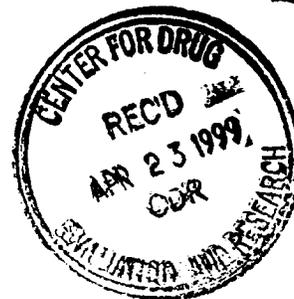


Appendix F
NDA Submission Letter



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April 9, 1999



Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD 510)
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Attention: Central Document Room
Park Building, Room 214
1240 Parklawn Drive
Rockville, MD 20852

Subject: New Drug Application
insulin glargine injection
NDA 21-081

Dear Dr. Sobel,

In conformance with 21 CFR 314.1, Hoechst Marion Roussel, Inc. is submitting a New Drug Application for insulin glargine injection. The development of insulin glargine has been a collaborative effort between the applicant and the Reviewing Division at the FDA. This NDA provides support for the use of insulin glargine injection once-daily by subcutaneous administration for patients with diabetes mellitus who require a basal insulin for the control of hyperglycemia. The submission is 479 volumes in length.

In the analysis of the Phase III study results, the applicant has identified an advantage of insulin glargine compared to NPH human insulin in the frequency of the occurrence of clinically important hypoglycemic episodes. With equal maintenance of glycemic control (glycohemoglobin) and equal or better fasting glucose control in subjects treated with insulin glargine compared with NPH, significantly fewer subjects treated with insulin glargine reported severe and nocturnal hypoglycemia. A rationale for the observed advantage in clinical hypoglycemia is based on the smooth, peakless time-action profile of insulin glargine compared to that of NPH observed in Phase I studies. We believe these results justify consideration by the Agency to give insulin glargine priority review.

The applicant is cognizant in making this request for priority review of the discussions held with the Agency regarding the practical limitations of the reporting of admittedly subjective hypoglycemic symptoms by subjects in an open study design. However, in the process of data collection and analysis this limitation in the data has been taken into account and an attempt has been made to make the data as objective as possible. Several measures of hypoglycemia are reported, including all symptomatic hypoglycemic events with subsets of severe symptomatic hypoglycemia, using the DCCT definition of the patient requiring assistance of another person, and nocturnal symptomatic hypoglycemia. In addition, subjects were requested to determine blood glucose values at the time of the episode and episodes with blood glucose values less than 50 mg/dL and less than 36 mg/dL are presented. Furthermore, we have identified a subgroup of subjects reporting severe neurologic symptoms of hypoglycemia, including coma, convulsions and syncope. With progressively more restrictive and more clinically important definitions of hypoglycemia, the advantage of insulin glargine compared to NPH is more apparent. Finally, we have compared the frequency of hypoglycemic episodes to those reported in major clinical trials

of subjects with type 1 and type 2 diabetes. The rates of severe hypoglycemia in subjects with type 1 diabetes are comparable to those reported in the DCCT and in subjects with type 2 diabetes the rates are comparable to those reported in the UKPDS. Therefore, we believe the results are objective and represent a real clinical advantage of insulin glargine that justifies consideration to make insulin glargine available to patients with diabetes as quickly as possible.

Based on the above, the applicant requests priority review and approval of insulin glargine.

The following components make up the NDA submission for insulin glargine. All applicable 356h items, except Item/Section 12 are being submitted as a paper archival copy. Item 12 is being submitted as an electronic archival copy in compliance with the September 1997 electronic guidance. In addition to the paper copy, an electronic review aid is being supplied on six compact discs to allow electronic review and hypertext linking of the NDA. An aid for the reviewer follows this letter.

<u>Item/Section</u>	<u>Volume(s)</u>
1) Index	1.1
2) Labeling	1.1
3) Summary	1.2
4) Chemistry, manufacturing and controls	1.3 – 1.15
5) Nonclinical pharmacology and toxicology	1.16 – 1.59
6) Human pharmacokinetics and bioavailability	1.60 – 1.59
7) Microbiology – not applicable	
8) Clinical data	1.160 – 1.476
9) Safety summary – not applicable	
10) Statistical section	1.477
11) Case report tabulations	1.478
12) Case report forms – submitted electronically	1.479
13/14 Patent information/certification	1.1
15) Establishment description – not applicable	
16) Debarment certification	1.1
17) Field copy certification	1.1
18) User fee cover sheet	1.1
19) Financial disclosure	1.1

This submission is paginated to reflect the section number, followed by the volume number (v) and the page number (p).

A separate identical copy of Section 4. Chemistry, manufacturing and controls, has been sent to Alan Mehl at the Kansas City District Office. A statement certifying this is provided in Item 17 of this submission.

Over the course of the development of insulin glargine, the following agreements have been made between the Agency and the applicant:

- The Agency agreed to accept the 12-month safety data from study 3002 after the submission and filing of the initial NDA for insulin glargine.
- If any additional CRFs are requested by the Agency for the ex-US studies (other than those required in the initial submission) the Agency agreed to accept a by-subject database printout of the case report form data.

- The Agency agreed to the applicant's proposal for collection of financial disclosure information from Phase III and Phase I studies.
- The Agency agreed to the applicant's proposal to provide tabulation reports for Section 11 in Sections 6 and 8 of the NDA. The tabulations for each report are presented as data listings located with the reports in sections 6 and 8. A cross-reference table is provided in Section 11 to these listings. The table of all clinical studies also contains this cross-reference.
- The Agency agreed the sponsor could submit the 120-day safety update at day 75 after the initial submission.
- The electronic version of the NDA will be provided to the Agency within two weeks of the initial submission.
- After conversations with Enid Galliers and Julie Rhee the pediatric report will be submitted to the Agency before the filing meeting for the NDA. This should allow time for the pediatric report to be considered at the filing meeting for HOE 901.

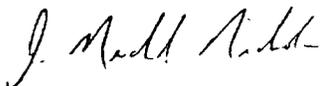
Additional agreements regarding the CMC and clinical sections of the submission are provided in those respective sections.

Under separate cover, the User Fee for this NDA has been submitted according to the Prescription Drug User Fee Act (see Item 18 of this submission [User Fee ID No. 3691]).

Please address any comments or questions regarding this application to Lavonne Patton, authorized representative for Quintiles, the U.S. Agent for Hoechst Marion Roussel, Inc. the official applicant of the NDA.

Lavonne Patton, Ph.D.
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10245 Hickman Mills Drive
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Sincerely,



J. Michael Nicholas, Ph.D.
Director, Marketed Products
US Regulatory Affairs
Hoechst Marion Roussel