

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## REQUEST FOR CONSULTATION

TO (Office/Division): DDMAC  
Division Of Drug Marketing, Advertising And  
Communication  
Sam Skariah  
White Oak Office Building 51 (WO51)  
Room # 3226, phone: 7-8444

FROM (Name, Office/Division, and Phone Number of Requestor):  
John Bishai Ph.D.  
Regulatory Project Manager  
DMEP, HFD-510, phone #: 6-1311

DATE  
September 21, 2009

IND NO.

NDA NO.  
21-919

TYPE OF DOCUMENT  
REMS-DHCP letter

DATE OF DOCUMENT  
September 3, 2009

NAME OF DRUG  
Byetta (exenatide)

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-diabetic agent

DESIRED COMPLETION DATE  
October 15, 2009

NAME OF FIRM: Amylin Pharmaceuticals

### 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 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

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| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
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#### III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

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| <input type="checkbox"/> PHASE 4 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

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|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the Dear Healthcare Professional letter submitted on September 3, 2009 which contains the Sponsors's REMS-specifically a DHCP letter

EDR link:

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Supp Doc: 34-REMS/Amendment

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PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21919	ORIG-1	AMYLIN PHARMACEUTICA LS INC	BYETTA (EXENATIDE) INJECTION

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/s/  
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JOHN M BISHAI  
09/21/2009

## REQUEST FOR CONSULTATION

TO (Office/Division): CDER OSE Consults  
Millie Wright  
Mildred.Wright@fda.hhs.gov  
Office of Safety and Epidemiology  
WO22 RM4492, phone: 6-1027

FROM (Name, Office/Division, and Phone Number of Requestor):  
John Bishai Ph.D.  
Regulatory Project Manager  
DMEP, HFD-510, phone #: 6-1311

DATE  
9/16/2009

IND NO.

NDA NO.  
21-919

TYPE OF DOCUMENT  
Original Submission

DATE OF DOCUMENT  
April 5, 2005

NAME OF DRUG  
Byetta (exenatide)

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-diabetic agent

DESIRED COMPLETION DATE  
October 30, 2009

NAME OF FIRM: Amylin Pharmaceuticals

### 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     |
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| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION    | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY                 | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

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| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
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| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
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#### III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
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#### IV. DRUG SAFETY

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| <input type="checkbox"/> PHASE 4 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 checked="" 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

- |                                   |                                      |
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| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
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COMMENTS / SPECIAL INSTRUCTIONS: Please perform an AERS search for pancreatic cancer and (medullary) thyroid tumors. Specifically, we ask that you pull the cases referenced in the attached report and to provide reporting rates of these cancers relative to other anti-diabetic therapies.

Direct link to edr: \\Cdsesub1\evsprod\NDA021995\021995.enx

Please refer to the Berstein Report which is a report comparing AERS reports for Byetta, Januvia, and other products specifically looking at Adverse Event Database, Real World Tolerability, & Expert Interviews.

The document can be found in the DMEP eRoom:

[http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0\\_f0f0](http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_f0f0)

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21919	ORIG-1	AMYLIN PHARMACEUTICA LS INC	BYETTA (EXENATIDE) INJECTION

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/s/

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JOHN M BISHAI  
09/17/2009



NDA 21-919

**GENERAL ADVICE**

AMYLIN PHARMACEUTICALS, INC  
Attention: Dawn Viveash, M.D.  
Vice President, Regulatory Affairs and Safety  
9360 Towne Centre Drive, Suite 110  
San Diego, CA 92121

Dear Dr. Viveash:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Byetta (exenatide) injection

We also refer to your January 5, 2009 submission, containing an interim report for a "Retrospective Cohort Study of Acute Pancreatitis in Relation to Use of Byetta and other Antidiabetic Agents." We have reviewed the referenced material and have the following comments.

1. The interim report did not provide information or measures of acute pancreatitis severity nor did it provide the number of deaths associated with acute pancreatitis by cohort. The medical chart review should provide data on pancreatitis severity and death associated with pancreatitis. If these data are not available, the researchers should acknowledge this as a limitation. The National Death Index of the National Center for Health Statistics could be consulted to identify deaths and causes of death for subjects in whom there is uncertainty about vital status.
2. The definition of likely acute pancreatitis included emergency department visits OR hospitalizations with a primary discharge diagnosis of acute pancreatitis. Since patients who were sent home after being diagnosed with acute pancreatitis are probably different in disease seriousness and other ways from those admitted, you should present the number of cases of emergency visits and hospitalizations by cohort and consider taking into account ED visits versus hospitalizations in your analyses. Alternatively, you could limit the study to hospitalized cases only; however, this would result in a reduced sample size.
3. You note that the definition of current exposure (the days' supply plus an additional 31 days) may have misclassified non-exposure as exposure. Consequently, you plan a sensitivity analysis to evaluate this. If the sensitivity analysis indicates a fair amount of misclassification, you should reanalyze the data using new definitions for current, recent, and past exposure.

4. Obesity is an important risk factor for type 2 diabetes mellitus (T2DM) and for gallstone disease, the leading cause of pancreatitis. Another important risk factor for pancreatitis is alcohol use. Covariates such as body weight, body mass index (BMI), and alcohol use are often absent in claims data and from medical charts. Consequently, misclassification of covariate data is likely for key predictors of acute pancreatitis that account for a large proportion of cases. Furthermore, much of the covariate information is obtained from baseline data that could have changed by the time of development of pancreatitis. You should disclose the following:
  - to what extent the BMI and alcohol use data are present in the database,
  - how you will handle missing covariate data, and
  - how you will handle covariate data missing from around the time of acute pancreatitis development.
5. The current report is an interim report with an “interim analyses”. You will need to re-perform the analyses following reclassification of exposure, confirmation of diagnoses, and the addition of more complete and valid covariate information.
6. While acute pancreatitis is likely to be confirmed in those having it as the primary discharge diagnosis, it may also be confirmed in those with it listed further down the diagnosis list. In addition to “likely acute pancreatitis” you should also provide analyses for all listed diagnoses of acute pancreatitis for the sake of completeness and to show consistency or lack of consistency with the primary results.
7. You state that you will obtain data from medical charts. As medical charts are not always available to validate outcomes and to obtain covariate information, you should predict what proportion of charts is likely to be unavailable and how you will treat missing data for charts that are unavailable.
8. Patients eligible for both the exenatide cohort and the other antidiabetic drug cohort were preferentially entered into the exenatide cohort due to sample size considerations. Since exenatide is indicated for adjunctive treatment of T2DM, the number of patients eligible for entry into both the exenatide cohort and the other antidiabetic drug cohort was probably large. You should provide the number who were eligible for entry into both cohorts and should explain the ramifications of preferentially allocating exposure to exenatide for risk assessment when exposure actually included exenatide plus another antidiabetic drug. You should consider a design that analyzes for concomitancy of antidiabetic drugs since risk might be associated not so much with the initiation of an antidiabetic drug as the combination or number of them.
9. Exenatide is indicated for adjunctive treatment of T2DM. You should justify the inclusion of patients with type 1 diabetes mellitus (T1DM). In addition, risks for the “other antidiabetic drug” group should be listed by drug to determine if one or more antidiabetic drug, including insulin for T1DM, contributes to unusual risk levels.
10. The 578 cases for non-use of exenatide in Table 3 appear to be an error as the number seems improbable. Please verify and/or correct this.

