**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

| | |
|---|---|
| NDA: 21-629/S-015 | Submission Date: June 27, 2007 |
| Brand Name | APIDRA |
| Generic Name | rDNA human insulin analog |
| Reviewer | Manoj Khurana, Ph.D. |
| Team Leader | Sally Y. Choe, Ph.D. |
| OCP Division | Clinical Pharmacology 2 |
| OND Division | Metabolism and Endocrinology Products |
| Sponsor | Sanofi-Aventis, U.S. LLC |
| Submission Type | Supplemental NDA |
| Formulation | Solution for SC injection |
| Indication | Treatment of with diabetes mellitus |

## 1. Executive Summary

Sanofi-Aventis, U.S. LLC submitted the efficacy supplement for pediatric indication under NDA 21-629/015 for Apidra (HMR-1964 Insulin glulisine). The original NDA application was approved on April 16, 2004. Under the current submission, the sponsor submitted final clinical study reports from two clinical studies, Study D3001 and Study 1017, which were conducted in support for use of Apidra in patients 4 through 17 years old with diabetes mellitus. While the Study D3001 was conducted for efficacy and safety, Study 1017 was a clinical pharmacology study submitted previously under the original NDA 21-629 submission. Study 1017 report was reviewed by Dr. Xiaoxiong (Jim) Wei previously and is included with this application as a supporting study for the efficacy trial (Study D3001). The insulin glulisine formulation in these studies is the same as the currently marketed formulation.
Since Study 1017 report has been reviewed previously, this reviewer focused on review for the proposed labeling changes.

### 1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has found the Supplemental NDA 21-629/015 for Apidra (HMR-1964 Insulin glulisine) *acceptable* pending agreement on the language of package insert.

### 1.2 Phase IV Commitments

None

### 1.3 Summary of Important Clinical Pharmacology Findings

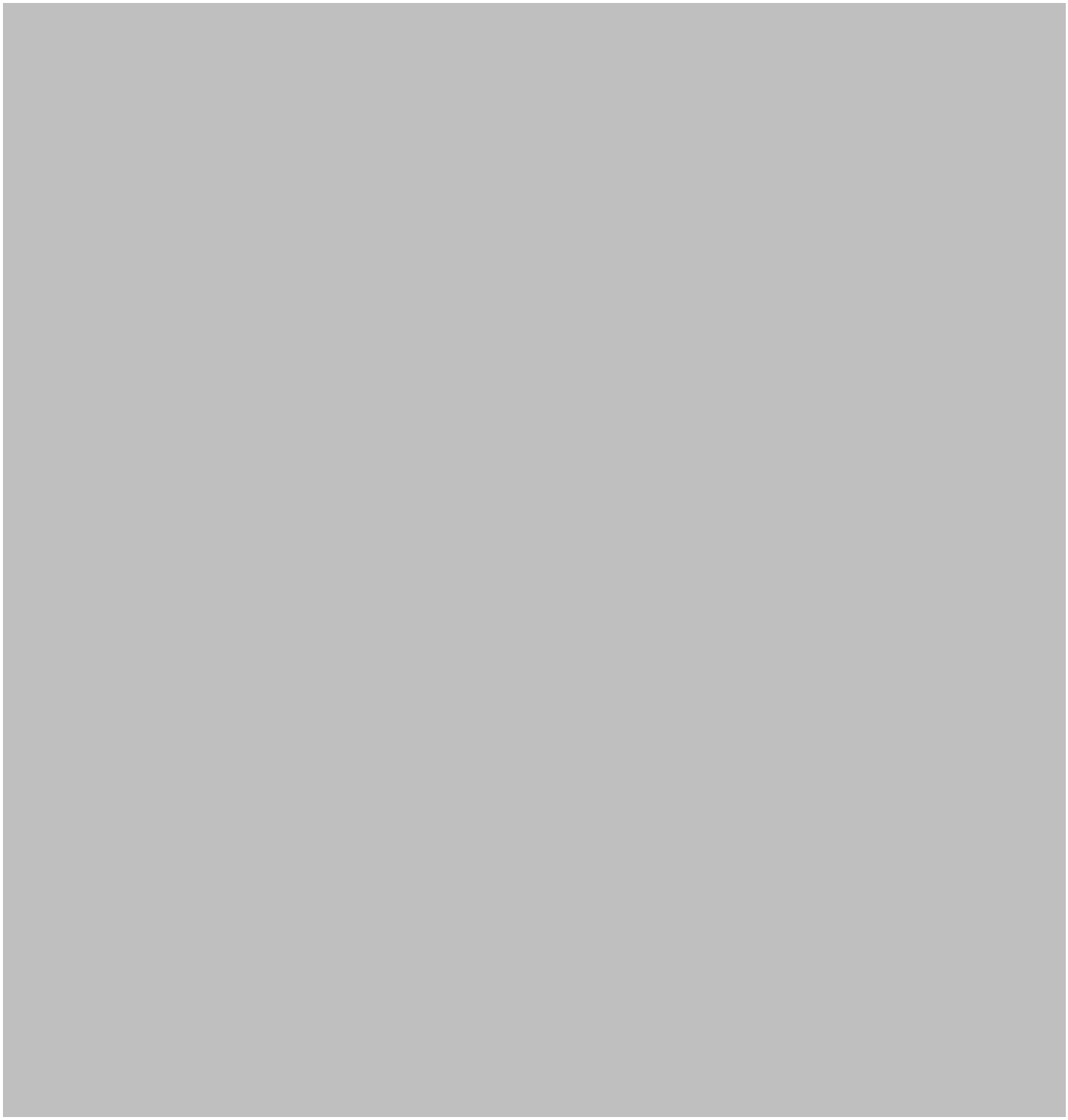
During the review of the proposed labeling changes pertaining to the Study 1017, this reviewer noticed that some of pharmacokinetic parameters such as Cmax and Tmax in the clinical pharmacology section of the label were not reflective of the observed data. It was found that throughout the label, these parameters were based on model predicted values instead of observed data.

