storage condition of 5 °C. When stored at 25 °C, in-use condition, the shelf-life is 1 month for vials.

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

Aprida™ is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. Aprida, like other insulins, is thus intended as life-saving drug for a chronic disease. The time-concentration and time-action profiles of glulisine, which show a more rapid onset, earlier peak effect in lowering blood glucose levels, and a shorter duration of action than the short-acting insulin preparation regular human insulin, characterize it as a member of the rapid-acting insulin subfamily of short-acting insulin preparations¹.

The dosage of Aprida, as any insulin or insulin analog drug product, is individualized and determined based on physician consultation. The product is intended for subcutaneous administration (abdominal wall, the thigh or the deltoid). Aprida should be given within 15 minutes before or immediately after a meal, and normally used with regimens that include a longer-acting insulin or basal insulin analog. As for all insulins, because the rate of absorption, and consequently the onset and duration of action, may be affected by injection site, exercise and other variables, blood glucose should be monitored.

¹ Aprida is the third rapid-acting insulin analog [NDA] submitted to the Agency, the two other rapid-acting insulin analog NDA submissions, Humalog (Lilly, insulin lispro; NDA 20563) and NovoLog (Novo Nordisk, insulin aspart; NDA 20986) were approved on 14-JUN-1996 and 07-JUN-2000, respectively.



CHEMISTRY REVIEW



Executive Summary Section

Aprida is also recommended for use in programmable external infusion pumps for subcutaneous administration. Aprida from the vial is loaded into the reservoir of the pump infusion set. Infusion sets consist of a reservoir, tubing, catheter and needle. A list of the specific pumps and infusion sets recommended for use with Aprida is given in the Patient Package Insert. The results of the studies to support the compatibility of the pumps and infusion sets with Aprida are provided.

The drug product, Aprida 100 units per mL (U-100) is supplied in 10 mL vials. Unopened Aprida vials should be stored in a refrigerator, 2 °C – 8 °C (36 °C – 46 °F), protected from light. It should not be stored in the freezer and it should not be allowed to freeze. Opened vials (in use), whether or not refrigerated, must be used within 28 days. If during the in use condition refrigeration is not possible, the open vial in use can be kept unrefrigerated for up to 28 days away from direct light, as long as the temperature does not exceed 25 °C (77 °F). When using Aprida in external infusion pumps, the reservoir/cartridge and infusion sets should be discarded after 48 hours of use or after exposure to temperatures that exceed 37 °C (98.6 °F).

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable from a CMC viewpoint. This recommendation is based upon several issues identified in this review. Several minor issues have also been identified. The applicant is requested to incorporate both immunogenicity testing as part of the drug substance specifications. Those two tests, adequately described in the application, were used in the characterization studies of the drug substance. Also, the preservative effectiveness for the observed decrease in the level of *m*-cresol at the needle end of the catheter tubing of the insulin pump should be demonstrated. A final recommendation by the Office of Compliance, regarding two contract testing facilities is still pending.

III. Administrative

A. Reviewer's Signature

See electronic signature page.

B. Endorsement Block

Chemist Name/Date:	Xavier Ysern, PhD/06-FEB-2004
Chemistry Team Leader Name/Date	Stephen Moore, PhD/Date
Project Manager Name/Date	Julie Rhee/Date

C. CC Block

Nasr Moheb, PhD	HFD-800
Eric Duffy, PhD	HFD-820
Duu-Gong Wu, PhD	HFD-820

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(b4)



CHEMISTRY REVIEW



Establishment : CPN : 9610806 FBI : 3000222873

AVENTIS BEHRING GMBH

EMIL VON BEHRINGSTRASSE 76

MARBURG, , GM

DMP No:

AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-DEC-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CPN : FBI :



CHEMISTRY REVIEW



06-FEB-2004

FDA CDER RES

Page 2 of 2

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

DMF No:

AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
 Last Milestone: ASSIGNED INSPECTION TO IB
 Milestone Date: 06-AUG-03