11. The lack of inclusion of patients who develop acute pancreatitis on an outpatient basis may lead to possible biases in results. The study could be limited to hospitalized cases; however, this would lead to a reduced sample size.
12. You should acknowledge that use of propensity score modeling does not preclude the potential for residual biases that impact risk for the outcome of interest.
13. You have not provide information for the risk of acute pancreatitis with exenatide monotherapy as compared with exenatide combination therapy. Data on exenatide with and without concomitant medications should be analyzed for differences in acute pancreatitis.
14. You have not provide information on whether individual antidiabetic drugs, besides exenatide, combinations of concomitant antidiabetic drugs, or the number of antidiabetic drugs per patient are associated with higher risks of acute pancreatitis. Data on individual antidiabetic drugs (besides exenatide), combinations of antidiabetic drugs, and number of antidiabetic drugs per patients should be analyzed for risk with acute pancreatitis.
15. Table 1c indicates that more than 50% of exenatide initiator dispensings had dispensings for each of Class I and Class II “pancreatotoxic drugs” during the baseline period prior to cohort entry. No list of individual pancreatotoxic drugs and frequencies by cohort are provided. The most frequently used individual pancreatotoxic drugs in each cohort should be listed. Furthermore, an effort should be made to determine if these pancreatotoxic drugs were being used around the time of pancreatitis development.
16. You should provide timelines for the medical chart review, reanalyses of the data, completion of the study, and final study report submission to the Agency.
17. The i3 drug safety study was commissioned and is funded by Amylin Pharmaceuticals. In the interim report, the investigators did not provide any statements that declare their scientific independence from Amylin. The investigators should describe the company’s input and any contracts or formal or informal “understandings” that prohibit or interfere with publishing the findings, favorable to the drug or not, in a peer-reviewed medical journal.

If you have any questions, call John Bishai, Regulatory Project Manager, at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Mary Parks  
7/15/2009 05:23:11 PM

## Consultation on Exenatide Detail at ENDO 2009

Requesting Division: Division of Drug Marketing, Advertising and Communications (DDMAC) / Office of Safety Evaluation / CDER  
Division Consulted: Division of Metabolism and Endocrinology Products (DMEP)  
Review Date: June 30, 2009  
Clinical Reviewer: Valerie Pratt  
Through: Karen Mahoney, Acting Team Leader, Diabetes Products Team II, DMEP  
Mary Parks, Director, DMEP

### INTRODUCTION

DDMAC is evaluating several oral statements for Byetta that were made at The Endocrine Society's 91<sup>st</sup> Annual Meeting between the dates of June 10-12, 2009.

This consultation is based on the following material reviewed:

- Kendra Y. Jones' June 17, 2009 memorandum summarizing oral statements made by representatives from Eli Lilly and Amylin Pharmaceuticals at The Endocrine Society's annual meeting
- Current FDA-approved exenatide prescribing information
- Reprints:
  - Kendall, DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, Baron AD: Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Patients With Type 2 Diabetes Treated With Metformin and a Sulfonylurea. *Diabetes Care*. 2005;28(5): 1083-1091.
  - Defronzo R, Ratner R, Han J, Lo, D. Fineman M, Baron A: Effects of Exenatide (Exendin-4) on Glycemic Control and Weight Over 30 Weeks in Metformin-Treated Patients with Type 2 Diabetes. *Diabetes Care*. 2005;28(5): 1092-1100.
- Lilly press releases:
  - Exenatide once weekly provided sustained improvements in glycemic control with weight loss over 2 years: DURATION-1 interim long-term data presented at American Diabetes Association (ADA) Scientific Sessions 2009
  - Meta-analysis of clinical data showed no increased risk of cardiovascular events associated with exenatide use: Data presented at ADA 2009

Please note that DMEP answers are shown in **bold** throughout this consultation memorandum.

### DDMAC Questions and DMEP Answers

**NOTE: Exenatide's trade name is Byetta. The exenatide once weekly (or LAR) new drug application (NDA) is currently under review; the proposed trade name is Bydureon.**

1. According to the Eli Lilly representative, 94% of patients in a study lost 7-8 lbs in 30 days without diet or exercise. Are you aware of substantial evidence that supports this statement? If so, please explain.

**In the long term controlled studies of exenatide which were originally submitted to NDA 21-773, the change from baseline body weight after placebo lead-in x 4 weeks, exenatide 5 mcg twice daily (BID) x 4 weeks, and exenatide 10 mcg BID x 22 weeks was 2.8 kg (6.16 lb), 1.6 kg (3.52 lb), and 1.6 kg (3.52 lb) when used in combination with metformin, sulfonylurea (SFU), and metformin+SFU, respectively, without diet or exercise. The reprint provided by the sponsor at ENDO 2009 describes similar "progressive dose-dependent weight loss."<sup>1</sup> The reprint's cover sheet also points out that "exenatide is not indicated for weight loss or weight management."**

**A cohort of 163 patients from the 30-week placebo-controlled trials who completed a total of 52 weeks of treatment with exenatide 10 mcg BID had body weight changes from baseline of -2.2 kg (-5.72 lb) and -3.6 kg (-7.9 lb) at 30 and 52 weeks, respectively, without diet or exercise.**

**I am not aware of an exenatide study that demonstrates 94% of subjects lost 7-8 lb (3.2-3.6 kg) in 30 days without diet or exercise. If such a study existed, the results would be atypical.**

2. The Eli Lilly representative stated that "Although Byetta is not indicated for use by itself because it was not FDA approved this way and the FDA requires additional studies, it can be used by itself." DDMAC is concerned that this statement misleadingly implies that the use of Byetta as a monotherapy is safe and effective prior to the approval of this regimen. We note that the NDA for the use of Byetta as a monotherapy is under review. Do you agree that the use of Byetta as a monotherapy constitutes a new indication that has not been approved by the FDA? Can you provide an update on the approval status?

**The NDA for the use of exenatide as monotherapy was submitted March 19, 2008. Action on the application has been delayed due to concerns about hemorrhagic and necrotizing pancreatitis and internal safety labeling discussions. Therefore, exenatide is not currently indicated for use as monotherapy. DMEP hopes to take an action on this application soon.**

3. During the discussion, the Eli Lilly representative explained that Byetta had a

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<sup>1</sup> DeFronzo R, Ratner R, Han J, Lo, D, Fineman M, Baron A: Effects of Exenatide (Exendin-4) on Glycemic Control and Weight Over 30 Weeks in Metformin-Treated Patients with Type 2 Diabetes. Diabetes Care. 2005;28(5): 1092-1100.

positive effect on cholesterol and triglyceride levels. She also stated that this effect shows that there are cardiovascular benefits associated with Byetta and those studies are still ongoing. We are concerned that these statements misleadingly overstate the efficacy of Byetta by suggesting a cardiovascular benefit with its use that has not been demonstrated by substantial evidence. Are you aware of substantial evidence to support these claims? Please explain your answer. We note that Lilly issued a press release on 6/8/09 regarding findings presented at American Diabetes Association from a meta-analysis of cardiovascular events associated with Byetta.

