APPLICATION NUMBER:
21-629

CHEMISTRY REVIEW(S)
NDA 21-629

Aprida™
[insulin glulisine (rDNA origin) injection]

Aventis, Inc.

CMC Review # 2

Xavier Ysern, PhD
HFD-510
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Chemistry Assessment

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Attached

Updated EER Summary Report dated 30-MAR-2004 .........................................................................................9
1. NDA: 21-629

2. REVIEW #: 2

3. REVIEW DATE: 30-MAR-2004

4. REVIEWER: Xavier Ysern, PhD

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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)


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

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

3B-Lys-29B-Glu-human insulin

\[ \text{C}_{258}\text{H}_{384}\text{N}_{16}\text{O}_{78}\text{S}_{6} \quad \text{MW} = 5823 \text{ Da.} \]

17. RELATED/SUPPORTING DOCUMENTS:

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(*) Supportive information. The applicant does not seek approval of the glass cartridge presentation.

1 Action codes for DMF Table:
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3 – Reviewed previously and no revision since last review
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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)

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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 p-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.

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: Xavier Ysem, PhD/30-MAR-2004
Chemistry Team Leader Name/Date: Stephen Moore, PhD/Date
Project Manager Name/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.

(C64)
## ESTABLISHMENT EVALUATION REQUEST

### SUMMARY REPORT

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### 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 (HPD-322) 301-827-9051

---

**Establishment:** CPN: 9610129 FRI: 3002807197

AVENTIS BEHRING GMBH
FRANKFURT AM MAIN, GM

**DMF No:**

**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

**Last Milestone**: OC RECOMMENDATION

**Milestone Date**: 15-OCT-03

**Decision**: ACCEPTABLE

**Reason**: DISTRICT RECOMMENDATION

---

**Establishment**: CPN : 9610806  
FEI : 300022873

AVENTIS BERING GMBH

EMIL VON BERINGSTRASE 76

MARBURG, GE

**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**: CPN :  
**FEI**:  

---

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CHEMISTRY REVIEW
Chemistry Review Data Sheet

30-MAR-2004

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: CPM: PSI:

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

Aprida™
[insulin glulisine (rDNA origin) injection]

Aventis, Inc.

Xavier Ysern, PhD
HFD-510
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CHEMISTRY REVIEW

Chemistry Review Data Sheet

1. NDA 21-629
2. REVIEW #: 1
3. REVIEW DATE: 06-FEB-2003
4. REVIEWER: Xavier Ysern, PhD
5. PREVIOUS DOCUMENTS:
   
   Previous Documents Document Date
   IND 61,956 (HMR1964 Aventis Pharmaceuticals Inc.) 02-MAY-2001
   
6. SUBMISSION(S) BEING REVIEWED:
   
   Submission(s) Reviewed Document Date
   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 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: 1 (New Molecular Entity)
      Chem. Type:
      Submission Priority: Standard
   
9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
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
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3B-Lys-29B-Glu-human insulin

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\[
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C_{25}H_{38}N_{10}O_{20}S_{6} & MW = 5823 Da. \\
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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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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)

B. Other Documents:

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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.

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,
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 production 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.
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 (—) test 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, APRIDATM (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:
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. 

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 preparations.¹

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.
EXECUTIVE SUMMARY

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

(b4)
**Establishment Evaluation Request**

**Summary Report**

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**FDA Contacts:**
- H. Khee: Project Manager (HFD-510) 301-827-6424
- E. Yerem: Review Chemist (HFD-510) 301-827-6420
- S. Moore: Team Leader (HFD-510) 301-827-6401

---

**Overall Recommendation:**

Establishment: CVN: 9610129

FBI: 3001807157

AVENTIS REHNING GMBH
FRANKFURT AM MAIN, GE

**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

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 15-OCT-03

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION
Establishment: CFH: 9610906  FHE: 3000222873

AVENTIS BERING GMBH

EMIL VON BERINGSTRASSE 76
MARBURG, GE

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
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
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
Stamp: 18-JUN-2003
Regulatory Due: 18-APR-2004
Applicant: AVENTIS PHARMA
NO CITY, , XX
IS
Priority: 510
Org Code: 

Action Goal: 18-FEB-2004
District Goal: 
Brand Name: APIDRA
Estab. Name: 
Generic Name: INSULIN GLULISINE
Dosage Form: (FOR INJECTION)
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: 
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

RoFile: SVS 
OAI Status: NONE

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APPEARS THIS WAY ON ORIGINAL

DISTRICT RECOMMENDATION

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

MF No: AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER

M Milestone Name Date Type Insp. Date Decision & Reason Creator
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SUBMITTED TO OC 04-AUG-2003
SUBMITTED TO DO 04-AUG-2003 GMP
ASSIGNED INSPECTION T 06-AUG-2003 GMP
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.
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3. Issuance: CFN FEI

MF No: AADA:
Responsibilities:

Profile: CTL OAI Status: NONE

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

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