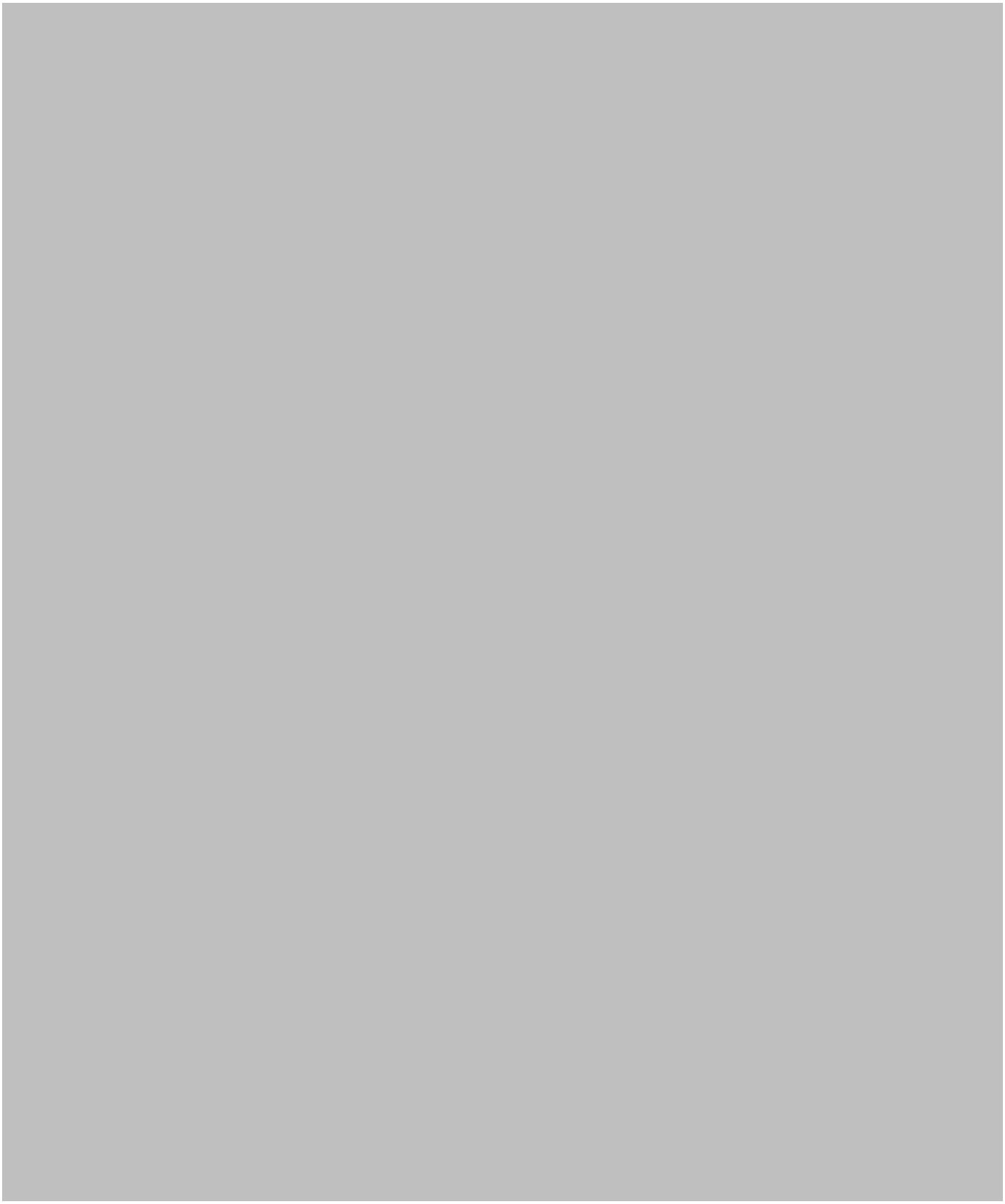
The Agency requested the sponsor to revise the proposed label with observed PK parameters and provide the electronic raw data set in the form of SAS data sets for clinical studies 1006, 1008, and 1010 from which PK information has been described in the label. The revisions in the label with regards to Cmax and Tmax were reviewed and additional recommendation for label has been made. See Appendix 4.1 for detailed review of the sponsor's revised PK parameters.

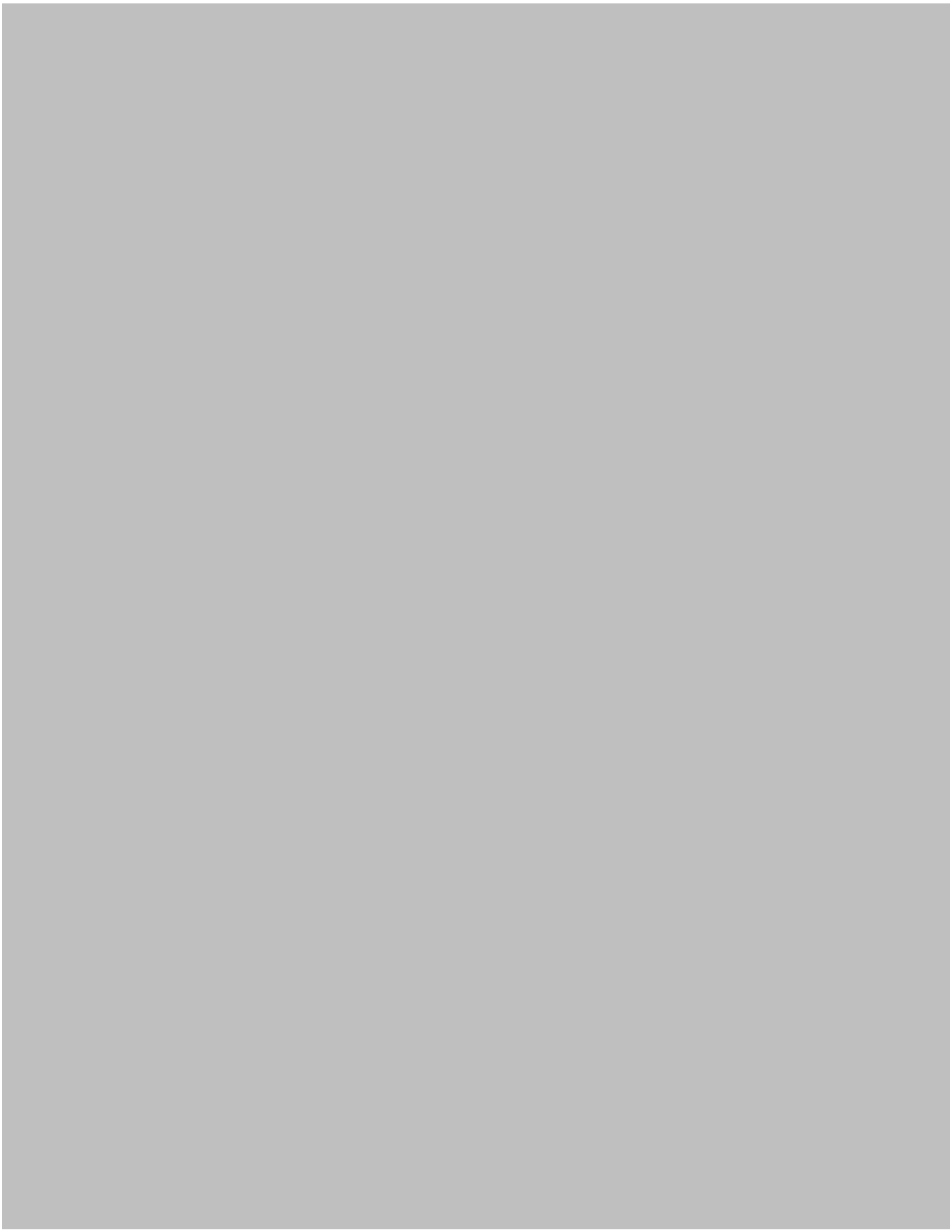
## 3. Detailed Labeling Recommendations

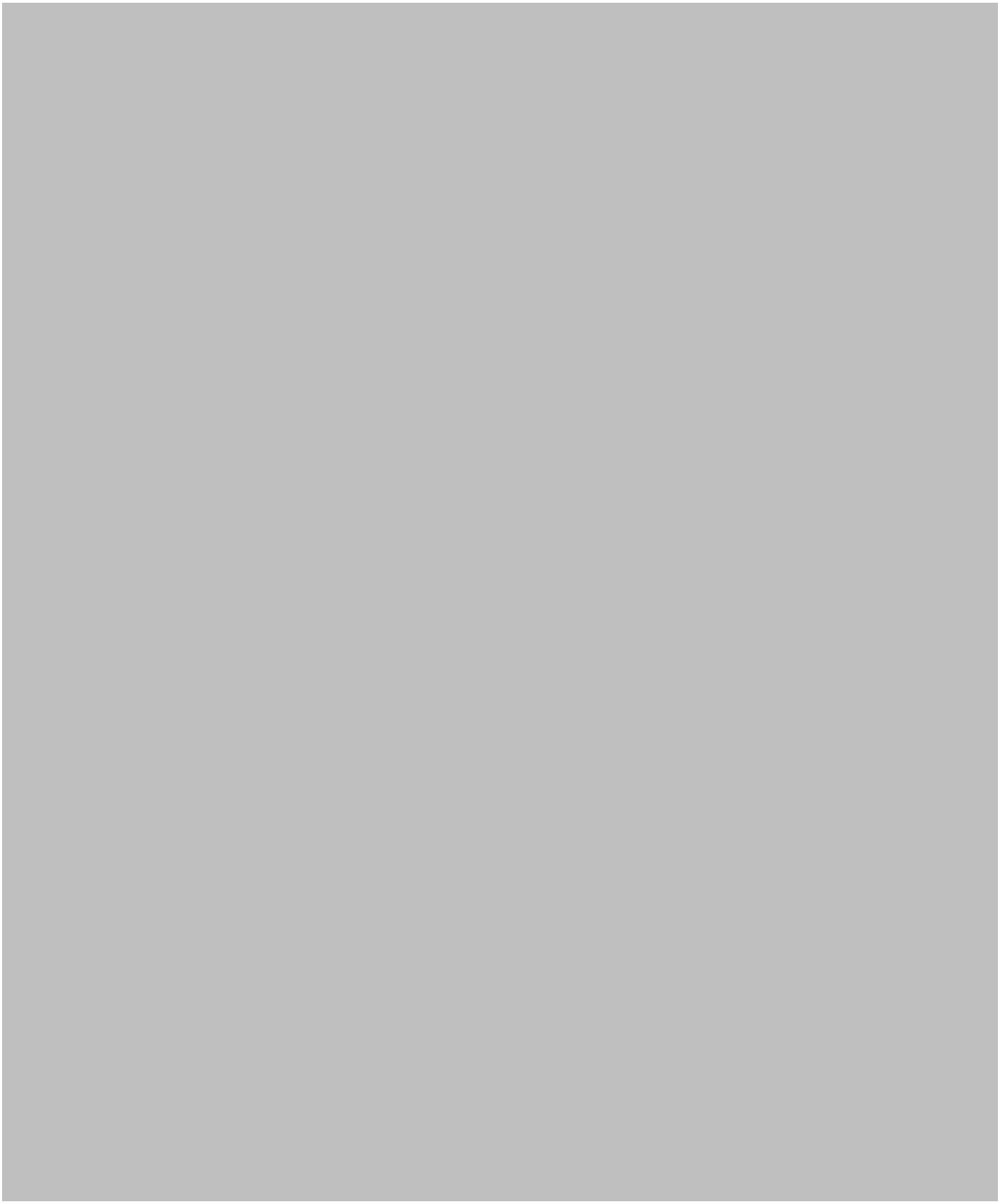
**Recommendation:** (**RED** indicates addition and ~~strikethrough text~~ indicates deletion.)

### 12. CLINICAL PHARMACOLOGY

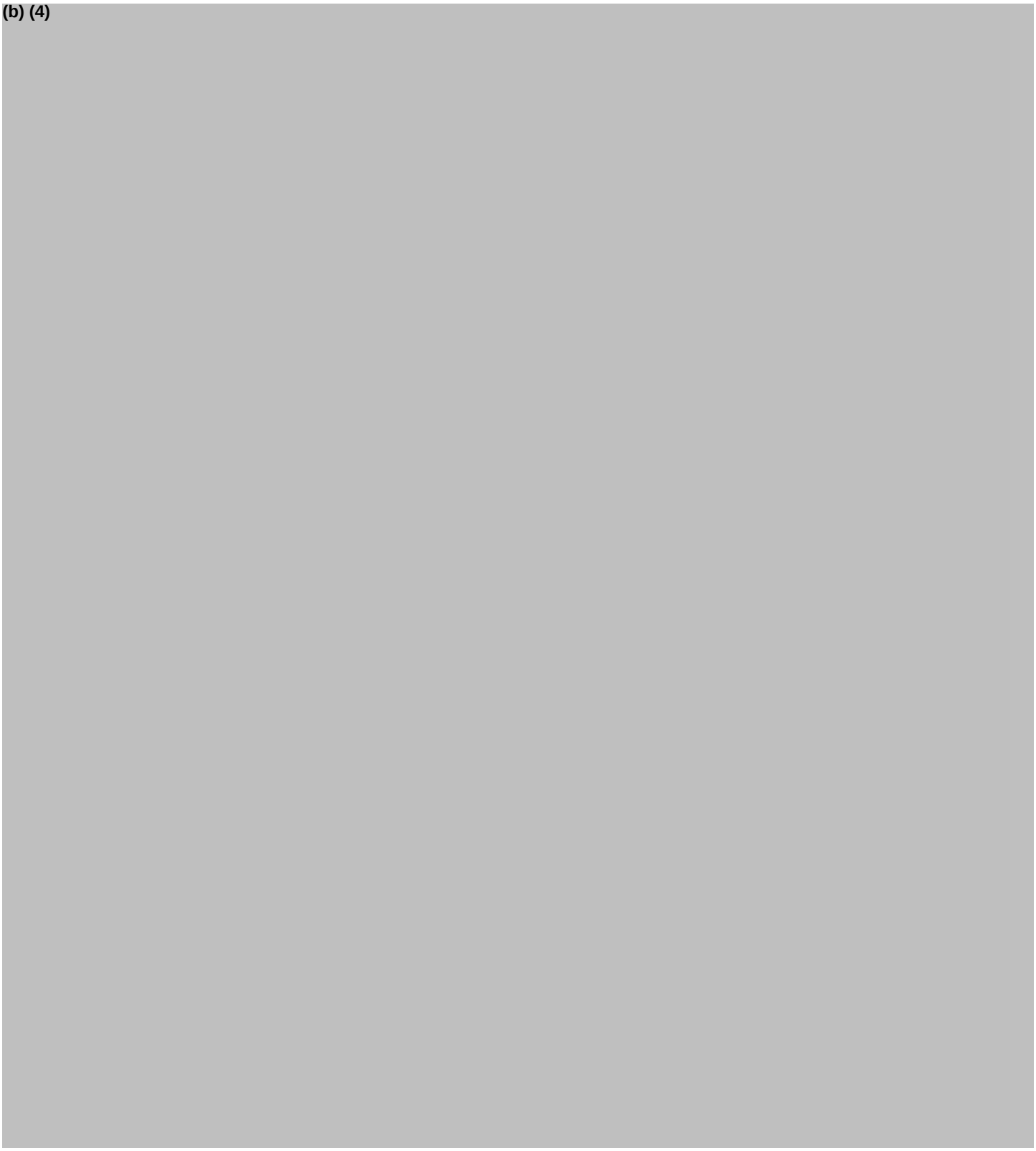








**(b) (4)**



## 4. Appendix

### 4.1 Comparison of Non-compartmental Analysis Data:

#### 4.1.1 Clinical Pharmacology Study 1006

Summary of Sponsor's Pharmacokinetic Analysis is provided in the Tables below:

***HMR1964A / 1006 - Results from non-compartmental analysis (NCA)***
***Subjects with head-to-head comparison HMR1964 versus regular human insulin (RHI)***
***Cmax [µIU/mL] derived from observed concentrations***

| | | Insulin | |
|---|---|---|---|
| | | HMR1964 | RHI |
| **Parameter** | | | |
| **Cmax** | **Median** | 82 | 40 |
| | **Min** | 71 | 36 |
| | **Max** | 115 | 58 |

***HMR1964A / 1006 - Results from non-compartmental analysis (NCA)***
***Subjects with head-to-head comparison HMR1964 versus regular human insulin (RHI)***
***Tmax [min] derived from observed concentrations***

| | | Insulin | |
|---|---|---|---|
| | | HMR1964 | RHI |
| **Parameter** | | | |
| **Tmax** | **Median** | 90 | 225 |
| | **Min** | 70 | 130 |
| | **Max** | 120 | 330 |

**Note:** Sponsor calculated the summary statistics for Cmax and Tmax obtained by non-compartmental analysis using the average of the values obtained for the two visits (Visit 1 and 4 or Visit 2 and 3) for each subject. In this reviewer's opinion the individual values can be used and provide more realistic statistics and better understanding of the range of parameter values considering the small sample size (n=8) as is shown in the Reviewer's Analysis section below.

Reviewer's Analysis:

Individual PK Parameters for Insulin:

| | | VISIT | | | | VISIT | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 4 | 2 | 3 | 1 | 4 | 2 | 3 |
| **TRT** | **ID** | **Cmax** | **Cmax** | **Cmax** | **Cmax** | **Tmax** | **Tmax** | **Tmax** | **Tmax** |
| **HMR 1964** | **4** | (b) (4) | | | | | | | |
| | **9** | | | | | | | | |
| | **12** | | | | | | | | |
| | **14** | | | | | | | | |
| | **19** | | | | | | | | |
| | **20** | | | | | | | | |
| | **23** | | | | | | | | |
| | **24** | | | | | | | | |
| **Regular human insulin** | **4** | | | | | | | | |
| | **9** | | | | | | | | |
| | **12** | | | | | | | | |
| | **14** | | | | | | | | |
| | **19** | | | | | | | | |
| | **20** | | | | | | | | |
| | **23** | | | | | | | | |
| | **24** | | | | | | | | |

CMAX:

| | | Insulin | |
|---|---|---|---|
| | | **HMR1964** | **RHI** |
| **Parameter** | **Statistics** | | |
| **Cmax** | **Median** | 83.54 | 41.055 |
| | **Min** | 53.4 | 32.79 |
| | **Max** | 164.97 | 60.59 |

TMAX:

| | | Insulin | |
|---|---|---|---|
| | | **HMR1964** | **RHI** |
| **Parameter** | **Statistics** | | |
| **Tmax** | **Median** | 100 | 240 |
| | **Min** | 60 | 80 |
| | **Max** | 120 | 360 |

The summary statistics from reviewer's analysis were different from the sponsors' analysis due to all data being used for computing summary statistics by this reviewer.

### 4.1.2 Clinical Pharmacology Study 1008

Summary of Sponsor's Pharmacokinetic Analysis is provided in the Tables below:

***HMR1964A / 1008 - Results from non-compartmental analysis (NCA)***
***Cmax [µIU/mL] derived from observed concentrations***

| | | Treatment | |
|---|---|---|---|
| | | **HMR1964 (before meal)** | **RHI (30 min before meal)** |
| **Parameter** | | | |
| **Cmax** | **Median** | 83 | 50 |
| | **Min** | 40 | 35 |
| | **Max** | 131 | 71 |

***HMR1964A / 1008 - Results from non-compartmental analysis (NCA)***
***Tmax [min] derived from observed concentrations***

| | | Treatment | |
|---|---|---|---|
| | | **HMR1964 (before meal)** | **RHI (30 min before meal)** |
| **Parameter** | | | |
| **Tmax** | **Median** | 60 | 120 |
| | **Min** | 40 | 60 |
| | **Max** | 120 | 239 |

Reviewer's Analysis:

| **Treatment** | **HMR 1964 (before meal)** | | **RHI (30 min before meal)** | |
|---|---|---|---|---|
| **ID** | **Cmax** | **Tmax** | **Cmax** | **Tmax** |
| **1** | 61.7 | 90 | 38.91 | 61 |
| **2** | 130.64 | 40 | 71.04 | 60 |
| **3** | 86.25 | 41 | 64.88 | 120 |
| **4** | 72.98 | 90 | 44.65 | 239 |
| **5** | 88.86 | 60 | 49.52 | 60 |
| **6** | 79.14 | 90 | 51.44 | 90 |
| **7** | 106.3 | 40 | 64.52 | 90 |
| **8** | 75.55 | 60 | 40.4 | 120 |
| **9** | 83.94 | 60 | 43.19 | 90 |
| **10** | 78.49 | 90 | 49.82 | 120 |
| **12** | 103.7 | 60 | 50.1 | 121 |
| **13** | 66.98 | 90 | 35.04 | 180 |
| **14** | 68.83 | 60 | 56.22 | 120 |
| **15** | 82.51 | 60 | 55.26 | 180 |
| **16** | 87.3 | 90 | 38.63 | 180 |
| **17** | 117.12 | 40 | 68.17 | 120 |
| **18** | 62.16 | 120 | 37.83 | 180 |
| **19** | 87.24 | 40 | 54.8 | 120 |
| **20** | 94.8 | 40 | 35.61 | 120 |
| **5011** | 40.31 | 40 | 58.09 | 120 |
| **N** | **20** | **20** | **20** | **20** |
| **Median** | **83.23** | **60** | **49.96** | **120** |
| **Min** | **40.31** | **40** | **35.04** | **60** |
| **Max** | **130.64** | **120** | **71.04** | **239** |

The results from reviewer's analysis matched to the sponsors' results.

### 4.1.3 Clinical Pharmacology Study 1010

Summary of Sponsor's Pharmacokinetic Analysis is provided in the Tables below:

***HMR1964A / 1010 - Results from non-compartmental analysis (NCA)***
***Cmax [µIU/mL] derived from observed concentrations***

| | | Insulin | |
|---|---|---|---|
| | | HMR1964 | RHI |
| **Parameter** | | | |
| **Cmax** | **Median** | 192 | 86 |
| | **Min** | 98 | 43 |
| | **Max** | 380 | 175 |

***HMR1964A / 1010 - Results from non-compartmental analysis (NCA)***
***Tmax [min] derived from observed concentrations***

| | | Insulin | |
|---|---|---|---|
| | | HMR1964 | RHI |
| **Parameter** | | | |
| **Tmax** | **Median** | 85 | 150 |
| | **Min** | 49 | 90 |
| | **Max** | 150 | 240 |

Reviewer's analysis:

| TRT | HMR 1964 | | Regular human insulin | |
|---|---|---|---|---|
| **ID** | **Cmax** | **Tmax** | **Cmax** | **Tmax** |
| **11** | 152 | 80 | 101 | 150 |
| **12** | 200 | 120 | 87 | 150 |
| **13** | 161 | 61 | 90 | 90 |
| **14** | 148 | 120 | 100 | 120 |
| **15** | 149 | 90 | 105 | 150 |
| **16** | 216 | 90 | 97 | 180 |
| **17** | 254 | 80 | 131 | 150 |
| **18** | 351 | 70 | 130 | 120 |
| **19** | 98 | 70 | 53 | 240 |
| **21** | 353 | 49 | 121 | 120 |
| **22** | 146 | 120 | 125 | 120 |
| **23** | 301 | 50 | 124 | 90 |
| **24** | 245 | 80 | 68 | 240 |
| **25** | 184 | 120 | 120 | 120 |
| **26** | 170 | 120 | 54 | 300 |
| **27** | 288 | 90 | 107 | 80 |
| **28** | 135 | 150 | 93 | 150 |
| **29** | 380 | 80 | 203 | 180 |

| | | | | |
|---|---|---|---|---|
| **N** | **18** | **18** | **18** | **18** |
| **Median** | **192** | **85** | **103** | **150** |
| **Min** | **98** | **49** | **53** | **80** |
| **Max** | **380** | **150** | **203** | **300** |

The results from reviewer's analysis matched to the sponsors' results.

## 4.2 Study 1017 Synopsis




**CLINICAL STUDY REPORT No. F2002CLN0613**

**PHARMACOKINETICS AND SAFETY OF 0.15 IU/kg HMR1964 (INSULIN GLULISINE) AND REGULAR HUMAN INSULIN INJECTED SUBCUTANEOUSLY AS A SINGLE DOSE IN PEDIATRIC SUBJECTS WITH TYPE 1 DIABETES IN A SINGLE-CENTER, DOUBLE-BLIND, RANDOMIZED, TWO-WAY CROSSOVER STUDY**

**HMR1964A/1017**

**(FARMOVS 352/2002)**

| | |
|---|---|
| Clinical development phase | I |
| Investigator | [redacted] |
| | See Appendix A.2.1 List and description of investigators |
| Date first subject was enrolled | 15 October 2002 |
| Date last subject completed the study | 13 January 2003 |
| Clinical Pharmacologist / Medical Expert<br>Clinical Pharmacokineticist<br>Study Manager<br>Biostatistician | (b) (4) |
| Report type | Clinical/biometric, Final |
| Date of issue | 14 April 2003 |

GCP Statement: See ETHICS AND ADMINISTRATION

# STUDY SYNOPSIS

## HMR1964A/1017

### Title
Pharmacokinetics and safety of 0.15 IU/kg HMR1964 (insulin glulisine) and regular human insulin injected subcutaneously as a single dose in pediatric subjects with type I diabetes in a single-center, double-blind, randomized, two-way crossover study

### Investigator, study site
(b) (4)

### Phase
I

### Indication
Type 1 diabetes

### Objectives
*Primary objective*

To investigate the pharmacokinetics of insulin glulisine and regular human insulin (HOE31HPR100) in pediatric type I diabetic subjects.

*Secondary objectives*

To investigate prandial glucose profiles of insulin glulisine and regular human insulin administered before a standardized meal in pediatric type I diabetic subjects. To investigate the safety following a single subcutaneous dose of insulin glulisine in pediatric type I diabetic subjects.

### Design
This study used a single-center, single-dose, double-blind, randomized, two-way crossover design.

- Insulin glulisine administered 2 minutes before a standardized liquid meal
- Regular human insulin administered 2 minutes before a standardized liquid meal

The study consisted of 4 trial periods – trial period 0 (screening visit), trial periods 1 and 2 (treatment visits) and trial period 3 (follow-up visit).

### Population
Twenty (20) pediatric type I diabetic subjects (10 per age class) of either gender. The 2 age classes were build by children aged between 5 and 11 years and adolescents aged between 12 and 17; HbA1c ≤ 11%.

### Treatments
Insulin glulisine (Batch no. 1377): 0.15 IU/kg, single dose injected subcutaneously in the periumbilical abdomen 2 minutes before a standardized liquid meal.

Regular human insulin (Batch no. 40W069): 0.15 IU/kg, single dose injected subcutaneously in the periumbilical abdomen 2 minutes before a standardized liquid meal.

### Pharmacokinetic data

The *serum insulin* profile was characterized by the following pharmacokinetic parameters:

- Area under the insulin concentration-time curve between
  - 0 h and 1 h after injection ($AUC_{(0-1h)}$, µIU.min/mL)
  - 0 h and 2 h after injection ($AUC_{(0-2h)}$, µIU.min/mL)
  - 0 h and 4 h after injection ($AUC_{(0-4h)}$, µIU.min/mL)
  - 0 h and 6 h after injection ($AUC_{(0-6h)}$, µIU.min/mL)
- Maximum concentration ($C_{max}$, µIU/mL)
- Time to maximum concentration ($T_{max}$, min)
- Mean residence time (MRT, min)

### Pharmacodynamic data

The analysis variables were taken from profiles up to 6 hours:

- Area under the baseline subtracted glucose concentration time curve between
  - 0 h and 1 h ($AUC_{(0-1h)}$, mg.h/dL)
  - 0 h and 2 h ($AUC_{(0-2h)}$, mg.h/dL)
  - 0 h and 4 h ($AUC_{(0-4h)}$, mg.h/dL)
  - 0 h and 6 h ($AUC_{(0-6h)}$, mg.h/dL)
- Time to maximum baseline subtracted blood glucose concentration ($t_{max}$, min)
- Maximum blood glucose concentration ($GLU_{max}$, mg/dL)
- Maximum blood glucose excursion from baseline ($\Delta GLU_{max}$, mg/dL)
- Minimum blood glucose concentration ($GLU_{min}$, mg/dL)
- Time to minimum blood glucose concentration ($t_{min}$, min)

Different from the procedure outlined in the protocol, additional analyses of glucose exposure and excursion were confined to data obtained within 4 hours after injection.

- Time to maximum baseline subtracted glucose concentration within 4 hours ($t_{max-4h}$, min)
- Maximum blood glucose concentration within 4 hours ($GLU_{max-4h}$, mg/dL)
- Maximum blood glucose excursion from baseline within 4 hours ($\Delta GLU_{max-4h}$, mg/dL)
- Minimum blood glucose concentration after $GLU_{max-4h}$ within 6 hours ($GLU_{min-4h}$, mg/dL)
- Time to minimum blood glucose concentration after $GLU_{max-4h}$ within 6 hours ($t_{min-4h}$, min)

### Safety data

Hematology, clinical chemistry, human insulin antibodies at baseline, urinalysis, physical examination, blood pressure, pulse rate, core body temperature, inspection of injection site and adverse events.

### Study duration and dates

The study took place between 15 October 2002 and 13 January 2003.

### Statistical procedures

Descriptive statistics were given for demographic, pharmacokinetic, pharmacodynamic and safety parameters.

*Pharmacokinetics:*

Analyses of variance (ANOVA) on AUCs, MRT and $C_{max}$ with adjustments for treatment, period, sequence and subject within sequence effects were performed by age class using the natural log transformed values to compare treatments within age class. Point estimates and 95% confidence intervals were calculated for the treatment ratios per age class.

ANOVAs with adjustments for age class, period, sequence and subject within sequence effects were performed by treatment to compare age classes within treatment. Point estimates and 95% confidence intervals were calculated for the age class ratios per treatment.

$T_{max}$ was analyzed by non-parametric analyses. 95% non-parametric confidence intervals for the respective median treatment and age class differences were calculated

*Pharmacodynamics:*

ANOVAs were performed on uncorrected blood glucose concentrations for AUCs, $GLU_{max}$- and $GLU_{min}$-parameters and on baseline corrected glucose concentrations for AUCs, $\Delta GLU_{max}$- and $\Delta GLU_{min}$-parameters. The interpretation was based on 95% confidence intervals. These ANOVAs, adjustments for treatment, period, sequence and subject within sequence effects included, were performed by age class, and point estimates and 95% confidence intervals were calculated for the treatment ratios. Corresponding analyses were performed for the whole sample.

ANOVAs with adjustments for age class, period, sequence and subject within sequence effects were performed by treatment to compare age classes within treatment. Point estimates and 95% confidence intervals were calculated for the age class differences per treatment.

Fieller's Theorem was used to calculate the 95% confidence intervals for the mean ratios of all pair-wise comparisons.

As supportive information, mean differences of all pair-wise comparisons were calculated for baseline corrected parameters.

The time-parameters were analyzed by non-parametric analyses. 95% non-parametric confidence intervals for the respective median treatment and age class differences were calculated

## Interim analysis

Not applicable to this study.

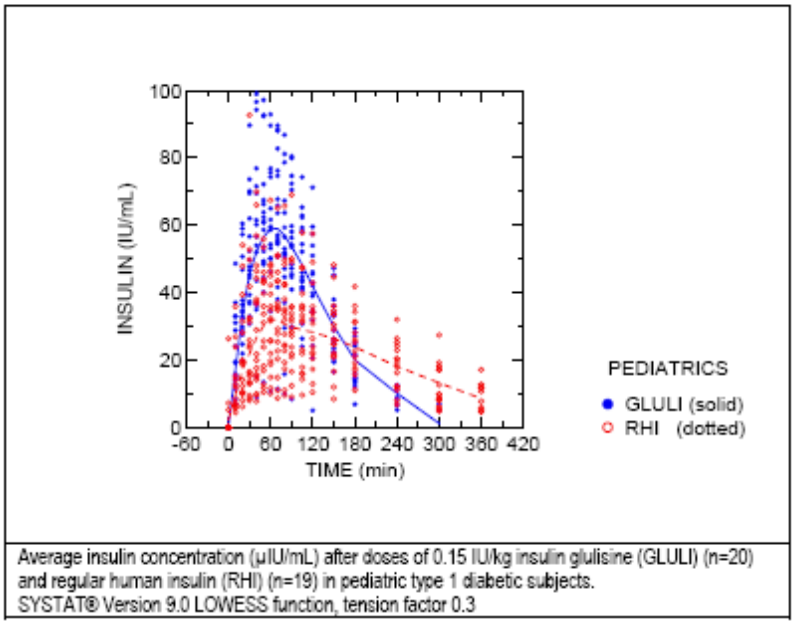
## Results - Study subjects and conduct

A total of 20 type 1 diabetic pediatric subjects, consisting of 10 children (5 male and 5 female), between 7 and 11 years of age, with body mass indices between 16.4 and 22.7 $kg/m^2$ and 10 adolescents (4 male and 6 female), between 12 and 16 years of age, with body mass indices between 17.7 and 26.3 $kg/m^2$ were enrolled, randomized and exposed to study medication (safety population). All 20 subjects completed the study according to the protocol and were included in the pharmacodynamic and pharmacokinetic analyses. One subject was excluded from pharmacokinetic analysis of regular human insulin. There were no major protocol deviations during the study.

## Results – Pharmacokinetics

In pediatric type I diabetic subjects, equally in each age class children and adolescents, insulin glulisine was more rapidly absorbed than regular human insulin. The fractional AUCs were larger, and $C_{max}$ was higher with an earlier $T_{max}$ for insulin glulisine. MRT was distinctly shorter indicating the shorter residence of insulin glulisine in the systemic circulation compared to regular human insulin.

The 2 age classes, children and adolescents, presented an almost equal pharmacokinetic profile after insulin glulisine with a slight trend towards higher exposure in adolescents. In contrast, the comparison between age classes for regular insulin revealed on average 60% higher exposure in adolescents.




Average insulin concentration (µIU/mL) after doses of 0.15 IU/kg insulin glulisine (GLULI) (n=20) and regular human insulin (RHI) (n=19) in pediatric type 1 diabetic subjects.
SYSTAT® Version 9.0 LOWESS function, tension factor 0.3

| Variable | Geometric mean | | Point estimate (95% confidence interval)* |
|---|---|---|---|
| | Glulisine (n = 20) | RHI (n = 19) | Glulisine / RHI (n = 19) |
| $AUC_{(0-1h)}$ [µIU.min/mL] | 2287 | 1246 | 176 % (126.9 ; 243.8 %) |
| $AUC_{(0-2h)}$ [µIU.min/mL] | 5232 | 2994 | 169 % (126.9 ; 224.3 %) |
| $AUC_{(0-4h)}$ [µIU.min/mL] | 7624 | 5703 | 130 % (99.3 ; 170.3 %) |
| $AUC_{(0-6h)}$ [µIU.min/mL] | 8361 | 7052 | 116 % (89.5 ; 149.8 %) |
| $C_{max}$ [µIU/mL] | 58 | 33 | 171 % (126.9 ; 229.4 %) |
| $T_{max}$ [min] | 54** | 66** | -8 min (-24 ; 7 min)## |
| MRT [min] | 88 | 137 | 64 % (59.0 ; 70.4 %) |

* Point estimates and 95% confidence intervals for the ratio of treatment means, based on (ln) transformed data
\# Point estimates and 95% confidence intervals for the respective median differences from non-parametric data analysis
** Median

## Results – Pharmacodynamics

Blood glucose exposures and excursions were lower after insulin glulisine than after regular human insulin, when given immediately before meal, in the pediatric population as a whole as well as in both age classes, children and adolescents. A standardized liquid meal was given to compensate for the glucose lowering effect of the added exogenous insulin and to prevent hypoglycemic events in this non-clamp study, but not given to precisely quantify and compare the glucodynamic responses to either insulin.

| Variable | Arithmetic mean | | Point estimate (95% CI)# |
|---|---|---|---|
| | Glulisine (n = 20) | RHI (n = 20) | Glulisine / RHI (n = 20) |
| $AUC_{(0-4h)}$ [mg.h/dL] | 419 | 627 | 67% (55.3 ; 79.6%) |
| $AUC_{(0-6h)}$ [mg.h/dL] | 641 | 801 | 80% (66.6 ; 95.4%) |
| $GLU_{max-4h}$ [mg/dL] | 298 | 352 | 85% (76.8 ; 93.3%) |
| $\Delta GLU_{max-4h}$ [mg/dL] | 166 | 224 | 74% (63.4 ; 85.8%) |
| $t_{max-4h}$ [min] | 120** | 120** | 0.0 (-24.0 ; 29.0)## |

# Point estimates and 95% CIs for the ratio of treatment means, according to Fieller's Theorem, based on untransformed data.
## Point estimates and 95% CIs for the respective median differences, from non-parametric data analysis.
** Median

## Results - Safety

Twenty subjects were evaluable for safety.

No serious adverse events were reported during the study. A total of 19 adverse events were reported in 9 subjects of which 1 (urticaria) was reported to be related to study drug (regular human insulin).

Twelve subjects showed symptomatic hypoglycemia (18 events) during the study, of which 9 subjects were reported with episodes before administration of study medication. In addition, 6 subjects (11 events) showed hypoglycemia without any symptoms. None of these cases met the protocol definition of severe hypoglycemia. Oral carbohydrates were required for all episodes of hypoglycemia, only one i.v. glucose infusion was required to prevent imminent nocturnal hypoglycemia prior to injection of study medication.

No clinically relevant abnormalities in laboratory variables (hematology and clinical chemistry) were observed. Local tolerance was good.

## Conclusions

In pediatric type I diabetic subjects, equally in each age class children and adolescents, insulin glulisine was more rapidly absorbed and had a shorter residence in the systemic circulation compared to regular human insulin.

Insulin glulisine displays pharmacokinetic and pharmacodynamic properties in pediatric type 1 diabetic subjects, which classify insulin glulisine as a rapid acting insulin analogue also in this patient population.

Both treatments were safe and well tolerated.

## 4.3 OCP FILING MEMO

| *Office of Clinical Pharmacology*<br>*New Drug Application Filing and Review Form* | | | |
|---|---|---|---|
| **General Information About the Submission** | | | |
| | Information | | Information |
| NDA Number | 21-629/015 | Brand Name | Apidra® |
| OCP Division (I, II, III, IV, V) | DCP II | Generic Name | rDNA human insulin analog |
| Medical Division | DMEP | Drug Class | |
| OCP Reviewer | Sang M. Chung, Ph.D. | Indication(s) | For treatment of (b) (4) with diabetes mellitus (b) (4) (b) (4) |
| OCP Pharmacometrics Reviewer | | Dosage Form | Injection |
| OCPB Team Leader | Sally Choe, Ph.D. (Acting) | Dosing Regimen | Apidra® should be given within 15 minutes before a meal or within 20 minutes after starting a meal. The dosage should be individualized. |
| Date of Submission | June 27, 2007 | Route of Administration | Subcutaneous |
| Estimated Due Date of OCP Review | March 14, 2008 | Sponsor | Sanofi-Aventis, U.S. LLC |
| PDUFA Due Date | | Priority Classification | Standard |
| Division Due Date | | | |

| **Clin. Pharm. and Biopharm. Information** | | | | |
|---|---|---|---|---|
| | **"X" if included at filing** | **Number of studies submitted** | **Number of studies reviewed** | **Critical Comments If any** |
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **X** | | | |
| **Tabular Listing of All Human Studies** | **X** | | | |
| **HPK Summary** | **X** | | | |
| **Labeling** | **X** | | | |
| **Reference Bioanalytical and Analytical Methods** | | | | |
| **I. Clinical Pharmacology** | **X** | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | **X** | | | |
| ***Healthy Volunteers-*** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| ***Patients-*** | X | | | Study 1017 |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |

| | | | | |
|---|---|---|---|---|
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| PD: | X | | | Study 1017 (blood glucose) |
| Phase 2: | | | | |
| Phase 3: | | | | |
| PK/PD: | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| Population Analyses - | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability: | | | | |
| Relative bioavailability - | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies: | | | | |
| Dissolution: | | | | |
| (IVIVC): | | | | |
| Bio-wavier request based on BCS | | | | |
| BCS class | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies: | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | 1 | 1 | | |

| Filability | | |
|---|---|---|
| | "X" if yes | Comments |
| **Application filable ?** | **X** | **Comments to the Sponsor:**<br>Electronic data for the clinical pharmacology study (Study 1017) were not included in the submission. Please, provide electronic data for primary analyses: individual pharmacokinetic and pharmacodynamic data, and individual serum insulin and glucose concentrations. |

| Submission in brief | Reviewer's Comments: |
|---|---|
| | This is an efficacy supplement for pediatric indication.<br><br>Two studies were conducted for the proposed indication: one study for clinical pharmacology (Study 1017) and the other study for efficacy and safety (Study D3001). The clinical pharmacology study was submitted previously with the original NDA 21-629 submission and has been reviewed by Dr. Xiaoxiong (Jim) Wei. The insulin glulisine formulation was the same as the currently marketed formulation in the studies.<br><br>The clinical pharmacology study was conducted in the 20 pediatric type I diabetic subjects (two age groups: age between 5 and 11 years, and age between 12 and 17). Single dose (0.15 IU/kg) of insulin glulisine or regular insulin was administered before a standardized liquid meal. Serum insulin concentration-time profiles and glucose concentration-time profiles were shown in Figure 1 and 2.<br><br>The clinical pharmacology study was conducted at (b) (4) (b) (4) and the analytical study was conducted at (b) (4) (b) (4) DSI inspection will not be requested on Study 1017 sites since this study report has been reviewed previously and is a supporting study for the efficacy trial (Study D3001) rather than a pivotal study.<br><br>Clinical Pharmacology reviewer will focus on proposed labeling<br><br>[redacted] |

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/s/
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Sang Chung
8/30/2007 01:10:59 PM
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Sally Choe
8/31/2007 07:27:23 AM
BIOPHARMACEUTICS

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/s/
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Manoj Khurana
7/17/2008 02:55:38 PM
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Sally Choe
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