**Exenatide does not have an indication for reduction of cardiovascular (CV) events. The drug representative's statements misleadingly overstate the efficacy of Byetta by suggesting a cardiovascular benefit.**

- **On May 4, 2009, the sponsor submitted the exenatide LAR NDA (b) (4) which included a CV risk meta-analysis. The sponsor included 8 placebo-controlled studies and 4 active comparator (insulin)-controlled studies (duration 12-52 weeks) of exenatide (Byetta). This meta-analysis is described in the sponsor's press release.**

**For primary major adverse cardiovascular events (MACE), the upper limit of the 95% confidence interval (CI) was 1.31, near the diabetes guidance-recommended upper bound of 1.3. For the secondary CV endpoint (i.e. primary MACE plus arrhythmia, heart failure, and mechanical-related events), the upper limit of the 95% CI was 1.03. This indicates that it is unlikely that exenatide carries an increased CV risk but does not show that it has a CV benefit. The meta-analysis states, "The risk ratios for both endpoints were consistently <1, indicating a *potential* benefit of exenatide versus comparator." Thus, the drug representative's claim that exenatide has CV benefits is unsubstantiated.**

- **Regarding serum lipids, a publication referenced in the meta-analysis describes a decrease in triglycerides (-12%, p=0.0003), total cholesterol (-5%, p=0.0007), and LDL-cholesterol (-6%, p<0.0001) and increase in HDL-cholesterol (24%, p<0.0001) in 217 type 2 diabetes treated with exenatide for at least 3 years.<sup>2</sup> However, the majority of the treatment period was open-label.**

**In the meta-analysis document, a separate analysis of exenatide LAR data focused on study 2993-LAR105, a 30 week, controlled trial comparing exenatide LAR with exenatide. Results, shown below, suggest that both exenatide and exenatide LAR improve triglycerides, total cholesterol, and systolic and diastolic blood pressure, although HDL-cholesterol is also**

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<sup>2</sup> Klonoff D, Buse J, Nielsen L, Guan X, Bowlus C, Holcombe J, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Current Medical Research and Opinion*. 2008;24:275-286.

**reduced. (Note: High HDL-cholesterol is associated with reduced CV risk.)**

**Table 1: Change From Baseline to Week 30 in Cardiometabolic Risk Factors in Study 2993LAR-105 (Intent-to-Treat Population [N = 295])**

Parameter	BYETTA (Exenatide BID) (N = 147)		Exenatide Once Weekly (N = 148)	
	Mean (SE)	LS Mean (SE)	Mean (SE)	LS Mean (SE)
	Baseline	Change	Baseline	Change
Body Weight (kg)	101.9 (1.7)	-3.6 (0.5)	101.7 (1.5)	-3.7 (0.5)
Triglycerides (mg/dL)	157.8 (8.0)	-11 (0.03)%	166.0 (8.7)	-15 (0.03)%
Total Cholesterol (mg/dL)	182.2 (4.0)	-3.8 (2.4)	173.2 (3.4)	-11.9 (2.3)
HDL-Cholesterol (mg/dL)	46.4 (0.9)	-1.3 (0.6)	43.9 (0.8)	-0.9 (0.6)
LDL-Cholesterol (mg/dL)	100.3 (3.3)	1.2 (2.0)	91.6 (2.9)	-4.9 (2.0)
Systolic Blood Pressure (mmHg)	129.5 (1.2)	-3.4 (1.1)	127.8 (1.1)	-4.7 (1.1)
Diastolic Blood Pressure (mmHg)	79.6 (0.6)	-1.7 (0.7)	77.7 (0.7)	-1.7 (0.7)

BID = twice daily; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LS = least squares; SE = standard error.  
 Note: For the comparator-controlled (30-week assessment) period, subjects received either exenatide once weekly 2 mg for 30 weeks or BYETTA 5 mcg SC BID for the first 4 weeks and 10 mcg SC BID for the next 26 weeks.

- Change from baseline in triglycerides is LS mean percent change; all other data is presented as LS mean change.

Cross-References: Study 2993LAR-105, [Supporting Data Summaries 2.2.2.1.1, 2.7.2.1.1, and 3.4.3.](#)

**The sponsor’s press release describes interim results from the DURATION-1 study that were presented at the American Diabetes Association’s 2009 meeting. In the controlled portion of the open-label study, 295 subjects received exenatide LAR or exenatide for 30 weeks followed by 74 weeks of treatment with exenatide LAR for all subjects during an open-ended assessment period. According to the press release, serum lipids improved significantly (total cholesterol  $-8.6\pm 2.9$  mg/dl, LDL-cholesterol  $-4.5\pm 2.2$  mg/dl, triglycerides  $-15\pm 3\%$ ).**

**Although the above studies suggest that exenatide and exenatide LAR may improve serum lipids, neither drug has undergone the rigorous testing and evaluation process necessary to obtain this indication or state this claim. Furthermore, given the increased scrutiny that diabetic drugs are under since the release of the December 2008 guidance “Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes,” references to improved serum lipids or cardiovascular benefits have greater significance and should only be used when applicable.**

**The sponsor is planning a CV outcomes trial with the goal of demonstrating superiority of exenatide LAR. The meta-analysis press release also states, “The CV outcomes trial...[will] determine if there are CV benefits of exenatide treatment.”**

Date: June 11, 2009

Representative: Amylin Representative

4. According to the Amylin representative, approximately 80% of patients lost about 7-8 lbs in a study over 30 weeks? When DDMAC inquired about information to support this statement, the representative explained that it wasn’t in the pieces

displayed because the information was against a drug that was not yet approved. She then escorted DDMAC to the Amylin Medical Information booth where two reprints were obtained (see citations from the reprints below) in response to the inquiry. DDMAC is concerned that these reprints do not support this claim. Do these reprints constitute substantial evidence to support this claim? Are you aware of substantial evidence that supports this statement? If so, please explain.

**The 2 reprints do not support the claim that 80% of patients lost 7-8 lbs in a 30 week study of an unapproved drug, as the studies describe 1.6-2.8 kg (3.52-6.16 lb) weight loss with exenatide, an approved drug. The representative may be referring to the results of study 2993LAR-105 shown above, which describe 3.7 kg (8.14 lb) weight loss with exenatide LAR.**

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/s/

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Valerie Pratt  
7/1/2009 11:29:29 AM  
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Valerie Pratt  
7/1/2009 11:29:52 AM  
MEDICAL OFFICER

Eric Colman  
7/1/2009 11:47:51 AM  
MEDICAL OFFICER  
Eric Colman for Mary Parks

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	<b>REQUEST FOR CONSULTATION</b>
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TO ( <i>Division/Office</i> ): Valerie Pratt, M.D., Medical Officer; John Bishai, Regulatory Project Manager Division of Metabolism and Endocrinology Products	FROM( <i>Division/Office</i> ): Kendra Y. Jones, Regulatory Review Officer, Division of Drug Marketing, Advertising and Communications
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DATE: 06/25/2009	IND NO.	NDA NO. 21-773 & 21-919	TYPE OF DOCUMENT: Representatives' Oral Statements	DATE OF DOCUMENTS: 6/10/09 – 6/12/09
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NAME OF DRUG Byetta® (exenatide) injection	PRIORITY CONSIDERATION YES	CLASSIFICATION OF DRUG: Incretin Mimetic	DESIRED COMPLETION DATE: 7/20/09
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NAME OF FIRM: Eli Lilly & Amylin Pharmaceuticals

**REASON FOR REQUEST**

**I. GENERAL**

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

DDMAC is evaluating several oral statements for Byetta that were made at The Endocrine Society's 91<sup>st</sup> Annual Meeting between the dates of 6/10/09 – 6/12/09. A memo from the discussions with the representatives will be provided with this consult. We also welcome your input about any additional concerns you may have. Please do not hesitate to contact me with any questions at 301-796-3917. Thanks so much for your assistance in this matter.

Date: June 10, 2009  
Representative: Eli Lilly Representative

1. According to the Eli Lilly representative, 94% of patients in a study lost 7-8 lbs in 30 days without diet or exercise. Are you aware of substantial evidence that supports this statement? If so, please explain.
2. The Eli Lilly representative stated that "Although Byetta is not indicated for use by itself because it was not FDA approved this way and the FDA requires additional studies, it can be used by itself." DDMAC is concerned that this statement misleadingly implies that the use of Byetta as a monotherapy is safe and effective prior to the approval of this regimen. We note that the NDA for the use of Byetta as a monotherapy is under review. Do you agree that the use of Byetta as a monotherapy constitutes a new indication that has not been approved by the FDA? Can you provide an update on the approval status?
3. During the discussion, the Eli Lilly representative explained that Byetta had a positive effect on cholesterol and triglyceride levels. She also stated that this effect shows that there are cardiovascular benefits associated with Byetta and those studies are still ongoing. We are concerned that these statements misleadingly overstate the efficacy of Byetta by suggesting a cardiovascular benefit with its use that has not been demonstrated by substantial evidence. Are you aware of substantial evidence to support these

claims? Please explain your answer. We note that Lilly issued a press release on 6/8/09 regarding findings presented at American Diabetes Association from a meta-analysis of cardiovascular events associated with Byetta.

Date: June 11, 2009

Representative: Amylin Representative

4. According to the Amylin representative, approximately 80% of patients lost about 7-8 lbs in a study over 30 weeks? When DDMAC inquired about information to support this statement, the representative explained that it wasn't in the pieces displayed because the information was against a drug that was not yet approved. She then escorted DDMAC to the Amylin Medical Information booth where two reprints were obtained (see citations from the reprints below) in response to the inquiry. DDMAC is concerned that these reprints do not support this claim. Do these reprints constitute substantial evidence to support this claim? Are you aware of substantial evidence that supports this statement? If so, please explain.

A copy of the following pieces will be delivered to you:

- DDMAC Memo: Summary of oral statements regarding Byetta at The Endocrine Society's Annual Meeting
- The most current version of the FDA approved PI
- *Reprints From Amylin Medical Information*
  - Kendall, DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, Baron AD: Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Patients With Type 2 Diabetes Treated With Metformin and a Sulfonylurea. *Diabetes Care*. 2005;28(5): 1083-1091.
  - Defronzo R, Ratner R, Han J, Lo, D. Fineman M, Baron A: Effects of Exenatide (Exendin-4) on Glycemic Control and Weight Over 30 Weeks in Metformin-Treated Patients With Type 2 Diabetes. *Diabetes Care*. 2005;28(5): 1092-1100.
- Background Material: 6/8/09 Press Release Issued By Eli Lilly and Amylin Pharmaceuticals

SIGNATURE OF REQUESTER Kendra Y. Jones	METHOD OF DELIVERY (Check one) MAIL FACSIMILE <input checked="" type="checkbox"/> HANDDELIVER <input checked="" type="checkbox"/> EMAIL/DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

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Kendra Jones

6/25/2009 04:26:04 PM

**Memo to the File**  
**OSE-OND Meeting on Byetta**  
**June 15, 2009**  
**4:30-5:00 p.m.**

Members of OND and OSE met on Monday, June 15<sup>th</sup> to discuss:

- Status and timetable for completion of OSE reviews for Byetta and Januvia
- Relationship of review issues to regulatory decisions that need to be made
- Discussion of next steps regarding labeling changes
- Agreement on path forward and next steps

Those in attendance were: OSE: Gerald Dal Pan, Solomon Iyasu, Mark Avigan, and Mildred Wright; OND: Curtis Rosebraugh, Mary Parks, Amy Egan, and John Bishai.

Due to time constraints, discussion focused on the last 2 bullets.

All parties agreed to the following:

- Information regarding the association between Byetta and hemorrhagic/necrotizing pancreatitis needs to get into the label soon.
- The information that needs to be conveyed in the label includes the need to discontinue Byetta if pancreatitis is suspected, and not to re-initiate Byetta if pancreatitis is confirmed.
- As an interim step, this language will be added to the Warnings and Precautions section of the PLR label.
- The sponsor will be notified that this decision is viewed as an interim decision and that a Boxed Warning is still under consideration pending further analyses and reviews.
- The decision as to whether this language needs to be elevated to a Boxed Warning will be deferred until all reviews have been completed and reviewed by Drs. Rosebraugh and Dal Pan and their decisional memos have been drafted.
- Should the recommendation at that time be to elevate the warning to a Boxed Warning, the sponsor will be required to do so under FDAAA. New safety information to invoke FDAAA will be based on the sponsor's ongoing epidemiologic study (final report expected 3<sup>rd</sup> quarter 2009), an updated review of AERS cases, and/or the sponsor's PSUR (due in September).

The meeting was adjourned at 5:05 p.m. with all parties in concurrence.

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/s/

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Amy Egan  
6/20/2009 11:23:40 AM  
MEDICAL OFFICER

## REQUEST FOR CONSULTATION

TO (Office/Division): CDER OSE Consults  
Millie Wright  
Mildred.Wright@fda.hhs.gov  
Office of Safety and Epidemiology  
WO22 RM4492, phone: 6-1027

FROM (Name, Office/Division, and Phone Number of Requestor):  
John Bishai Ph.D.  
Regulatory Project Manager  
DMEP, HFD-510, phone #: 6-1311

DATE  
5/15/2009

IND NO.

NDA NO.  
21-919

TYPE OF DOCUMENT  
Safety Information  
Amendment- Epi study

DATE OF DOCUMENT  
January 5, 2009

NAME OF DRUG  
(b) (4) (exenatide for  
injectable suspension)

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-diabetic agent

DESIRED COMPLETION DATE  
June 15, 2009

NAME OF FIRM: Amylin 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 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> 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 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 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"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** Please review the the interim report, referenced in Sequence 0018 entitled, "A Retrospective Cohort Study of Acute Pancreatitis in Relation to Use of Byetta and Other Antidiabetic Agents," The objective of this analysis was to estimate the absolute and relative incidence rates of likely acute pancreatitis among cohorts of diabetics initiating exenatide or other antidiabetic drugs and a non-diabetic comparison group.