 Establishment : CPN : FEI :

DMF No:

AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
 Last Milestone: ASSIGNED INSPECTION TO IB
 Milestone Date: 06-AUG-03

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Xavier Ysern
3/19/04 07:00:52 PM
CHEMIST

Stephen Moore
3/19/04 07:14:05 PM
CHEMIST



Aventis Pharmaceuticals, Inc.
200 Crossing Blvd., P.O.Box 6890
Bridgewater, NJ 08807-0890

Environmental Assessment or Request for Categorical Exclusion

The Approval of the HMR 1964 NDA will increase the use of the active moiety. However, five year drug substance production estimate for HMR 1964 for all dosage forms and strengths included in this application is low and the use is assumed to be evenly distributed throughout the U.S. Therefore, the Expected Introduction Concentration (EIC) at the point of entry into the aquatic environment in any of the next five years of production is markedly lower than 1ppb. The approval therefore complies with the categorical exclusion criteria (21 CFR 25.31(b)).

Based on the information provided in the Guidance for Industry: Environmental Assessment for the Drugs and Biologics Application, July 1998, no calculation is provided to support the above claim. Following is the part of the above reference Guidance that indicates no calculation is required:

"An applicant need not provide data to demonstrate that the action qualifies for categorical exclusion. CDER and CBER can rely on other information in an application to evaluate the appropriateness of a claim for categorical exclusion."

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application: NDA 21629/000 Action Goal:
 Stamp: 18-JUN-2003 District Goal: 18-FEB-2004
 Regulatory Due: 18-APR-2004 Brand Name: APIDRA
 Applicant: AVENTIS PHARMA Estab. Name:
 NO CITY, , XX Generic Name: INSULIN GLULISINE
 1S
 Priority: 510 Dosage Form: (FOR INJECTION)
 Org Code: Strength: 3.49 MG/ML (100 IU/ML)

Application Comment: PLEASE LET KNOW THE REVIEWER (XAVIER YSERN) WHEN THE INSPECTION
 WOULD TAKE PLACE, TO GO WITH THE INSPECTOR. LET ME KNOW IN ADVANCE
 TO PLAN (on 04-AUG-2003 by X. YSERN (HFD-510) 301-827-6420)

FDA Contacts: H. RHEE (HFD-510) 301-827-6424 , Project Manager
 X. YSERN (HFD-510) 301-827-6420 , Review Chemist
 S. MOORE (HFD-510) 301-827-6401 , Team Leader

Overall Recommendation: ACCEPTABLE on 30-MAR-2004 by S. ADAMS (HFD-322) 301-827-9051

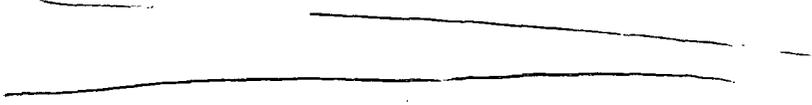
Establishment: CFN 9610129 FEI 3002807197
 AVENTIS BEHRING GMBH
 FRANKFURT AM MAIN, , GM

MF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Profile: SVS OAI Status: NONE

Instab. Comment:



Event Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	04-AUG-2003				YSERNX
SUBMITTED TO OC	04-AUG-2003				YSERNX
SUBMITTED TO DO	04-AUG-2003	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	06-AUG-2003	PS			DAMBROGIOJ
INSPECTION PERFORMED	22-SEP-2003		22-SEP-2003		ADAMSS
INSPECTION SCHEDULED	15-OCT-2003		22-SEP-2003		ADAMSS
DO RECOMMENDATION	15-OCT-2003			ACCEPTABLE INSPECTION	ADAMSS
AWAITING EIR. BASED ON REVIEW OF FIRM'S RESPONSE.					
OC RECOMMENDATION	15-OCT-2003			ACCEPTABLE	DAMBROGIOJ

