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Julie Rhee  
10/17/03 09:25:08 AM

# REQUEST FOR CONSULTATION

(Division/Office): Dr. Douglas Throckmorton, DCRDP, HFD-110

FROM: Julie Rhee, DMEDP, HFD-510

DATE October 6, 2003	IND NO.	NDA NO. 21-629	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT June 18, 2003
NAME OF DRUG Apidra (insulin glulisine [rDNA origin])		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE December 12, 2003

NAME OF FIRM: Aventis

## REASON FOR REQUEST

### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

### III. BIOPHARMACEUTICS

- |   |   |
|---|---|
| DISSOLUTION                               | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| BIOAVAILABILITY STUDIES                   | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

### V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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#### COMMENTS/SPECIAL INSTRUCTIONS:

Please see the attached e-mail request from Dr. Joanna Zawadzki. As Dr. Zawadzki has indicated in her e-mail, the submission is available thru EDR.

Thank you.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

**Rhee, H Julie**

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**From:** Zawadzki, Joanna K  
**Sent:** Friday, October 03, 2003 11:32 AM  
**To:** Rhee, H Julie  
**Cc:** Zawadzki, Joanna K  
**Subject:** FW: NDA 21629 insulin glulisine



N21629  
ology Consult Re

### Cardiology Consult Request

This consult is directed to the attention of Dr. Shari Targum (4-5377), with whom it was previously briefly discussed.

### BACKGROUND:

NDA 21,629 for Apidra (insulin glulisine), submitted by Aventis Pharmaceuticals on June 18, 2003, is the third submission for a rapid-acting insulin analog. The two other rapid-acting insulin analog NDA submissions, Humalog (Lilly, lispro; NDA 20563) and NovoLog (Novo Nordisk, aspart; NDA 20986) were approved on 6/14/96 and 6/7/00, respectively.

The NDA submission consists of data from four Phase 3 open-label, multinational, randomized, controlled, parallel-group studies. Three studies were completed in patients with Type 1 diabetes mellitus, and one study was completed in patients with Type 2 diabetes mellitus. There are two 26-week studies: Study 3001 in adults with Type 1 diabetes mellitus (comparing glulisine and lispro) and Study 3002 in adults with Type 2 diabetes mellitus (comparing glulisine and regular insulin). Two smaller studies in adults with Type 1 diabetes mellitus are also submitted: Study 3004, a 12-week study in adults with Type 1 diabetes mellitus, (comparing pre- and post-meal injection of glulisine to pre-meal injection of regular insulin), and Study 3006, a small 12-week pump study (comparing glulisine and aspart). The data from Study 3005, the second 26-week study in adults with Type 2 diabetes mellitus (also comparing glulisine and regular insulin), and the two extension studies (Studies 3011 and 3012) were not included in the NDA submission and are to be submitted with an Integrated Summary of Safety with the 120-day safety update.

In the 26-week Type 1 diabetes mellitus study (Study 3001), there is a 9-fold increase in treatment-emergent cardiac disorders (i.e., 9/339 [2.7%] glulisine-treated patients versus 1/333 [0.3%] in the lispro-treated patients). A 2-fold increase in cardiac events in Type 1 patients (5/582 [0.9%] glulisine-treated patients versus 1/278 [0.4%] regular insulin treated patients). No increase in the number of cardiac events is noted in the 26-week study in Type 2 diabetes mellitus, and the second 26-week study in Type 2 diabetes mellitus should be submitted shortly.

The NDA has been submitted electronically, with the network path \\CDSESUB1\N21629\N\_000\2003-06-18. We originally were unable to open the electronic document using Acrobat 5.0, as Acrobat 4.0 is needed to open the document.

### Consult Question

Are the observed emergent cardiac events in the Type I diabetes mellitus patients treated with glulisine in NDA 21,629 related to treatment with the drug?

Consult completion requested 12/15/03.

Joanna K. Zawadzki, MD 7-6403 OND/ODEII/DMEDP

Sorry - the consult form is now attached.

-----Original Message-----

**From:** Zawadzki, Joanna K  
**Sent:** Friday, October 03, 2003 11:31 AM  
**To:** Rhee, H Julie  
**Cc:** Zawadzki, Joanna K  
**Subject:** NDA 21629 insulin glulisine

Julie,

(1) Attached is the cardiology consult request. It is fairly long and may need to be appended to the consult request form.

(2) When I open the NDA in the EDR, there is a button labeled pdfhelp.pdf. It does not open. Does it open on your computer?

Thank you.

Joanna

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/s/

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David Orloff  
10/8/03 06:29:30 PM



September 10, 2003

Dr. David Orloff  
Director, Division of Metabolic and Endocrine Drug Products (HFD-510)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Central Document Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

**NDA 21-629: APIDRA™  
HMR 1964 – Insulin glulisine (rDNA human insulin analog)  
Clarification responses to CMC reviewer questions  
regarding APIDRA™ NDA submission**

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003. On July 29, 2003, CMC Reviewer Dr. Xavier Ysern contacted Aventis Pharmaceuticals, Inc. and requested clarification of the names and addresses of two testing facilities identified in the APIDRA™ NDA. In addition, Dr. Ysern requested clarification regarding \_\_\_\_\_ of the APIDRA™ NDA submission. On July 30, 2003, Dr. Ysern received a follow-up call from Odile Ernoux (Director, Regulatory Affairs), Chanda Moseley (Regulatory Affairs), and Gary Ruezinsky (Regulatory CMC). During this time, clarification was given to address Dr. Ysern's questions.

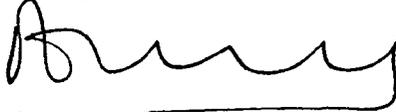
The purpose of this September 10, 2003 correspondence is to *officially* submit responses to the clarification requests of Dr. Ysern. Responses to the questions regarding the testing facilities and \_\_\_\_\_ have been provided electronically on the enclosed CD and can be found within the CMC "*substan*" and "*product*" folders, respectively. Aventis certifies that all electronic media have been scanned and found to be free of any known computer viruses (Symantec Norton Anti-Virus, Version 7.50.846, current 50903s 9/3/2003, Scan Engine 4.1.0.6.).

We consider the filing of the original New Drug Application for APIDRA™ to be a confidential matter, and request that the Food and Drug Administration make neither its

content, nor any future communications in regard to it, public without first obtaining the written permission of Aventis Pharmaceuticals, Inc.

Aventis Pharmaceuticals, Inc. looks forward to working with the Division to facilitate the review of the APIDRA™ NDA. Should you have any questions regarding this material, please contact the undersigned by telephone at (908) 231-3536 or by fax at (908) 304-6318 or, in my absence, please contact Steve Caffè, M.D. by telephone at (908) 231-5863.

Sincerely,

A handwritten signature in black ink, appearing to read 'Odile ERNOUX', written over a horizontal line.

~~Odile ERNOUX~~, M.D.  
Director, Regulatory Affairs  
Aventis Pharmaceuticals, Inc.  
Phone: (908)-231-3536  
Fax: (908)-304-6318

enclosure: 1

# REQUEST FOR CONSULTATION

(Division/Office): Lahn Green, OPSS/DDRE, HFD-440

FROM: Julie Rhee, DMEDP, HFD-510

Mail: ODS (Room 15B-08, PKLN Bldg.)

DATE September 4, 2003	IND NO.	NDA NO. 21-629	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT June 18, 2003
NAME OF DRUG Apidra (insulin glulisine [rDNA origin])		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE February 27, 2003

NAME OF FIRM: Aventis Pharmaceutical, Inc.

## REASON FOR REQUEST

### I. GENERAL

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| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

### III. BIOPHARMACEUTICS

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|--|---|
| DISSOLUTION                                      | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

### V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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#### COMMENTS/SPECIAL INSTRUCTIONS:

This is an NME application for rapid-acting insulin from Aventis. This is CTD NDA--the entire NDA is submitted electronically and is available thru EDR. Please review risk management aspect of the NDA. Dr. Joanna Zawadzki (7-6403) is the medical officer assigned to this NDA. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

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Julie Rhee  
9/4/03 03:38:45 PM

## **DSI CONSULT: Request for Clinical Inspections**

**Date:** August 15, 2003

**To:** Joanne Rhoads, M.D.  
Director  
Division of Scientific Investigations, HFD-45

**From:** Julie Rhee, Regulatory Project Manager, HFD-510

**Subject:** **Request for Clinical Inspections**  
NDA 21-629 Apidra™ (insulin glulisine [rDNA origin])  
Aventis Pharmaceuticals Inc.

### **Protocol/Site Identification:**

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

<b>Indication</b>	<b>Protocol #</b>	<b>Site (Name and Address)</b>	<b>Number of Subjects</b>
Treatment of adult patients with diabetes mellitus	Study 3002	DSI may select site(s)	
Treatment of adult patients with diabetes mellitus	Study 3004	DSI may select site(s)	

**Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.**

Contact person at Aventis Pharmaceuticals is Odile Ernoux, M.D., Director, Regulatory Affairs, at (908) 231-3536.

### **Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) January 30, 2004. We intend to issue an action letter on this application by (action goal date) on or before April 18, 2004.

Should you require any additional information, please contact Julie Rhee at 827-6424.

Concurrence: (if necessary)

David Orloff, M.D., Acting Medical Team Leader  
Joanna Zawadzki, M.D., Medical Reviewer

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/s/

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Mary Parks  
8/15/03 10:53:24 AM  
for Dr. Orloff



**FILING REVIEW LETTER**

NDA 21-629

8/11/03

Aventis Pharmaceutical Inc.  
Attention: Steve Caffè, M.D.  
Head, U.S. Regulatory Affairs  
200 Crossing Boulevard  
P.O. Box 6890  
Bridgewater, NJ 08807-0890

Dear Dr. Caffè:

Please refer to your June 18, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apidra (insulin glulisine [rDNA origin]).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on August 17, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
Chief, Project Management Staff  
Division of Metabolic  
and Endocrine Drug Products, HFD-510  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Kati Johnson

8/11/03 04:48:18 PM

**Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420; Parklawn  
Rm. 6-34  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** August 5, 2003

**IND NUMBER:** 61,956

**NAME OF DRUG:** **Apidra**  
(Insulin Glulisine Injection)  
100 units/mL (U-100)

**IND SPONSOR:** Aventis Pharmaceuticals Inc.

**I. INTRODUCTION**

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products, for an assessment of the proprietary name "Apidra" regarding potential name confusion with other proprietary or established drug names. The container labels, carton package, and patient package insert labeling for Apidra were submitted for review and comment.

**PRODUCT INFORMATION**

Apidra is the proposed proprietary name for insulin glulisine (rDNA origin), a human insulin analog that is a rapid-acting parenteral blood glucose lowering agent. The dosage of Apidra should be individualized and determined based on the physician's advice in accordance with the needs of patients. Apidra is normally be used in regimens that include a longer-acting insulin or basal insulin analog. Apidra should be given within fifteen minutes before or immediately after a meal. It will be available in a strength of 100 units per mL (U-100).

**II. RISK ASSESSMENT**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>i,ii</sup> as well as several FDA databases<sup>iii</sup> for existing drug names which sound-alike or look-alike to "Apidra" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database<sup>iv</sup> and the data provided by Thomson & Thomson's SAEGIS<sup>TM</sup> Online Service<sup>v</sup> were also conducted. An expert panel discussion was conducted to

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<sup>i</sup> MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>ii</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>iii</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

<sup>iv</sup> WWW location <http://www.uspto.gov>.

<sup>v</sup> Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com).

review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

#### A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Apidra. Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified four medication names that have potential for confusion with Apidra. These products are listed in Table 1 (see below and page 4), along with the dosage forms available and usual FDA-approved dosage.
2. DDMAC did not have any concerns with Apidra in regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

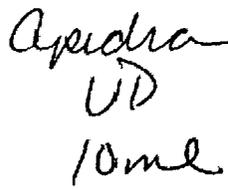
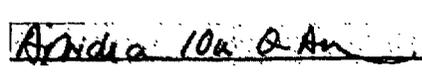
Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Apidra	Insulin Glulisine Injection 100 units/mL	Dosage is individualized and determined based on the physician's advice in accordance with the needs of the patient.	
Ephedra (Otc)	Ephedra Sinica Capsules 375 mg	Take 1 or 2 capsules daily with a meal or a glass of water.	**S/A, LA
Arixtra (Rx)	Fondaparinux Solution for Injection 2.5 mg/0.5 mL	2.5 mg subcutaneously once daily; usually for 5 to 9 days; max 11 days. Once homeostasis is achieved, give first dose 6 to 8 hours post-op.	**S/A, LA
Cipro (Rx)  Cipro XR (Rx)  Cipro I.V. (Rx)	Ciprofloxacin  Tablets: 100 mg, 150 mg, 500 mg, and 750 mg  Powder for oral suspension: 5 grams/100 mL and 10 grams/100 mL  Tablets: 500 mg  Concentrate: 10 mg/mL Premixed: 2 mg/mL	<u>Complicated Urinary Tract Infection:</u> 500 mg (400 mg I.V.) every 12 hours for 7 to 14 days.  <u>Uncomplicated Urinary Tract Infection:</u> 100 mg or 250 mg every 12 hours for 3 days.  <u>Acute Sinusitis:</u> 500 mg (400 mg I.V.) every 12 hours for 10 days.  <u>Nosocomial Pneumonia:</u> 400 mg intravenously every 8 hours for 10 to 14 days.	**L/A
Capitol (Rx)	Chloroxine Shampoo 2%	Massage thoroughly onto wet scalp. Allow lather to remain on scalp for 3 minutes. Repeat application and rinse. Use two treatments per week.	**S/A, L/A

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Apidra	Insulin Glulisine Injection 100 units/mL	Dosage is individualized and determined based on the physician's advice in accordance with the needs of the patient.	
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES:

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Apidra with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 129 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Apidra (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

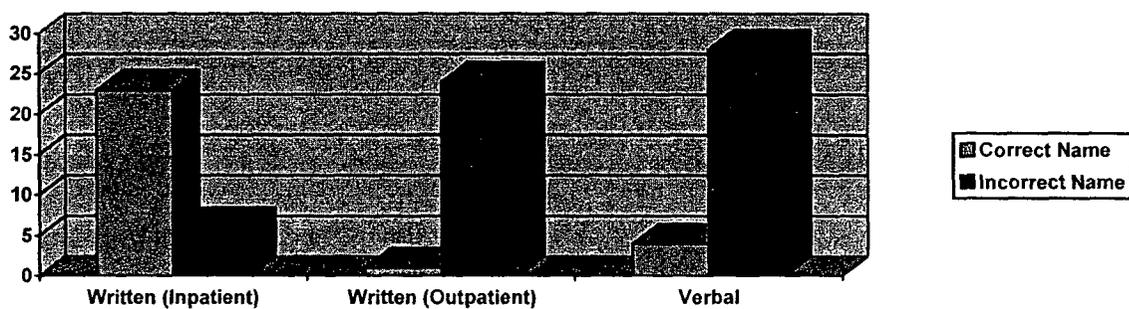
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> 	<p>Apidra, 10 units every morning, dispense 10 mL.</p>
<p><u>Inpatient RX:</u></p> 	

## 2. Results:

The results are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	29 (67%)	23 (79%)	6 (21%)
Written Outpatient	43	25 (58%)	1 (4%)	24 (96%)
Verbal	43	32 (74%)	5 (16%)	27 (84%)
Total	129	86 (67%)	29 (34%)	57 (66%)



Among the verbal prescription study participants for Apidra, 27 of 32 (84%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of “Apidra”. The incorrect responses were *Apridia* (13), *Apridra* (13), and *Apridria* (1). None of the interpretations are similar to a marketed drug product.

Among the written prescription study participants for Apidra, 30 of 54 (56%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of “Apidra”. The incorrect responses were *Apedia* (1), *Apedra* (5), *Afedra* (1), *Epedra* (1), *Epidra* (14), *Epidro* (1), *Ipidra* (1), *Petra* (1) *Ephedra* (4), a currently marketed over the counter herbal supplement, and *Efedra* (1), which is phonetically identical to Ephedra.

### C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name “Apidra”, the primary concerns raised were related to one over-the-counter herbal product, Ephedra, and three look-alike and/or sound-alike names that are currently available in the U.S. marketplace: Arixtra, Cipro, and Capitrol.

We conducted prescription studies to simulate the prescription ordering process. Our study confirmed confusion between Apidra and the over the counter herbal drug product Ephedra. Four respondents in the written studies identified the drug name as Ephedra. Additionally, two participants commented that the proposed name, Apidra, was too similar to Ephedra in sound and appearance. The remaining incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Apidra. Although there are limitations to the predictive value of these studies primarily

due to sample size, we have acquired safety concerns due to positive interpretations. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

1. Ephedra can have sound-alike and look-alike similarities to the proposed name, Apidra (see below). Ephedra contains ephedra sinica, and is marketed in the United States as an over-the-counter dietary supplement that claims to promote weight loss, increase energy, and enhance athletic performance. Ephedra is not an FDA-approved drug product. Ephedra and Apidra sound-alike and look-alike in that each name has three syllables, and the ending of each name is identical (“dra”). Additionally, the first letter of each name, although different, can be pronounced the same (“E” vs. “A”). Ephedra and Apidra can potentially overlap in dosing regimen (daily). However, they differ in route of administration (oral vs. subcutaneous) and dosage form (capsules vs. injection). Also, the second syllable of each name (“phed” vs. “pid”) is phonetically different, which helps to somewhat distinguish the names from each other when spoken. Because Ephedra is available over the counter, it will not be stored in pharmacies near Apidra, which requires refrigeration. Although four participants in the written study identified the proposed name as “Ephedra”, one participant identified the proposed name as “Efedra”, and two participants in the study commented that the names were similar to each other in sound and appearance, DMETS believes that the differences in dosage form, route of administration, and storage will minimize the risk of confusion and error between Ephedra and Apidra.

Ephedra

Apidra

2. Arixtra was identified to have sound-alike and look-alike similarities to the proposed name, Apidra (see below). Arixtra contains the active ingredient fondaparinux, and is indicated for the prophylaxis of deep vein thrombosis. Arixtra and Apidra share sound-alike similarity in that each name contains three syllables, and has the same vowel sound (“A”) at the beginning of the name. The beginning of each name (“Ari” vs. “Api”) sounds similar when pronounced, and ending of the names (“tra” vs. “dra”) are similar when both pronounced and written. However, the second syllable of each name (“pid” vs. “rix”), is different in look and sound, which helps to distinguish the names from each other. Arixtra and Apidra also share an overlapping route of administration (subcutaneous) and dosage form (solution for injection). It is also possible for Apidra and Arixtra to have overlapping numerals in their dosing strength (2.5 mg vs. 25 units), and both can be given once daily. However, there are differences between Arixtra and Apidra in that Arixtra is used for a duration of five to nine days, up to a maximum of eleven days, and then discontinued, unlike Apidra. Also, Arixtra is supplied as a pre-filled syringe with a needle, whereas Apidra will be available in a ten milliliter vial. Despite similarities between the two products, DMETS believes that differences in the sound-alike and look-alike characteristics, in addition to the differences in duration of use and packaging, will minimize the risk of confusion and error between Arixtra and Apidra.

Arixtra

Apidra

3. Cipro has look-alike similarity to the proposed name, Apidra. Cipro contains ciprofloxacin, a quinolone antibiotic, indicated for the treatment of infections caused by susceptible organisms. The beginning of each name can look similar (“Cip” vs. “Ap”), particularly if the letter “A” in Apidra is scripted and not closed (see below). Additionally, the suffix of each name contains similar letter combinations (“ro” vs. “ra”). However, the names differ in number of letters (five vs. six), and the upstroke of the letter “d” in Apidra, helps to distinguish the names from each other when written. Although Cipro is dosed in milligrams and Apidra is dosed in units, the product have overlapping numerals in their strengths (100) and have an overlapping dosage form (injection). Additionally, because the dosing regimen or both products varies, there can be overlap in this regard as well. Despite the similarities in dosage form, strength, and possible dosing regimen, DMETS believes that the differences in the look-alike characteristics minimize the risk of confusion and error between Cipro and Apidra.

Cipro                      Apidra  

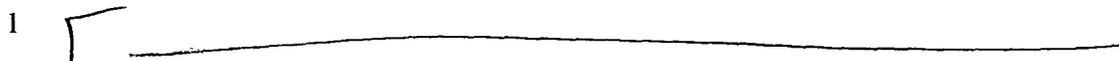

4. Capitrol has sound-alike and look-alike similarities to the proposed name, Apidra. Capitrol contains chloroxine, and is indicated for the treatment of mild to moderately severe seborrheic dermatitis of the scalp. Both names contain three syllables; the middle syllable (“pit” vs. “pid”) and last syllable (“trol vs. “dra”) of each name sound slightly similar when pronounced, except for the ending letter “l” in Capitrol. Additionally, the first letter of each name can look similar when written (“C” vs. “A”), although these letters are clearly distinguishable from each other when spoken. The names are also distinguished by the presence of the letter “l” at the end of the name “Capitrol when written”. Capitrol and Apidra also differ in dosage form (shampoo vs. injection), route of administration (topical vs. subcutaneously), and strength (2% vs. 100 units/mL). DMETS believes that these differences minimize the risk of confusion and error between Capitrol and Apidra. Furthermore, Capitrol and Apidra will not sit near each other on pharmacy shelves, further decreasing the risk of confusion between the two products.

Capitrol                      Apidra  


### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the container label, carton and package insert labeling for Apidra, DMETS has focused on safety issues relating to possible medication errors, and has identified areas of possible improvement, which might minimize potential user error.

#### A. CONTAINER LABEL

1 

2 

**B. CARTON LABELING**

1. \_\_\_\_\_
2. \_\_\_\_\_

**C. PACKAGE INSERT LABELING**

No comment.

**IV. RECOMMENDATIONS**

- A. DMETS has no objections to the use of the proprietary name "Apidra". DMETS decision is tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.
- B. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review.
- C. DDMAC finds the name Apidra acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

**/S/**

\_\_\_\_\_  
Tia M. Harper-Velazquez, Pharm.D.  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Concur:

**/S/**

\_\_\_\_\_  
Alina Mahmud, R.Ph.  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

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/s/

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Tia Harper-Velazquez  
8/29/03 10:47:23 AM  
PHARMACIST

Alina Mahmud  
8/29/03 10:50:52 AM  
PHARMACIST

Jerry Phillips  
8/29/03 11:17:03 AM  
DIRECTOR

## MEMORANDUM OF FILING MEETING MINUTES

**MEETING DATE:** July 29, 2003  
**TIME:** 11:30 – 12:30 pm  
**LOCATION:** Parklawn Building 14B45  
**APPLICATION:** NDA 21-629 Apidra (insulin glulisine [rDNA origin])  
**TYPE OF MEETING:** NDA filing meeting  
**MEETING RECORDER:** Julie Rhee

### ATTENDEES:

Joanna Zawadzki, M.D., Medical Officer, DMEDP  
Xavier Ysern, Ph.D., Chemist, DMEDP  
Jeri El-Hage, Ph.D., Pharm/Tox Team Leader, DMEDP  
Herman Rhee, Ph.D., Pharm/Tox reviewer, DMEDP  
Todd Sahlroot, Ph.D., Statistical Team Leader, DBII  
Lee Pian, Ph.D., Statistical Reviewer, DBII  
Jim Wei, Ph.D., Biopharm Reviewer, OCPB  
Andrea Slavin, Consumer Safety Officer, DSI  
Justina Molzon, Associate Director for International Programs  
Farid Benhammou, Intern, International Programs  
Julie Rhee, Regulatory Project Manager, DMEDP

### BACKGROUND:

NDA 21,629 for Apidra (insulin glulisine [rDNA origin]) was submitted by Aventis Pharmaceuticals on June 18, 2003. This application is the third submission for rapid-acting insulin analog. The two other rapid-acting insulin analog are Lilly's NDA 20-563 Humalog (insulin lispro, approved 6/14/96) and Novo's NDA 20-986 NovoLog (insulin aspart, approved 6/7/00).

The entire submission was submitted electronically following the Common Technical Document (CTD) format. However, some reviewers have experienced a problem in opening the electronic document because of a recurrent error message. Mr. Gary Gensinger, Information Technology (IT) specialist, spoke with the Aventis IT people and concluded that the problem appeared to be related to the Acrobat version. Our reviewers had Acrobat 5.0 but it seemed that they need Acrobat 4.0. in order to open the document.

Mr. Gensinger arranged thru OIT to install Acrobat 4.0 on this NDA's reviewer team.

## **SUMMARY OF NDA APPLICATION:**

The NDA submission consists of data from four Phase 3 open-label, multinational, randomized, controlled, parallel-group studies. Three studies were completed in patients with Type 1 diabetes mellitus, and one study was completed in patients with Type 2 diabetes mellitus. There are two 26-week studies: Study 3001 in adults with Type 1 diabetes mellitus (comparing glulisine and lispro) and Study 3002 in adults with Type 2 diabetes mellitus (comparing glulisine and regular insulin). Two smaller studies in adults with Type 1 diabetes mellitus are also submitted: Study 3004, a 12-week study in adults with Type 1 diabetes mellitus, (comparing pre- and post-meal injection of glulisine to pre-meal injection of regular insulin), and Study 3006, a small 12-week pump study (comparing glulisine and aspart). The data from Study 3005, the second 26-week study in adults with Type 2 diabetes mellitus (also comparing glulisine and regular insulin), and the two extension studies (Studies 3011 and 3012) were not included in the NDA submission.

## **PROPOSED INDICATION:**

Treatment of adult patients with Type 1 and Type 2 diabetes mellitus

## **DISCUSSION POINTS:**

### Pharmacology:

- i. The application is filable.
- ii. Forty-five day filing memo will be done. However, there is no filing comment that needs to be conveyed to the sponsor.

### Chemistry:

- i. The application is filable.
- ii. A consult request needs to be sent to CDRH for the review of insulin pump.
- iii. EER has not been requested yet.

### Biometrics:

- i. There are two studies completed in patients with Type 1 diabetes. There is one completed and one ongoing study in patients with Type 2 diabetes.
- ii. Biometrics can review the data we have but need clinician's inputs to decide whether the Type 2 data that was submitted is sufficient for filing.

Biopharm:

- i. The application is filable.
- ii. Filing memo is prepared but is not entered in the DFS yet. There are no filing comments to be sent to the sponsor.

Clinical:

- i. A safety signal, i.e., excess cardiac events, is noted in patients with type 1 diabetes mellitus treated with glulisine, in the 26-week study (Study 3001). A similar signal was not seen in patients with type 2 diabetes mellitus.
- ii. Study 3005 is a pivotal study in patients with type 2 diabetes mellitus but it is ongoing and data were not included in the NDA. Since Study 3005 data are not submitted in the NDA, Dr. Zawadzki is going to discuss with Dr. Orloff whether or not the application is filable\*.

During the November 25, 2002, pre-NDA meeting, the Division informed Aventis that all efficacy data needs to be included in the NDA at the time of NDA submission.

- iii. Although Aventis plans to market a 10 mL vial presentation, the sponsor conducted studies using insulin pens. This is not a refuse-to-file (RTF) filing issue but it is a review issue.

\* Following Dr. Zawadzki's discussion with Dr. Orloff, it was decided to file the NDA as outlined in the addendum to the Medical Officer's Review.

Microbiology:

The application is filable with no filing comments.

General:

- i. If the application is filed, DMEDP will recommend one site each from Study 3001 and Study 3002 for DSI inspection. Since Study 3001 was done in Europe and South Africa, a study site from Study 3002 (done in North America and Australia) may be an alternate possibility.
- ii. Advisory Committee meeting might be needed to discuss adverse events such as cardiac events.
- iii. Since PUDFA user fee due date is April 18, 2004, a target date for the final review (signed by team leader) to be in DFS is February 15, 2004.

**DECISIONS (AGREEMENTS) REACHED:**

- i. The NDA is filable.
- ii. Target date for the final review to be signed off in DFS is February 15, 2004.
- iii. For DSI inspection, DMEDP recommends one site each from Study 3001 and Study 3002. However, since Study 3001 was done in Europe and South Africa, a study site from Study 3002 (done in North America and Australia) may be an alternate possibility. DSI may choose study sites for an inspection.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

Whether or not to have an Advisory Committee meeting will be decided after reviewers had more time to review the application.

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Julie Rhee  
8/27/03 03:56:28 PM

**45 Day Meeting Checklist  
NONCLINICAL PHARMACOLOGY/TOXICOLOGY**

NDA No. 21-629/Aventis/Apidra(Insulin glulisine, HMR1964)/July 29, 2003

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA?  <b>Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (None)</b>	X		<p>Have electronic files of the carcinogenicity studies been submitted for statistical review? N/A</p> <p><b>Studies completed:</b></p> <ul style="list-style-type: none"> <li>1) Insulin+IGF receptor binding studies</li> <li>2) 1-, 6-M s.c. toxicity in rats</li> <li>3) 1-, 6-Month s.c. toxicity in dogs</li> <li>4) 1-Y carcinogenity in rats</li> <li>5) Genotoxicity(Ames, CHL chromosomal aberration)</li> <li>6)Embryofetal development in rabbits and Pre- &amp; Post natal studies in rats</li> <li>7)Local toxicity + Antibody study</li> </ul>

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ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		

<p>7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?</p>	<p>X</p>		
<p>8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m<sup>2</sup> or comparative serum/plasma AUC levels?</p>	<p>X</p>		

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ON ORIGINAL**

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file:			

Herman Rhee, Ph.D.  
 Reviewing Pharmacologist

Jeri Elhage, Ph.D.  
 Supervisory Pharmacologist

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/s/

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Herman Rhee  
7/29/03 03:55:35 PM  
PHARMACOLOGIST

Jeri El Hage  
7/31/03 04:03:38 PM  
PHARMACOLOGIST

**REQUEST FOR CONSULTATION**

(Division/Office): Marci Kiestler, DDMAC, HFD-42

FROM: Julie Rhee, DMEDP, HFD-510

DATE June 27, 2003	IND NO.	NDA NO. 21-629	TYPE OF DOCUMENT New NDA (NME)	DATE OF DOCUMENT June 18, 2003
NAME OF DRUG Apidra™ (insulin glulisine [rDNA origin] for injection)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE December 31, 2003

NAME OF FIRM: Aventis Pharmaceuticals

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

- |  |   |
|--|---|
| DISSOLUTION  | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| BIOAVAILABILITY STUDIES                              | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input checked="" type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

**V. SCIENTIFIC INVESTIGATIONS**

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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**COMMENTS/SPECIAL INSTRUCTIONS:**

The proposed labeling are available in EDR. Please review them and provide comments. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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Julie Rhee  
6/27/03 03:33:17 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-629

6/23/03

Aventis Pharmaceutical Inc.  
Attention: Steve Caffè, M.D.  
Head, U.S. Regulatory Affairs  
200 Crossing Boulevard  
P.O.Box 6890  
Bridgewater, NJ 08807-0890

Dear Dr. Caffè:

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

Name of Drug Product: Apidra™(insulin glulisine [rDNA origin] for injection)  
Review Priority Classification: Standard (S)  
Date of Application: June 18, 2003  
Date of Receipt: June 18, 2003  
Our Reference Number: NDA 21-629

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 17, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 18, 2004.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

NDA 21-629

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Metabolic and Endocrine Drug Products, HFD-510

Attention: Division Document Room, 8B45

5600 Fishers Lane

Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6424.

Sincerely,

  
{See appended electronic signature page}

Julie Rhee

Regulatory Project Manager

Division of Metabolic

and Endocrine Drug Products, HFD-510

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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Julie Rhee

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# USER FEE COVER SHEET

## See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS  Aventis Pharmaceuticals Inc. 200 Crossing Boulevard P.O. Box 6890 Bridgewater, NJ 08807-0890	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 21-629
2. TELEPHONE NUMBER (Include Area Code)  ( 908 ) 304-7000	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.  IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:  _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME  Insulin Glulisine (INN, USAN) - APIDRA™	6. USER FEE I.D. NUMBER 4507 (assigned 02/10/2003)

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  YES  NO  
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
CBER, HFM-99  
1401 Rockville Pike  
Rockville, MD 20852-1448

and Food and Drug Administration  
CDER, HFD-94  
12420 Parklawn Drive, Room 3046  
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Steve Caffé, M.D. Head, U.S. Regulatory Affairs	DATE June 18, 2003
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## OFFICE DIRECTOR'S SUMMARY MEMORANDUM

<b>Date:</b>	Thursday, April 15, 2004
<b>NDA:</b>	21-629
<b>Sponsor:</b>	Aventis
<b>Proprietary Name:</b>	Apidra (insulin glulisine) 100 IU/ml
<b>Date of submission</b>	June 18, 2003

**Introduction:** This is the first review cycle for this drug product, which is a recombinant insulin analogue intended for subcutaneous injection or for use with an insulin pump. This molecule differs from native human insulin as two of the amino acids, asparagine at the 3<sup>rd</sup> and lysine at the 29<sup>th</sup> positions of the beta chain, are substituted with lysine and glutamic acid, respectively. These substitutions are in a region that is not expected to impact on human insulin receptor interactions, but are felt to interfere with hexamerization of the insulin molecule and to stabilize the insulin in its monomeric state, thereby leading to a faster onset and offset of action compared to regular insulin. The sponsor for this product is Aventis and Apidra is considered a new molecular entity by virtue of its unique amino acid structure. Aventis submitted five efficacy-safety studies to support their approval and proposed indications, along with data to inform the use of Apidra in insulin pumps. The studies, as appropriate for insulin studies, are positive-control, non-inferiority studies. The comparators were either regular insulin or insulin lispro, a similar substituted short-acting insulin product. Patients all received appropriate basal insulin therapy as well (either NPH human or Lantus).

As it is clear from both animal pharmacology and human pharmacology studies that this novel molecule remains an active human insulin with actions common to active insulin, the main issues for this development program are ones of defining the pharmacokinetics/dynamics (i.e., how to dose it correctly) and the safety – particularly whether there is any excess immunogenicity with the non-native amino acid sequence.

**CMC/microbiology:** The drug substance is produced by recombinant technology, using *E. coli* carrying a safety plasmid (which includes the drug sequence). The drug product is a sterile aqueous solution for injection or use in an insulin pump. The excipients include m-cresol (as a preservative), tromethamine, sodium chloride, and polysorbate 20 (a surfactant). The product shows typical stability characteristics for an insulin and the sponsor provided data to establish a shelf-life of 24 months when stored under refrigerated conditions (5 degrees C). When stored at room temperature

under in-use conditions, it has a one month shelf-life. As stated above, the product is manufactured as sterile and the microbiology review has found the manufacturing and product characteristics satisfactory. All other aspects of the CMC section have been satisfactorily addressed by the sponsor and the 3 key DMFs are also adequate to support approval.

The environmental assessment waiver is acceptable and the EES has received an overall recommendation as of March 30<sup>th</sup>, 2004. The CMC discipline recommends approval.

**Pharm/Tox:** Preclinical pharmacology studies confirmed insulin glulisine to have a rapid onset and shorter duration than regular insulin. The sponsor supported the safety of this product with chronic toxicology studies, reproductive toxicology studies and mutagenicity testing. The mutagenicity testing was negative (and no formal carcinogenicity study was requested nor done, though the 12 month study included carcinogenicity endpoints). Chronic toxicity testing was done in beagles (6 months) and rats (12 months), with no findings outside of those expected and found with other insulin comparators. This included a slight increase in incidence of mammary tumors in rats in the 12-month study compared to untreated controls. Similarly, the reproductive toxicology showed no findings unexpected with an active insulin (that results in hypoglycemia). The Pharm/Tox team recommends approval.

**Biopharmaceutics:** The sponsor submitted 14 studies to support the biopharmaceutic evaluation of this application. The bioavailability of SQ insulin glulisine compared to IV is approximately 70%, varying a small degree depending on site. The volume of distribution is somewhat smaller than it is with regular insulin (13 L vs. 21 L), and the elimination half-life is shorter (13 min. vs. 17). The time to peak concentration at 51 minutes is shorter than either regular insulin at 82 minutes and lispro insulin at 58 minutes. PD measures have shown glulisine to be equipotent compared to regular insulin. All other PD assessments confirm glulisine's rapid onset and relatively short duration of action. Renal disease leads to decreased clearance of the glulisine, with a resultant increased exposure of approximately 25 – 40% in moderate to severe renal impairment. OCPB has found the data submitted by Aventis to support this application sufficient and recommends approval with appropriate labeling.

**Clinical / Stastical:** As stated above, the NDA submission for glulisine consists of data from five Phase 3 efficacy studies, which were randomized, controlled, parallel-group, active-controlled studies. None of the of the Phase 3 studies involved a placebo group and all were open-label. Studies 3001, 3002 and 3005 were 26 weeks in duration and studies 3004 and 3006 were 12 weeks long. Study 3004 was conducted to support a post mealtime

administration dosing recommendation and Study 3006, was designed to support the use of glulisine from an external insulin pump. For Type I diabetics, study 3001 was the primary efficacy study, with 3004 and 3006 also being performed in Type 1 patients. Studies 3002 and 3005 were conducted in Type 2 patients.

The total number of subjects enrolled in the phase 3 clinical trials was over 3350 patients, 1833 of whom received Glulisine, and 1524 subjects were treated with other short acting insulins (active comparators). Over 2400 patients were on study drug for 26 weeks. The majority of the glulisine patients completing these studies were continued on into 1-year followup studies, with 436 receiving glulisine for at least 52 weeks. This constitutes a very adequate database for assessing safety and efficacy of this drug.

#### EFFICACY:

Study 3001 was a 26-week, randomized, open-label, active-control study conducted in patients with Type 1 diabetes. The study compared glulisine to insulin lispro when administered just prior to a meal (i.e., within 15 minutes prior to eating). This study randomized 672 patients. Lantus was provided as the basal insulin and insulin therapy was stabilized in the four week run-in period. In this study, glycemic control (as assessed by Hgb A<sub>1</sub>C and basal insulin use) and the rates of significant hypoglycemia (i.e., requiring intervention from a third party) were comparable for the two treatment regimens. This study establishes efficacy and medium-term safety for glulisine relative to lispro insulin, an approved short-acting insulin, in type 1 patients.

Study 3002 was a 26-week study of similar design to 3001, performed in 876 Type 2 diabetic patients. In this study, the comparator was regular insulin given 30 to 45 minutes prior to the meal (as recommended) and NPH served as the basal insulin for both groups. Fifty eight percent of the patients were on an oral hypoglycemics at entry and by protocol they were to maintain their baseline dose. A reduction from baseline in HgbA<sub>1</sub>C was seen with both treatment arms, but the postprandial blood glucose levels in the glulisine group were actually lower than those seen in the regular human insulin comparator group. Despite this, the rates of significant hypoglycemia were comparable for the two treatment regimens. No other differences between glulisine and regular human insulin groups were seen in the number of daily short-acting insulin injections or basal or short-acting insulin doses. This study established the efficacy and medium-term safety of glulisine in the treatment of Type 2 DM.

Study 3004 examined alternate timing of glulisine administration in Type 1 diabetics. This was a 12-week study that enrolled 860 patients and compared

glulisine administered either within 15 minutes before a meal or immediately after a meal to regular human insulin subcutaneously 30 to 45 minutes prior to a meal. Glycemic control and the rates of hypoglycemia were comparable for the treatment regimens. Significant reductions from baseline in HgbA<sub>1</sub>C were also observed in all three treatment regimens and no changes from baseline were seen in the total daily number of short-acting insulin injections between the three treatment groups. This study supports labeling glulisine for administration either prior to a meal (within 15 minutes) or with a meal (with 15 minutes of starting the meal).

Study 3006 evaluated the use of glulisine when provided via external insulin pump giving SQ infusions. This was a 12-week active-control study comparing glulisine to insulin aspart, which is labeled for pump use. The study enrolled 59 Type 1 diabetics. There was an acceptably low level of occlusions with glulisine (and somewhat lower than that seen with aspart, when expressed as a monthly rate, with glulisine having 0.08 occlusions/month and insulin aspart having 0.15 occlusions/month. There was also a similar occurrence of infusion site reactions, with 10% of glulisine patients reporting such and 13% of insulin aspart patients.

## SAFETY

The safety of glulisine was largely addressed by the above clinical trials, along with the extensions out to one year. There was no clear signal of unusual safety experiences. The number of clinical trial deaths was balanced between glulisine and comparators, as were serious adverse events. Medically important hypoglycemia occurred in balanced numbers, with approximately 10.5% having such in Type 1 diabetics across all groups and 3.1% in Type 2 patients. Treatment emergent cardiovascular events were also balanced overall at 2.7% with glulisine and 3.0% in comparators. In study 3001 in Type 1 DM patients, there was an apparent imbalance in these cardiovascular events, with a rate of 2.7% in glulisine treated patients and 0.7% in the comparator arm. However, there were baseline imbalances in important attributes (notably blood pressures and history of hypertension), with higher rates in the glulisine group. These imbalances confound the interpretation of the reported imbalance in cardiovascular events. Given the overall findings for the entire population, there is little data to support a differential cardiovascular effect in glulisine-treated patients. A consult from Cardiorenal (HFD-110) agreed that there was not a clear signal of concern.

Injection site reactions were comparable between glulisine and its comparators and acceptable in rates of occurrence. Notably for a novel, substituted amino acid insulin, the occurrence of cross-reactive antibodies in patients was very low and did not seem to show any imbalance or clear treatment effect with glulisine compared to its active insulin comparators.

While there was an increase in specific-glulisine antibodies seen in exposed patients, these stabilized out within the first 6 months and they were relatively low in occurrence.

It should be mentioned that a "Risk Management Plan" was submitted by Aventis and reviewed by ODS, but there is not any known unusual risk to manage. The plan is rather non-specific and not an appreciable departure from the normal post-approval risk activities.

Labeling and nomenclature. Final labeling is acceptable.

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Regulatory Conclusions: Overall, insulin glulisine has been shown to be both sufficiently safe and effective for use as a short acting insulin product, either administered SQ or via an insulin pump.

Robert J. Meyer, MD  
Director,  
Office of Drug Evaluation II

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

/s/

-----  
Robert Meyer  
4/15/04 03:00:00 PM  
MEDICAL OFFICER



June 18, 2003

David Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products, HFD-510  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Central Document Room  
Document and Records Section  
12229 Wilkins Avenue  
Rockville, MD 20852-1833

**NDA 21,629: APIDRA™**  
**HMR1964 - Insulin glulisine (rDNA human insulin analog) for Injection, 100 IU/mL**  
**Original New Drug Application (NDA)**

Dear Dr. Orloff:

In conformance with 21 CFR 314.1, Aventis Pharmaceuticals Inc. is hereby submitting a New Drug Application (NDA) for APIDRA™ (insulin glulisine [rDNA origin]) for Injection, 100 IU/mL, for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. This submission is seeking approval for insulin glulisine supplied in 10 mL vials.

APIDRA™ is a rapid-acting human insulin analog. It is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12 — used for the expression of the ——— which codes for insulin glulisine. It differs from human insulin in that the amino acid asparagine in position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid.

This application is in the Common Technical Document (CTD) format and follows the August 2001 "Guidance for Industry: Submitting Marketing Applications according to ICH-CTD Format-General Considerations," along with the relevant subject matter guidelines as issued by the ICH.

This application is a fully electronic application and the archival copy has been prepared in accordance with the January 1999 "Guidance for Industry: Providing Regulatory Submissions in Electronic Format-NDAs". The electronic archival copy of this application consists of 1 DLT 35/70 Digital Tape (4.24 GB). Aventis certifies that all electronic media have been scanned and found to be free of any known computer viruses (Symantec Norton Anti-Virus, Version 7.51, current DEFS 6/5/2003 rev6, Scan Engine 4.1.0.6.).

The following original signed items from Module 1 are also provided in a paper form:

FDA Form 356H  
Patent Certification  
Debarment Certification  
Field Copy Certification  
FDA Form 3397, User Fee Cover Sheet  
FDA Form 3454, Financial Interests Certification  
FDA Form 3455, Financial Disclosure

All recommendations made by the Agency during the development of Apidra™ have been carefully considered and incorporated into the development program and the NDA. For the convenience of the reviewers, a complete regulatory history summarizing the interactions between the Agency and the applicant, as well as actions taken by the applicant on each Agency recommendation, is included in Module 1.9.

During the November 25, 2002, Pre-NDA meeting, the Division presented a series of recommendations and requests that would aid in its review of the NDA. These recommendations have been incorporated into the NDA as follows:

Module 1:

Documentation on the INN and on the USAN is provided in Module 1.8. A risk management plan is proposed in Module 1.10.

Module 2:

The contents of the traditional Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) have been incorporated into the Summary of Clinical Efficacy (SCE; Module 2.7.3) and the Summary of Clinical Safety (SCS; Module 2.7.4), respectively. However, as suggested by the Division, supportive end-of-text tables have been located to Module 5.3.5.3.

In the SCE, results are presented by study (study 3001 and study 3004: performed in patients with Type 1 diabetes mellitus (DM); study 3002: performed in patients with Type 2 DM). In the SCS, Treatment-Emergent Adverse Events (TEAE) are presented by individual study, pooled by type of diabetes and pooled across all completed phase III studies (studies 3001, 3002, 3004, 3006). For safety variables other than TEAEs, data are presented separately for Type 1 (in a pooled fashion across studies 3001, 3004 and 3006) and Type 2 diabetes (study 3002), as well as being pooled across all completed phase III studies.

Module 3:

Aventis has determined, since the Pre-NDA Meeting, that an approval for insulin glulisine supplied in \_\_\_\_\_ will not be sought at this time. Therefore, as recommended by the Division, all information pertaining to \_\_\_\_\_ has been removed from Module 3, except for certain stability reports, which remain relevant. In these instances, it is clearly stated that the \_\_\_\_\_ data are supportive only.

#### Module 4:

No additional recommendations were made by the Division concerning Module 4.

#### Module 5:

Individual subject narratives are provided for the following categories of safety events: all deaths, pregnancies, serious TEAEs, and TEAEs leading to permanent discontinuation of treatment. These narratives are located in the Clinical Study Reports and Related Information section (Module 5.3). We have also included narratives for all subjects experiencing severe symptomatic hypoglycemia, due to the fact that we have categorized any occurrence of this type of event as a serious adverse event. Case report forms for subjects who became pregnant, died, or who permanently discontinued study treatment due to an adverse event are located in Module 5.3.7. Additionally, programmed patient profiles are provided in Module 5.3.7.1 for the following categories of safety occurrences: all deaths, serious hypoglycemia, cardiac TEAEs (all cardiac TEAEs for Type 1, and serious cardiac TEAEs for Type 2), potential diabetic retinopathy TEAEs, potential systemic hypersensitivity reactions, clinically noteworthy abnormal values and pregnancies. Module 5.3.7.1 (Case Report Tabulation) also includes Datasets and Programs, which are provided for all phase III studies.

We have also performed additional analyses of the clinical data, as specifically requested by the Division, concerning the following potential safety events:

Diabetic retinopathy: Eye TEAEs, sorted for events potentially related to diabetic retinopathy, are presented in Module 2.7.4.2.1.6.

Autonomic neuropathy: Safety data in patients with autonomic neuropathy at baseline is presented in Module 2.7.4.5.1.6.

Cardiac events: Patient profiles are available for all patients with cardiovascular TEAEs, as described above and are included in Module 5.3.7 (all Type 1 DM subjects with cardiac TEAEs; all Type 2 DM subjects with serious cardiac TEAEs).

These patient profiles include information related to time to onset of cardiac event and time to onset of hypoglycemic events in patients with/without cardiac events. Additionally, a Kaplan-Meier analysis of time to first occurrence for all subjects with severe hypoglycemia may be located in Module 2.7.4.2.1.4.

Proposed labeling text for the package insert, cartons and containers is located in Module 1.5. For the convenience of the reviewers, the referenced annotations for the labeling text appear as endnotes and, thus, immediately follow the annotated label in Module 1.6.

The Division also requested during the Pre-NDA meeting that Aventis provide supplemental paper desk copies of the Phase 3 protocols and study reports. As discussed on June 12, 2003 between Ms. Julie Rhee (DMEDP) and Dr. Odile Ernoux (Aventis), we will provide these paper desk copies within two weeks of the date of this submission to aid in the Division's review of this application.

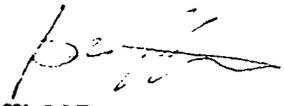
We consider the filing of this original New Drug Application to be a confidential matter, and request that the Food and Drug Administration make neither its content, nor any future communications in regard to it, public without first obtaining the written permission of Aventis Pharmaceuticals, Inc.

Aventis Pharmaceuticals, Inc. looks forward to working with the Division to facilitate the review of this application.

Please address any questions or comments you may have on this application to:

Odile Ernoux, M.D.  
Aventis Pharmaceuticals.  
Mail code: BX2-306C  
200 Crossing Boulevard  
Bridgewater, NJ 08807  
(phone): 908-231-3536  
(fax): 908-304-6318

Sincerely,

A handwritten signature in black ink, appearing to read "Steve Caffé", with a stylized flourish at the end.

Steve Caffé, M.D.  
Head, U.S. Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338  
Expiration Date: August 31, 2005  
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**  
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

**APPLICANT INFORMATION**

NAME OF APPLICANT Aventis Pharmaceutical Inc.	DATE OF SUBMISSION June 18, 2003
TELEPHONE NO. (Include Area Code) (908) 304-7000	FACSIMILE (FAX) Number (Include Area Code) (908) 304-6318
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 200 Crossing Boulevard PO Box 6890 Bridgewater, NJ 08807-0890	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE N/A

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21,629		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Insulin glulisine		PROPRIETARY NAME (trade name) IF ANY Apidra
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 3 <sup>B</sup> Lys-29 <sup>B</sup> -Glu-human insulin		CODE NAME (If any) HMR 1964
DOSAGE FORM: Injection	STRENGTHS: 100 IU/mL	ROUTE OF ADMINISTRATION: Subcutaneous

(PROPOSED) INDICATION(S) FOR USE:  
Treatment of adult patients with diabetes mellitus for control of hyperglycemia

**APPLICATION INFORMATION**

APPLICATION TYPE (check one)			
<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)			
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
Name of Drug _____		Holder of Approved Application _____	
TYPE OF SUBMISSION (check one)			
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT	<input type="checkbox"/> EFFICACY SUPPLEMENT
<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER	

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: \_\_\_\_\_

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY  CBE  CBE-30  Prior Approval (PA)

**REASON FOR SUBMISSION**

To obtain approval of a New Drug Application

PROPOSED MARKETING STATUS (check one)  PRESCRIPTION PRODUCT (Rx)  OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED eCTD THIS APPLICATION IS  PAPER  PAPER AND ELECTRONIC  ELECTRONIC

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

Please see Addendum 1 (attached)

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

Please see Addendum 2 (attached)

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input checked="" type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input checked="" type="checkbox"/>	4. Chemistry section
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input checked="" type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input checked="" type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input checked="" type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input checked="" type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
N/A	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input checked="" type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
N/A	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input checked="" type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input checked="" type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input checked="" type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input checked="" type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input checked="" type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
N/A	15. Establishment description (21 CFR Part 600, if applicable)
<input checked="" type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input checked="" type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input checked="" type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input checked="" type="checkbox"/>	19. Financial information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Documentation on the INN and USAN; Post-marketing risk management plans

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Steve Caffé, M.D. Head, U.S. Regulatory Affairs	DATE: June 18, 2003
ADDRESS (Street, City, State, and ZIP Code) 200 Crossing Boulevard, PO Box 6890, Bridgewater, NJ 08807-0890		Telephone Number (908 ) 231-5863 or 3536

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

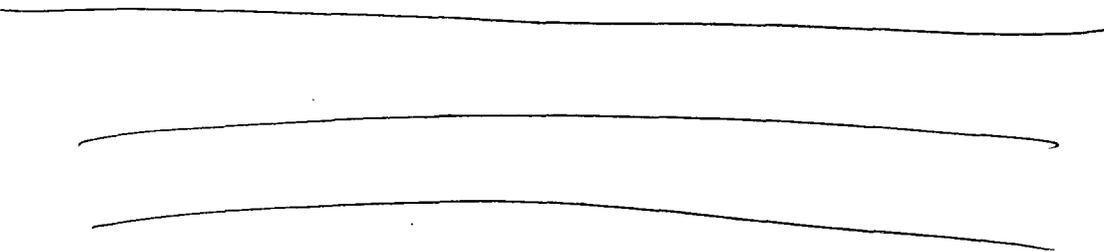
Department of Health and Human Services  
Food and Drug Administration  
CDER, HFD-99  
1401 Rockville Pike  
Rockville, MD 20852-1448

Food and Drug Administration  
CDER (HFD-94)  
12229 Wilkins Avenue  
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

## Establishment Information

### Establishment Information for the Drug Substance (D.S.) Used in HMR 1964 for Commercial Distribution

Building Address	Person to contact	Telephone Number	Registration No. (CFN)	Step of the Process	Readiness for Inspection
Aventis Pharma Deutschland GmbH Industriepark Höchst 65926 Frankfurt Germany	Dr. Wilfried Arz	+49 69 305 16583	FCGM051 (9610129 for inspections)	Synthesis, Packaging, Labeling and Testing (release and stability) of Active Substance	May 2003
					
Aventis Pharma Deutschland GmbH ProTox Marburg Emil von Behringstraße 76 35041 Marburg Germany	Dr. Christoph Hoeck	+49 6421 39 3909	FCGM047 (9610806 for inspections)	Bioactivity testing	May 2003

### Establishment Information for HMR 1964 Drug Product (D.P.) for Commercial Distribution

Building Address	Person to contact	Telephone Number	Registration No. (CFN)	Step of the Process	Readiness for Inspection
Aventis Pharma Deutschland GmbH Industriepark Höchst 65926 Frankfurt Germany	Dr. Hans-Thomas Hemrich	+49 69 305 83186	FCGM051 (9610129 for inspections)	Manufacturing, packaging, labeling, analytical testing and release	May 2003

NDA 21629  
APIDRA (Insulin glulisine, HMR1964)

Aventis, Inc.

userfee.pdf, pg 2



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

June 4, 2003

Mellon Bank  
Three Mellon Bank Center  
27<sup>th</sup> Floor  
(FDA 360909)  
Pittsburgh, PA 15259-0001

**RE: User Fee for HMR 1964 / insulin glulisine NDA # 21,629**

To whom it may concern:

Please find enclosed the required User Fee payment in the amount of \$533,400 for the upcoming Apidra™ (HMR 1964, insulin glulisine) submission. User Fee ID No. is 4,507.

If you have any questions or if I can be of further assistance, please contact me.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Steve Caffé".

Steve Caffé, M.D.  
Head, U.S. Regulatory Affairs  
Tel. (908) 231 5863 or 3536

**CONSULTATION RESPONSE**

**Division of Medication Errors and Technical Support  
Office of Drug Safety  
(DMETS; HFD-420)**

**DATE RECEIVED:** June 3, 2003

**DESIRED COMPLETION DATE :** Dec 12, 2003

**ODS CONSULT #:** 03-0180

**TO:** David Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products.  
HFD-510

**THROUGH:** Julie H. Rhee  
Project Manager  
HFD-510

**PRODUCT NAME:**  
Apidra  
(Insulin Glulisine Injection)  
100 units/mL (U-100)

**SPONSOR:** Aventis Pharmaceuticals

**IND #:** 61,956

**SAFETY EVALUATOR:** Tia M. Harper-Velazquez, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Metabolic and Endocrine Drug Products, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Apidra" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**RECOMMENDATIONS:**

1. DMETS has no objection to the use of the proprietary name "Apidra". DMETS decision is tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.
2. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the name "Apidra" acceptable from a promotional perspective.

**/S/**

\_\_\_\_\_  
Carol Holquist, R.Ph.  
Deputy Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242 Fax: (301) 443-9664

**/S/**

\_\_\_\_\_  
Jerry Phillips, R.Ph.  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

# REQUEST FOR CONSULTATION

(Division/Office):

**Director, Division of Medication Errors and  
Technical Support (DMETS), HFD-420  
PKLN Rm. 6-34**

FROM:

Julie Rhee, DMEDP, HFD-510, 7-6424

DATE June 3, 2003	IND NO. 61,956	NDA NO.	TYPE OF DOCUMENT Correspondence (request for tradename review)	DATE OF DOCUMENT May 30, 2003
NAME OF DRUG Apidra (HMR 1964 [rDNA origin])		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE December 3, 2003

NAME OF FIRM: Aventis Pharmaceuticals Inc.

## REASON FOR REQUEST

### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                       |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                              |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                                   |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                         |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                                  |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

#### COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Please review the proposed tradename "Apidra" to see whether or not it is acceptable. Apidra is rapid acting insulin manufactured by Aventis. The sponsor plans to submit an NDA during the 2Q, 2003.

Please let me know if you need any additional information. Thank you.

NATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

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Julie Rhee  
6/3/03 09:24:01 AM

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** November 7, 2000  
**Time:** 10:00 - 11:30 a.m.  
**Location:** Parklawn Bldg. 3<sup>rd</sup> fl c/r "Chesapeake"  
**Sponsor:** Aventis Pharmaceuticals \_\_\_\_\_  
**Type of Meeting:** Pre-IND  
**Meeting Chair:** David Orloff, M.D.  
**Meeting Recorder:** Julie Rhee

**Attendees:**

**FDA:**

David Orloff, M.D., Director, Division of Metabolic and Endocrine Drug Products  
Saul Malozowski, M.D., Medical Team Leader, DMEDP  
Elizabeth Koller, M.D., Medical Officer, DMEDP  
Joanna Zawadzki, M.D., Medical Officer, DMEDP  
Jeri El Hage, Ph.D., Pharm/Tox Team Leader, DMEDP  
Herman Rhee, Ph.D., Pharmacologist, DMEDP  
Hae-Young Ahn, Ph.D., Biopharm Team Leader, DPE II  
Jim Wei, Ph.D., Biopharm Reviewer, DPE II  
Julie Rhee, Regulatory Project Manager

**Aventis Pharmaceuticals:**

Peter Boderke, Ph.D., Pharmaceutical Sciences  
Annette Schlaefer, Analytical Sciences  
Ingo Stammberger, D.V.M., Toxicologist  
Gerhard Seipke, Ph.D., Preclinical Pharmacology  
Paul Warrant, Ph.D., Global Drug Regulatory Affairs  
Robert Costello, M.S., Global Biostatistics  
Monika Ziemer, M.D., Clinical Manager  
Reinhard Becker, M.D., Clinical Pharmacology  
Annke Frick, Ph.D., Drug Metabolism and Clinical PK  
Ralf Roskamp, M.D., Global Therapeutic Area Head  
Diava Bajorunas, M.D., Global Project Team Leader  
Claudia Herrmann, Ph.D., Project Manager  
Rainer Obermeier, Ph.D., Global Project Team Leader, Lead Optimization

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**Discussions/Sponsor's questions/FDA's responses:**

Preclinical:

**Does the Agency agree that the preclinical program is adequate and that further preclinical toxicology testing of HMR 1964 is not necessary to support the clinical development of this compound?**

*FDA response:*

1. *No. Preclinical program is NOT adequate and the Agency recommends the following additional studies:*
  - a. *Reproductive toxicology studies. A full battery of reproductive toxicity studies should be conducted with HMR1964. The fertility and teratology studies (Segments I and II) must be completed prior to initiation of Phase 3 studies. The Division recommends the inclusion of an insulin comparator group in all studies.*
  - b. *At minimum, one year carcinogenicity study should be conducted in rats. The high dose can be selected based on the maximum tolerated dose from the 6-month rat study. The study should include an insulin comparator group treated with a dose of insulin comparable to the high dose of HMR 1964. This study can be conducted concurrently with the Phase 3 clinical program.*
  - c. *The in vivo genotoxicity study should be completed and submitted for review prior to initiation of Phase 3 trials.*
  - d. *Immunogenicity studies should be conducted in rabbits or guinea pigs.*
  - e. *Antibody production and injection site reactions should be evaluated in the 6-month chronic toxicity studies in rats and dogs.*
  - f. *Follow ICH guideline (M3) for preclinical program.*

Clinical questions:

Question #1:

**The Phase 1 program, as outlined above, provides adequate Phase 1 information to support a New Drug Application for HMR 1964 for the proposed indication. Does the Agency agree with this assessment?**

*FDA response:*

*The Agency recommends the following additional studies to be conducted:*

Question #3:

**Does the Agency consider the design of the Phase III clinical studies as well as the statistical parameters for the primary efficacy determination, adequate to support a New Drug Application for this product?**

*FDA response:*

*The Agency would like to see the data from Phase 1 studies before they make any commitment concerning Phase 3 trials. However, the Agency has the following general recommendations:*

1. *Include autonomic neuropathy patients in Phase 3 studies. This is a recommendation, not a requirement.*
2. *At minimum, comparison of HMR1964 against regular insulin and lispro in type 1 or type 2 patients for 6-months followed by 6-months extension studies is recommended. Open label extension studies could be negotiated during EOP 2 meeting.*
3. \_\_\_\_\_ between treatment groups is acceptable for noninferiority claim.

Question #4a:

**The proposed clinical program, with approximately 900 subjects being exposed to the insulin analogue HMR 1964 is considered sufficient for an adequate safety evaluation. Does the Agency agree with this proposal?**

*FDA response:*

1. *No. The sponsor needs to add about 500 more patients for the total number of patients exposed to HMR1964. The sponsor should follow ICH guidelines for new chemical entities.*
2. \_\_\_\_\_
3. \_\_\_\_\_
4. *Minimum sample size required for an NDA submission is as follow:  
N=1,500 (for total exposure)  
N=600 (for 6-months exposure)  
N=100 (for 1-month exposure)*

Question #4b:

**Is the clinical development plan, as described, adequate to achieve the indication: “treatment of patients with diabetes mellitus requiring insulin treatment for the control of hyperglycemia”?**

*FDA response:*

*It will depend on the NDA data.*

Question #5:

**Based on these data and the previous experience with Lantus® (HOE 901), the sponsor does not plan to measure E. Coli protein antibodies in the clinical trials. Does the Agency agree with this proposal?**

*FDA response:*

*Yes. The measurement of E. coli protein antibodies, but not other insulin antibodies, in the clinical trials could be waived.*

Additional question dated 10/19/00:

**The sponsor would propose that the information to be provided in the IND is sufficient to support the initiation of two 6-month Phase III studies (Study 3001 to be conducted in Europe in subjects with Type 1 diabetes and Study 3002 to be conducted in the US in subjects with Type 2 diabetes), with an extension phase for evaluation of safety. Does the Agency agree with this assessment?**

*FDA response:*

*No, the Division does not agree that the preclinical information planned to be submitted with the IND is adequate to support the sponsor's Phase 3 program.*

*The sponsor can not submit the results from the 6-month chronic toxicity studies one month after the Phase 3 study 3002 is initiated, as proposed. This does not give FDA adequate time to review the studies and assure patient safety prior to patients going beyond one month duration of dosing (the duration supported by the one month toxicity studies to be submitted in the IND).*

*In addition, the sponsor will need to provide the in vivo genotoxicity study results and the results from fertility and teratology studies (Segment I and II reprotox) prior to initiation of their Phase 3 program, as stated in response to question 1.*

**Action Items:**

1. Data from reproductive toxicology (Segments I and II) and genotoxicity studies should be submitted prior to the initiation of Phase 3 studies.
2. The duration of clinical studies should be supported by the comparable duration of animal studies.
3. The sponsor plans to conduct reproductive toxicology studies. However, they have not decided when the studies would be initiated.
4. The sponsor does not plan to use Lantus® in the mixing studies with NPH or Ultralente.
5. Clinical studies are required to make a clinical claim.

**Undecided:**

1. The Agency is to get back to the sponsor concerning whether or not two-year carcinogenicity study would be required before an NDA is submitted.\*

\* Dr. Jeri El Hage called Dr. \_\_\_\_\_ on 11/16/00 and informed her that a one year carcinogenicity study in rats with insulin comparator arm would be acceptable.

**/S/**

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Julie Rhee  
Minutes Preparer

**/S/**

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David Orloff, M.D.  
Chair Concurrence

Drafted by: JRhee 11-15-00

Initialed by: Malozowskis 11-16-00/Ahn 11-16-00/Zawadzki 11-16-00/El Hage 11-16-00/Koller 11-20-00/HRhee 11-21-00/Wei 11-21-00

F/T by: JRHee 11-22-00

MEETING MINUTES