We ask that you please address the following requests:

1. Please comment on the interim results submitted in January 2009
2. Please comment on the protocol design and the planned medical chart review and provide a determination on whether this study will enable a reasonable assessment of risk of acute pancreatitis and its more severe form, hemorrhagic or necrotizing, for Byetta and other anti-diabetic therapies

3. If OSE has deemed that the prospective cohort study is inadequate, please provide a proposal on a more appropriate epi study design that can be conducted by this applicant or other GLP-1 receptor agonists as a postmarketing study requirement under FDAAA to evaluate risk for acute pancreatitis and HNP.

Direct link to edr: \\Cdsesub1\evsprod\NDA021919\021919.enx

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/s/

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John M Bishai

5/15/2009 12:36:10 PM

## Bishai, John

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**From:** Bishai, John  
**Sent:** Friday, January 30, 2009 12:12 PM  
**To:** Ellis, Staci  
**Cc:** Viveash, Dawn; Aljuburi, Lina  
**Subject:** NDAs 21-919 and 21-773 Recent Labeling discussions for Byetta

Hello Staci,

On January 22, 2009, the Division of Metabolism and Endocrinology Products (DMEP), The Office of Surveillance and Epidemiology (OSE), Amylin Pharmaceuticals, and Eli Lilly engaged in a labeling discussion for NDA 21-773 and 21-919 Byetta (exenatide) Injection. The agenda set forth was to discuss the association of severe pancreatitis, namely necrotizing and hemorrhagic forms, with Byetta. During the discussion, the Agency expressed its concern about the severe life-threatening forms of pancreatitis and has suggested the implementation of a Boxed Warning. Because this form of communication would not only be on the label but also be included in all forms of marketing/advertising, it would be an effective tool which would mitigate the risk of pancreatitis. It is understood that both Amylin and Lilly see these adverse events as very serious and agree to revise, as needed, the actual language on pancreatitis. However, as pointed out by Dr. Viveash, Amylin and Lilly feel that the Box Warning although effective may have negative effects on otherwise healthy patients with type 2 diabetes who are good candidates for Byetta who will either not initiate Byetta or will stop using the product unnecessarily. Other points were also made by Dr. Viveash, but most important was the possibility of increasing public awareness about the severe forms of pancreatitis associated with Byetta without the need of a Boxed Warning. Upon conclusion of our discussion, the Agency agreed to review and consider the aforementioned proposal. The Agency has provided some comments and requests (see below) that Amylin provide a written response no later than February 12, 2009.

1. Labeling and communication tools should be used in the most optimal fashion to communicate to Byetta-treated patients and prescribing physicians that severe life-threatening forms of pancreatitis have been associated with this agent. The Agency believes that a Boxed Warning is warranted as an important tool to mitigate risk for pancreatitis since it would influence opportunities (e.g., advertising) in which communication of this risk will take place. Without implementation of a Boxed Warning, how does Amylin suggest the risk for severe forms of pancreatitis optimally be communicated to both doctors and patients? Please keep in mind that these tools would seek to gain maximal adherence to the following measures:
  - a. Patients treated with Byetta need to seek advice from their doctor and discontinue treatment with this agent when they develop any symptoms that may represent early pancreatitis. If pancreatitis does occur, Byetta should not be reinstated.
  - b. Prescribing physicians need be instructed to do the following:
    - i. proactively instruct all patients whom are about to start Byetta about the risk
    - ii. quickly assess all patients for pancreatitis by serum amylase/lipase testing, as well as imaging, etc. in whom symptoms of nausea/vomiting and/or pain first appear
2. We also recommend the following items:
  - a. a post-marketing study to assess the risk to better identify which patients are most susceptible to severe pancreatitis

- b. a mechanistic study which may identify the physiological mechanism which results in pancreatitis, including the severe form
- c. more specific labeling language to advise patients who experience nausea and vomiting for more than X days to see their doctor for amylase/lipase testing in addition to imaging.

If you have any questions, please feel free to contact me.

Kind Regards,

John Bishai, Ph.D.

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

Email: [john.bishai@fda.hhs.gov](mailto:john.bishai@fda.hhs.gov)

Tel: 301.796.1311

Fax: 301.796.9712

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/s/

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John M Bishai  
1/30/2009 12:22:39 PM  
CSO

On Thursday January 22, 2009, the division of Endocrinology and Metabolism Products (DEMP) joined the Office of Surveillance and Epidemiology (OSE) to begin labeling discussions with Amylin Pharmaceuticals, Inc regarding NDA 21-919. The focus of the discussion was to convey the Agency's sentiment for a Boxed Warning. This originally stemmed from a few AERS reports submitted for serious necrotizing and hemorrhagic pancreatitis events. As part of the "Equal Voice" initiative, OSE led the labeling discussions and presented their points to the sponsor. Upon conclusion of the teleconference, both, OSE and DMEP, joined in an internal discussion to exchange their respective viewpoints on what had transpired. Both parties agreed to postpone the decision on the Boxed Warning until Amylin submitted their proposal which would provide an alternate means to the Boxed Warning yet still provide the patient and the physician adequate information about the severe outcomes which may be a result of this product. DMEP will draft an email outlining the specific criteria as proposed by OSE which need to be addressed by Amylin. Those items are as follows:

1. We believe a black box is warranted as an important labeling tool to mitigate risk for pancreatitis since it would influence opportunities (advertising etc) in which communication of this risk will take place.
2. We look forward to hear from the sponsor how it proposes that this risk would be optimally communicated to both doctors and patients.
3. Labeling and communication tools should be used in the most optimal fashion to communicate to Byetta treated patients and prescribing physicians that severe life-threatening forms of pancreatitis have been associated with this agent. These tools would seek to gain maximal adherence to the following measures:
  - Patients treated with Byetta would seek advice from their doctor and discontinue treatment with this agent when they develop any symptoms that may represent early pancreatitis. If pancreatitis occurs Byetta should not be reinstated
  - Prescribing physicians would proactively instruct all patients about to start Byetta about the risk, and quickly assess all patients for pancreatitis by serum amylase/lipase testing, as well as imaging etc in whom symptoms of nausea/vomiting and/or pain first appear
4. The sponsor's response should be timely (within the next month?) to enable us to move forward

### ***List of Attendees***

#### **Amylin**

Orville Kolterman, M.D., Senior Vice President, Research and Development

Dawn Viveash, M.D., Vice President, Regulatory Affairs and Global Safety

Cheryl Watton, M.D., Executive Director, Regulatory Affairs and Global Safety

Lisa Porter, M.D., Vice President, Clinical Development  
Denis Roy, Ph.D., Senior Director, Nonclinical Drug Safety  
Ruth Patterson, Ph.D., Senior Director, Health Outcomes  
Larry Shen, Ph.D., Executive Director, Corporate Analytics  
Staci Ellis, Associate Director, Regulatory Affairs  
Hutch Humphreys, Manager, Regulatory Affairs

**Eli Lilly**

John Holcombe, M.D., Medical Fellow II - US Medical.  
James K. Malone, M.D., Medical Director, Byetta  
Richard Bump, M.D., Senior Medical Director, Global Patient Safety  
Daniel K. Braun, M.D., Medical Fellow I - Global Patient Safety  
Kathryn E. Broderick, Pharm.D., Associate Director, US Regulatory Affairs  
David A. Vondle - Byetta Team Leader

**Division of Metabolism and Endocrinology (DMEP)**

Mary Parks, M.D.	Director
Hylton Joffe, M.D., M.M.Sc.	Diabetes Clinical Team Leader
Amy Egan, M.D.	Deputy Division Director for Safety
Valerie Pratt, M.D.	Clinical Reviewer
B. Timothy Hummer, Ph.D.	Pharmacology/Toxicology Reviewer
Lina AlJuburi, Pharm.D.	Chief, Project Management Staff
John Bishai, Ph.D.	Regulatory Project Manager

**Office of Surveillance and Epidemiology**

Mark Avigan, M.D.	Supervisory Medical Officer
John Senior, M.D.	Medical Reviewer
Lanh Green, Pharm. D.	Team Leader Division Of Pharmacovigilance I
Joslyn Swann, Pharm. D.	Director Regulatory Division Of Pharmacovigilance I
Solomon Iyasu, M.D.	Supervisor, Medical Officer
Allen Brinker, M.D., M.S.	Lead Med Officer Epidemiology
S. Rizwan Ahmad, Ph.D.	Epi Reviewer, Division of Epidemiology

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/s/

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John M Bishai  
1/29/2009 11:22:24 AM  
CSO



NDA 21-773, 21-919

(b) (4)

## INFORMATION REQUEST LETTER

Amylin Pharmaceuticals, Inc.  
Attention: Dawn Viveash, M.D,  
Vice President, Regulatory Affairs and Safety  
9360 Towne Centre Drive  
San Diego, CA 92121

Dear Dr. Viveash:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Byetta (exenatide) Injection.

We also refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Exenatide Once-Weekly Injection.

While reviewing the class of glucagon-like peptide 1 (GLP-1) analogs, it has become apparent that some GLP-1 analogs cause thyroid neoplasms in non-clinical studies. To explore whether these findings could have clinical significance, we are interested in learning whether there have been clinical cases of thyroid cancer with exenatide, the only FDA-approved GLP-1 analog, and with exenatide once-weekly injection. Therefore, please respond to the following request for information.

1. Across all completed controlled trials of exenatide for all indications, provide the incidence of thyroid cancer (any type) for exenatide-treated patients and non-exenatide-treated controls. If total exposure differs for exenatide-treated patients and non-exenatide-treated patients, also provide the rate per unit of subject-time, e.g. the number of cases per 100 subject-years or per 1000 subject-years.
2. Provide breakdowns of the above data by duration of exposure, presenting the incidence and rate among subjects exposed for <1 year and those exposed for  $\geq 1$  year.
3. Provide breakdowns of the data by type of thyroid cancer (e.g. papillary, follicular, medullary, anaplastic, etc).
4. Provide a listing of all cases of thyroid cancer across all clinical trials (controlled and uncontrolled) of exenatide for all indications. In the listing, include columns for treatment group, treatment dose, study, patient identification, gender, age at diagnosis, duration of treatment exposure at time of first sign of thyroid cancer (e.g. when nodule noted), type of thyroid cancer, risk factors for thyroid cancer, calcitonin level with

reference range, and outcome. Provide a similar listing, with applicable columns, for all postmarketing reports of thyroid cancer outside clinical trials.

5. Provide a narrative for each case of thyroid cancer.
6. Provide full surgical pathology reports, and full pathology reports of any biopsies.
7. Clarify if calcitonin concentrations were measured in any of your controlled clinical trials. If calcitonin was measured, please describe the timing of the measurements and whether stimulated calcitonin testing was performed and include the following information separately for unstimulated and stimulated calcitonin measurements: (a) summary statistics (mean, standard deviation, median, interquartile range), (b) categorical outlier analyses (e.g., >2x ULN, >3x ULN, >5x ULN, >10x ULN, >20x ULN), and (c) shift analyses (normal at baseline to high post-baseline) for exenatide-treated patients and non-exenatide-treated controls.

Please present the information requested above separately for exenatide and for exenatide once-weekly injection.

Please submit the requested information by December 19, 2008.

If you have any questions, call John Bishai, Ph.D., Regulatory Project Manager, at (301) 796-1311.

Sincerely,

Mary Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Mary Parks

10/31/2008 01:42:11 PM

## REQUEST FOR CONSULTATION

TO (Office/Division): CDER OSE Consults  
Cheryl Campbell  
cheryl.campbell@fda.hhs.gov  
Office of Safety and Epidemiology  
WO22 RM3417, phone: 6-0723

FROM (Name, Office/Division, and Phone Number of Requestor):  
John Bishai Ph.D.  
Regulatory Project Manager  
DMEP, HFD-510, phone #: 6-1311

DATE  
10/21/2008

IND NO.

NDA NO.  
21-919

TYPE OF DOCUMENT  
Draft Carton and  
Container Label Review

DATE OF DOCUMENT  
October 10, 2008

NAME OF DRUG  
Byetta

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-diabetic agent

DESIRED COMPLETION DATE  
December 1, 2008

NAME OF FIRM: Amylin 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 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

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|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 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"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** This a request for a Draft Carton and Container Label Review. The document can be found in the EDR (see link below). Please note this submission includes Medguide language on the carton label.

Direct link to edr: \\CDSESUB1\EVSPROD\NDA021919\021919.ENX

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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John M Bishai  
10/21/2008 04:31:45 PM



NDA 21-919

Amylin Pharmaceuticals, Inc.  
Attention: Dawn Viveash, M.D.  
Vice President, Regulatory Affairs and Safety  
9360 Towne Centre Drive, Suite 110  
San Diego, CA 92121

Dear Dr. Viveash:

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.

On September 19, 2008, we received your September 18, 2008, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 20, 2008.

If you have any questions, please call John Bishai, Ph.D., Regulatory Project Manager, at 301-796-1311.

Sincerely,

*{See appended electronic signature page}*

Lina AlJuburi, Pharm.D., M.S.  
Chief, Project Management Staff  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Lina Aljuburi  
9/19/2008 12:26:38 PM

# REQUEST FOR CONSULTATION

TO (Office/Division): Richardae (Chardae) Araojo, PharmD  
Regulatory Reviewer Maternal Health Team (MHT),  
Office of New Drugs FDA/CDER

FROM (Name, Office/Division, and Phone Number of Requestor): Lina  
AlJuburi, PharmD, MS Chief, Project Management Staff  
Division of Metabolism and Endocrinology Products,  
ODE-II, 301-796-1168

DATE March 13, 2008	IND NO. N/A	NDA NO. 21-919	TYPE OF DOCUMENT	DATE OF DOCUMENT March 19, 2008
NAME OF DRUG Byetta (exenatide) Injection		PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG anti- diabetic agent	DESIRED COMPLETION DATE Sept 9,2008

NAME OF FIRM: Amylin Pharmaceuticals Inc

## REASON FOR REQUEST I. GENERAL

NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE /  
ADDITION MEETING PLANNED BY PRE-NDA MEETING END-OF-PHASE 2a MEETING END-OF-PHASE 2 MEETING RESUBMISSION SAFETY /  
EFFICACY PAPER NDA CONTROL SUPPLEMENT RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL  
NEW CORRESPONDENCE FORMULATIVE REVIEW OTHER (SPECIFY BELOW):

## II. BIOMETRICS

PRIORITY P NDA REVIEW END-OF-PHASE 2 MEETING CONTROLLED  
STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW):

CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS  
OTHER (SPECIFY BELOW):

## III. BIOPHARMACEUTICS

DISSOLUTION BIOAVAILABILITY STUDIES PHASE 4 STUDIES DEFICIENCY LETTER RESPONSE PROTOCOL - BIOPHARMACEUTICS IN-VIVO  
WAIVER REQUEST

## IV. DRUG SAFETY

PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF  
SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP REVIEW OF MARKETING EXPERIENCE, DRUG USE  
AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS

## V. SCIENTIFIC INVESTIGATIONS

CLINICAL

NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The division is currently reviewing the label for Byetta, and during the process it was  
felt that the language used for nursing mothers should be reviewed by the Maternal Health team. Please refer to Section  
**8.3-Nursing Mothers:** **EDR LINK:** <\\CDSESUB1\EVSPROD\NDA021919\021919.enx>

(b) (4)

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one) DFS

EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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John M Bishai  
8/18/2008 03:14:26 PM

## REQUEST FOR CONSULTATION

TO (Office/Division): CDER OSE Consults  
Cheryl Campbell  
cheryl.campbell@fda.hhs.gov  
Office of Safety and Epidemiology  
WO22 RM3417, phone: 6-0723

FROM (Name, Office/Division, and Phone Number of Requestor):  
John Bishai Ph.D.  
Regulatory Project Manager  
DMEP, HFD-510, phone #: 6-1311

DATE  
June 19, 2008

IND NO.

NDA NO.  
21919

TYPE OF DOCUMENT  
Patient Labeling Review

DATE OF DOCUMENT  
March 19, 2008

NAME OF DRUG  
Byetta (exenatide) injection

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-diabetic agent

DESIRED COMPLETION DATE  
August 19, 2008

NAME OF FIRM: Amylin 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 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> 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 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 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"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This a request for a PPI review. The submission is dated March 19, 2008. The document can be found in the EDR (see link below).

Direct link to edr:\\CDSESUB1\EVSPROD\NDA021919\021919.enx

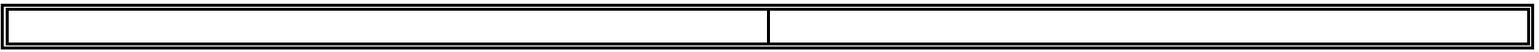
SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

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/s/

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John M Bishai  
6/20/2008 10:57:53 AM

**Bishai, John**

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**From:** Bishai, John  
**Sent:** Monday, June 16, 2008 9:59 AM  
**To:** 'Ellis, Staci'  
**Subject:** RE: Byetta NDAs 21-919 and 21-773 - List of open items

Hello Staci,

Thanks for the heads up on the type of data included in the May 30th submission. Considering this, we would like to request an updated, comprehensive analysis of renal adverse events in the Phase 3 - 4 placebo controlled clinical trials with a focus on adverse events of acute renal failure, hemodialysis, and on occurrences of out-of-range serum BUN and creatinine measurements. These data should be presented for all individual trials and pooled across all diabetes trials.

Also, the medical reviewer for this IND is Dr. Valerie Pratt.

If you have any questions, feel free to contact me.

Thanks,  
John

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**From:** Ellis, Staci [mailto:Staci.Ellis@amylin.com]  
**Sent:** Friday, June 13, 2008 5:33 PM  
**To:** Bishai, John  
**Subject:** RE: Byetta NDAs 21-919 and 21-773 - List of open items

Hello John

Just to add some clarification regarding the renal analyses in the PSURs for Byetta, please note that PSUR 6, which was just submitted on 30 May 08, did not contain an analysis of renal events because nothing new had been reported since the data cutoff for PSUR 5 that warranted an analysis at such time for inclusion in PSUR 6.

I hope this information is helpful. As always, please let me know if you have any further questions.

Regards,  
Staci

---

**From:** Bishai, John [mailto:John.Bishai@fda.hhs.gov]  
**Sent:** Tuesday, June 10, 2008 5:47 AM  
**To:** Ellis, Staci  
**Subject:** FW: Byetta NDAs 21-919 and 21-773 - List of open items

Hello Staci,

It looks like Amylin beat us to the punch regarding point #5.:

*5. PSUR Submission Timing Requirement - Waiver acknowledged per fax from Chung-Frost dated November 15, 2005. Amylin proposes to continue submitting PSURs every six months instead of annually, as per fax.*

[FDA RESPONSE](#): Please submit a formal request to OSE (Office of Surveillance and Epidemiology) for approval.

It seems that your latest submission, dated May 30, contains the PSUR for the renal SLR. If for some reason the reviewer needs more information, I will relay that information request.

Thanks,  
John

---

**From:** Bishai, John  
**Sent:** Tuesday, June 10, 2008 8:18 AM  
**To:** 'Ellis, Staci'  
**Subject:** RE: Byetta NDAs 21-919 and 21-773 - List of open items

I believe that it's with Chemistry, and it is currently being reviewed. Since this is a CBE Supplement, it is routed to someone else, the contact person is Teshara Bouie. Let me know if that name sounds familiar. If not, I can get her contact information for you.

Thanks,  
John

---

**From:** Ellis, Staci [mailto:Staci.Ellis@amylin.com]  
**Sent:** Monday, June 09, 2008 5:01 PM  
**To:** Bishai, John  
**Subject:** RE: Byetta NDAs 21-919 and 21-773 - List of open items

Hi John,

Thank you so much for the updates. I appreciate the feedback on potential timing as well. By the way, have you heard anything regarding our CBE-30, which was our Baxter submission that was submitted on May 2?

Thank you,  
Staci

---

**From:** Bishai, John [mailto:John.Bishai@fda.hhs.gov]  
**Sent:** Monday, June 09, 2008 1:36 PM  
**To:** Ellis, Staci  
**Subject:** RE: Byetta NDAs 21-919 and 21-773 - List of open items

Hello Staci,

I just wanted to address some issues you brought to my attention regarding NDAs 21-919 and 21-773.

NDA 21-919 (BYETTA Monotherapy)

1. 4-month safety update - submission forthcoming this week per Dr. Joffe's request  
Great! Upon arrival I will forward this to the medical officer and Dr. Joffe.

NDA 21-773 (BYETTA)

1. Pregnancy Registry Protocol, Serial 180 dated November 20, 2007  
This is still under review with Maternal Health Team. Unfortunately, I don't have a time-frame for completion.

(b) (4)

This is being reviewed by Clin Pharm. It is likely that an action will take place with NDA21-919 PLR Package Insert.