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

APPEARS THIS WAY
ON ORIGINAL

DISTRICT RECOMMENDATION

Establishment: CFN 9610806 FEI 3000222873
AVENTIS BEHRING GMBH
EMIL VON BEHRINGSTRABE 76
MARBURG, , GM

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Pa e: CTL OAI Status: NONE

Estab. Comment: THE CURRENT NAME OF THE FACILITY IS AVENTIS PHARMA DEUTSCHLAND GMBH,
PROTOX MARBURG (EMIL VON BEHRINGSTRABE 76/ 35041 MARBURG/ GERMANY).
THIS FACILITY WILL TEST FOR BIOACTIVITY OF THE DS. (on 04-AUG-2003 by
X. YSERN (HFD-510) 301-827-6420)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	04-AUG-2003				YSERNX
SUBMITTED TO OC	04-AUG-2003				YSERNX
SUBMITTED TO DO	04-AUG-2003	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	06-AUG-2003	GMP			DAMBROGIOJ
INSPECTION PERFORMED	31-OCT-2003		31-OCT-2003		ADAMSS
INSPECTION PERFORMED	31-OCT-2003		31-OCT-2003		JGIEFER

AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED
firm produces plasma products, licensed biologics and pharmaceuticals. The current
inspection covered the production of _____

The current inspection focused on the production activities that are being transferred
from the currently approved site to the proposed site. These activities include the

~~_____~~
~~_____~~
~~_____~~
~~_____~~

No samples were collected during the current inspection.

INSPECTION SCHEDULED	31-OCT-2003	31-OCT-2003	ADAMSS
DO RECOMMENDATION	31-OCT-2003	ACCEPTABLE	ADAMSS
		INSPECTION	

BASED ON REVIEW OF 483 AND INVESTIGATOR'S RECOMMENDATION. AWAITING EIR AND FIRM'S RESPONSE.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

**APPEARS THIS WAY
ON ORIGINAL**

OC RECOMMENDATION	31-OCT-2003	ACCEPTABLE	ADAMSS
		DISTRICT RECOMMENDATION	
DO RECOMMENDATION	09-DEC-2003	ACCEPTABLE	ADAMSS
		INSPECTION	
OC RECOMMENDATION	09-DEC-2003	ACCEPTABLE	ADAMSS
		DISTRICT RECOMMENDATION	

Establishment: CFN FEI

DMF No: AADA:

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment:

FACILITY (on 04-AUG-2003 by X. YSERN (HFD-510)
301-827-6420)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	04-AUG-2003				YSERNX
SUBMITTED TO OC	04-AUG-2003				YSERNX
SUBMITTED TO DO	04-AUG-2003	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	06-AUG-2003	GMP			DAMBROGIOJ
INSPECTION SCHEDULED	18-MAR-2004		19-MAR-2004		IRIVERA
CTION PERFORMED	19-MAR-2004		19-MAR-2004		ADAMSS
DO RECOMMENDATION	30-MAR-2004			ACCEPTABLE	ADAMSS
				INSPECTION	
BASED ON REVIEW OF 483. AWAITING FIRM'S RESPONSE AND EIR.					
OC RECOMMENDATION	30-MAR-2004			ACCEPTABLE	ADAMSS

DISTRICT RECOMMENDATION

3. Assignment: CFN

FBI

DMF No:

AADA:

Responsibilities:

Profile:

CTL

OAI Status: NONE

Estab. Comment:

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

(on 04-AUG-2003 by X. YSERN (HFD-510) 301-827-6420)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	04-AUG-2003				YSERNX
SUBMITTED TO DO	04-AUG-2003	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	06-AUG-2003	GMP			DAMBROGIOJ
INSPECTION PERFORMED	16-MAR-2004		16-MAR-2004		ADAMSS
INSPECTION SCHEDULED	18-MAR-2004		16-MAR-2004		IRIVERA
DO RECOMMENDATION	30-MAR-2004			ACCEPTABLE INSPECTION	ADAMSS
BASED ON REVIEW OF 483. AWAITING EIR AND FIRM'S RESPONSE.					
OC RECOMMENDATION	30-MAR-2004			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS