DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-773

Amylin Pharmaceuticals, Inc.
Attention: John Wood, MBA, RAC
Senior Director, Regulatory Affairs
9360 Town Centre Drive, Suite 110
San Diego, CA 92121-3030

Dear Mr. Wood:

Please refer to your June 29, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Byetta™ (exenatide) Injection, 250 mcg/mL.

We acknowledge receipt of your submissions dated August 12 and 18, October 28, November 4, and December 17, 2004, and January 27, March 25, and April 8 (2), 12 (2), 25, 26, and 27 (2), 2005.

This new drug application provides for the use of Byetta™ (exenatide) Injection to improve glycemic control in patients with type 2 diabetes mellitus who have not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.

We have completed our review of this application, as amended. It is approved effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for package insert, patient package insert, user manuals, and mock ups for carton and pen labels submitted April 26, 2005). Marketing this product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-773**." Approval of this submission by FDA is not required before the labeling is used.

The stability data submitted support a 24-month expiry for the multiple-dose, pre-filled, 1.2 and 2.4 mL pen injections assembled with cartridges containing 250 mcg/mL exenatide solution.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 through 11 years and deferring pediatric studies for ages 12 through 16 years for this application.

Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered to be a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. A deferred pediatric study under PREA for the treatment of type 2 diabetes in adolescents ages 12 through 16 years, who have not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea, to evaluate the pharmacokinetics and relevant pharmacodynamic effects of different subcutaneous doses of the drug.

Protocol Submission:	by July 29, 2005
Study Start:	by January 31, 2006
Final Report Submission:	by December 31, 2007

   Submit the final study report to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment should be clearly designated "**Required Pediatric Study Commitment**."

We remind you of your postmarketing study commitment in your submission dated April 25, 2005. This commitment is listed below.

2. A human in vivo drug interaction study between exenatide and a combination oral contraceptive (e.g., ethinyl estradiol plus norethindrone) to define the effect of timing of the exenatide injection relative to the administration of the oral contraceptive on the bioavailability of the components of the oral contraceptive.

Protocol Submission:	by July 29, 2005
Study Start:	by January 31, 2006
Final Report Submission:	by January 31, 2007

Submit clinical protocols to your IND for this product. Submit study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled **"Postmarketing Study Commitment Protocol," "Postmarketing Study Commitment Final Report," or "Postmarketing Study Commitment Correspondence."**

We also acknowledge your April 27, 2005, agreement to conduct a study to determine whether exenatide exists primarily as the free acid or as the acetate salt.

Although not approvability issues, we request a written response to the following at your earliest convenience.

Clinical Pharmacology and Biopharmaceutics

A. Exenatide reduced lovastatin AUC by 40%. This effect does not appear to be explained by delayed gastric emptying due to exenatide. We recommend that you investigate the mechanism(s) of the

lovastatin-exenatide interaction, potentially through in vitro and in vivo studies. The mechanism or mechanisms of the interaction may apply to other orally administered drugs taken with exenatide.

B. In addition, you should study how exenatide impacts the bioavailability of drugs that are instructed to be taken with food and thus may, by necessity, be taken in temporal proximity to exenatide.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Package Insert, Patient Package Insert, Pen User Manuals (5 mcg and 10 mcg), Carton and Pen Labels (5 mcg and 10 mcg)

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

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