3. S-009 Oral Contraceptive Labeling PAS, Serial 154 dated March 28, 2007

This is being reviewed by Clin Pharm. It is likely that an action will take place with NDA21-919 PLR Package Insert

4. S-011 Renal Failure Safety Labeling Change - CBE-0 - Serial 171 dated September 20, 2007 (PDUFA date March 19)

This is pending upon submission of a more current PSUR as I mention in our previous email, dated May 30th. (See below)

5. PSUR Submission Timing Requirement - Waiver acknowledged per fax from Chung-Frost dated November 15, 2005. Amylin proposes to continue submitting PSURs every six months instead of annually, as per fax.

Please submit a formal request to OSE (Office of Surveillance and Epidemiology) for approval.

If you have any questions, feel free to contact me.

Thanks,  
John Bishai, Ph.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Email: john.bishai@fda.hhs.gov  
Tel: 301.796.1311  
Fax: 301.796.9712

---

From: Bishai, John  
Sent: Friday, May 30, 2008 9:18 AM  
To: 'Ellis, Staci'  
Cc: Aljuburi, Lina  
Subject: Data request for supplements regarding NDA 21-773

Hello Staci,

We are currently reviewing your supplements (numbers 009, 010, 011, (b) (4)) for NDA 21-773. During the process, the reviewers have requested the following data:

1. An updated post-marketing analysis of renal events since a year has passed from the last (PSUR) submission, dated May 25 2007.
2. An updated, comprehensive analysis of renal adverse events in the Phase 3 - 4 placebo controlled clinical trials with a focus on adverse events of acute renal failure, hemodialysis, and on occurrences of out-of-range serum BUN and creatinine measurements. These data should be presented for all individual trials and pooled across all diabetes trials.

6/17/2008

If you have questions, feel free to contact me.

Thanks,  
John Bishai, Ph.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Email: john.bishai@fda.hhs.gov  
Tel: 301.796.1311  
Fax: 301.796.9712

**From:** Ellis, Staci [<mailto:Staci.Ellis@amylin.com>]  
**Sent:** Monday, June 02, 2008 5:01 PM  
**To:** Bishai, John  
**Subject:** Byetta NDAs 21-919 and 21-773 - List of open items

Hi John,  
As per our conversation, here is a list of the submissions and relative information that we talked about to help you out with following up.

NDA 21-919 (BYETTA Monotherapy)

1. 4-month safety update - submission forthcoming this week per Dr. Joffe's request

NDA 21-773 (BYETTA)

1. Pregnancy Registry Protocol, Serial 180 dated November 20, 2007

(b) (4)

3. S-009 Oral Contraceptive Labeling PAS, Serial 154 dated March 28, 2007

4. S-011 Renal Failure Safety Labeling Change - CBE-0 - Serial 171 dated September 20, 2007 (PDUFA date March 19)

5. PSUR Submission Timing Requirement - Waiver acknowledged per fax from Chung-Frost dated November 15, 2005. Amylin proposes to continue submitting PSURs every six months instead of annually, as per fax.

Thanks for your help with these! Have a good evening.

Regards,  
Staci Ellis  
Amylin Pharmaceuticals, Inc.  
Associate Director, Regulatory Affairs  
858-754-4903 work  
858-699-1361 cell

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/s/

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John M Bishai  
6/17/2008 10:36:58 AM  
CSO



NDA 21-919

AMYLIN PHARMACEUTICALS, INC  
Attention: Dawn Viveash, M.D.  
Vice President, Regulatory Affairs  
9360 Towne Centre Drive  
San Diego, CA 92121

Dear Dr. Viveash:

We acknowledge receipt on March 20, 2008, of your March 19, 2008, resubmission to your new drug application for Byetta (exenatide) injection.

We consider this a complete, class 2 response to our April 28, 2005, action letter. Therefore, the user fee goal date is September 20, 2008.

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 note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

If you have any questions, call me at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

John Bishai, Ph.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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John M Bishai

5/9/2008 04:40:38 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA (b) (4)

AMYLIN PHARMACEUTICALS, INC  
Attention: Dawn Viveash, M.D.  
Vice President, Regulatory Affairs  
9360 Towne Centre Drive  
San Diego, CA 92121

Dear Dr. Viveash:

We acknowledge receipt on March 20, 2008, of your March 19, 2008, resubmission to your new drug application for Byetta (exenatide) injection.

We consider this a complete, class 2 response to our April 28, 2005, action letter. Therefore, the user fee goal date is September 20, 2008.

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 note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

If you have any questions, call me at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

John Bishai, Ph.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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John M Bishai

5/7/2008 04:19:19 PM

## MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** April 28, 2005

**TO:** NDA Files

**FROM:** Lina AlJuburi, Pharm.D., M.S.  
Regulatory Project Manager  
Division of Metabolic and Endocrine Drug Products, HFD-510

**SUBJECT:** **NDA Trade Name Change and Administrative Split**  
NDA 21-773 and 21-919 Byetta (exenatide) Injection

### Background

On June 29, 2004, Amylin Pharmaceuticals, Inc. submitted NDA 21-773 (b) (4) (exenatide) Injection, 250 mcg/mL. The application was submitted with two proposed indications:

1. to improve glycemic control in patients with type 2 diabetes mellitus alone
2. to improve glycemic control in patients with type 2 diabetes as adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.

### Trade Name Change

The sponsor submitted a new trade name on November 4, 2004, replacing (b) (4) with Byetta. A trade name consult request for Byetta was sent to the Division of Medication Errors and Technical Support (DMETS) on November 18, 2004. Please refer to the DMETS review dated March 11, 2005, Medical Officer's review (section 1.2.4 addresses the trade name) dated April 22, 2005, and Division Director's memo dated April 26, 2005.

NDA 21-773 will be approved with the name Byetta (exenatide) Injection.

### Administrative Split

Review of the application, as amended, yielded the decision to take an approval (AP) action for use of exenatide in combination with metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea. However, an approvable (AE) action will be taken for the monotherapy indication. Two different actions for the same application necessitated an administrative split of the application.

**NDA 21-773 holds the approved indication: to improve glycemic control in patients with type 2 diabetes as adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.**

**NDA 21-919 holds the approvable indication: to improve glycemic control in patients with type 2 diabetes mellitus alone.** The single monotherapy study submitted (Study 2993-120, *A Phase 2, Randomized, Triple-Blind, Parallel-Group, Placebo-Controlled, Multicenter Study to Examine the Effect of Exenatide Monotherapy on Glucose Control in Subjects With Type 2 Diabetes Mellitus*) was only 28 days in duration and enrolled only 99 patients. As such, the study was inadequate to characterize the efficacy of exenatide as monotherapy for the treatment of patients with type 2 diabetes mellitus. Before the application may be approved, it will be necessary for the sponsor to submit data from at least one adequate and well-controlled trial of sufficient duration to assess the efficacy (i.e., HbA1c lowering) and safety of exenatide monotherapy in patients with type 2 diabetes mellitus.

NDA 21-773 Byetta (exenatide) Injection: Approval action to be taken on/before 29 Apr 05.

NDA 21-919 Byetta (exenatide) Injection: Approvable action to be taken on/before 29 Apr 05.

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/s/

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Lina Aljuburi  
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CSO