

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022200Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 022200

SUPPL #

HFD # 510

Trade Name Bydureon

Generic Name exenatide extended-release for injectable suspension

Applicant Name Amylin Pharmaceuticals, Inc.

Approval Date, If Known 1/27/12

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021773

exenatide

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:
1. LAR105
  2. 2993LAR-105Comparability
  3. BCB108
  4. BCB112
  5. BCB113
  6. BCB109
  7. BCB106
  8. GWCH
  9. GWBR

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

|                  |                              |  |
|------------------|------------------------------|--|
| Investigation #1 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #2 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #3 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #4 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #5 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #6 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #7 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #8 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #9 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

|                  |                              |  |
|------------------|------------------------------|--|
| Investigation #1 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #2 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #3 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #4 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #5 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #6 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #7 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #8 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| Investigation #9 | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. LAR105
2. 2993LAR-105Comparability
3. BCB108
4. BCB112
5. BCB113
6. BCB109
7. BCB106
8. GWCH

9. GWBR

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 067092                      !  
   !  
YES                       ! NO   
   ! Explain:

Investigation #2  
IND # 067092                      !  
   !  
YES                       ! NO   
   ! Explain:

Investigation #3  
IND # 067092                      !  
   !  
YES                       ! NO   
   ! Explain:

Investigation #4  
IND # 067092                      !  
   !  
YES                       ! NO   
   ! Explain:

Investigation #5  
IND # 067092                      !  
   !  
YES                       ! NO   
   ! Explain:

Investigation #6                      !



drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: Pooja Dharia, Pharm.D.  
Title: Regulatory Project Manager  
Date: 1/27/12

Name of Office/Division Director signing form: Mary Parks, M.D.  
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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POOJA DHARIA  
01/31/2012

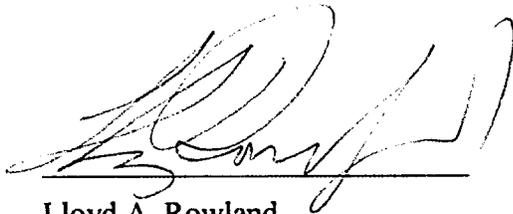
MARY H PARKS  
01/31/2012

### 1.3.3 Debarment Certification

#### NDA 022-200 Exenatide for Injectable Suspension

In compliance with the Section 306(k) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §335a(k), as amended by the Generic Drug Enforcement Act of 1992, we, Amylin Pharmaceuticals, Inc., state the following with respect to this new drug application complete response resubmission:

Amylin Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Lloyd A. Rowland  
Vice President, Compliance and Risk Management,  
and Chief Compliance Officer

12/July 2011  
Date

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

|   |                                      |   |
|---|--------------------------------------|---|
| NDA # 022200<br>BLA #   | NDA Supplement #<br>BLA Supplement # | If NDA, Efficacy Supplement Type:   |
| Proprietary Name: Bydureon<br>Established/Proper Name: exenatide extended-release for injectable suspension<br>Dosage Form: 2 mg  |                                      | Applicant: Amylin Pharmaceuticals, Inc.<br>Agent for Applicant (if applicable): N/A   |
| RPM: Pooja Dharia, Pharm.D.   |                                      | Division: Division of Metabolism and Endocrinology Products   |
| <p><u>NDA's:</u><br/>NDA Application Type: X 505(b)(1) <input type="checkbox"/> 505(b)(2)<br/>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> |                                      | <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u><br/>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature.<br/><input type="checkbox"/> This application relies on a final OTC monograph.<br/><input type="checkbox"/> Other (explain)</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> |
| ❖ Actions   |                                      |   |
| <ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>1/28/12</u></li> </ul>   |                                      | X AP <input type="checkbox"/> TA <input type="checkbox"/> CR  |
| <ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>   |                                      | <input type="checkbox"/> None<br>CR: 10/18/10, 03/12/10   |

The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

|   |   |
|---|---|
| <p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br/>                 Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>  | <p><input type="checkbox"/> Received</p>  |
| <p>❖ Application Characteristics<sup>2</sup></p> <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority<br/>                 Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch<br/> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch<br/> <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span><br/> <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span><br/> <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span><br/>                 Subpart I <span style="margin-left: 200px;">Subpart H</span><br/> <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR <span style="margin-left: 200px;">REMS: <input type="checkbox"/> MedGuide</span><br/> <input type="checkbox"/> Submitted in response to a PMC <span style="margin-left: 100px;"><input checked="" type="checkbox"/> Communication Plan</span><br/> <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 100px;"><input type="checkbox"/> ETASU</span><br/> <span style="margin-left: 400px;"><input type="checkbox"/> REMS not required</span></p> <p>Comments:</p> |   |
| <p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>   | <p><input type="checkbox"/> Yes, dates</p>  |
| <p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>   | <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>   |
| <p>❖ Public communications (<i>approvals only</i>)</p>  |   |
| <ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>  | <p>X Yes <input type="checkbox"/> No</p>  |
| <ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>  | <p>X Yes <input type="checkbox"/> No</p>  |
| <ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>   | <p><input type="checkbox"/> None<br/> <input checked="" type="checkbox"/> HHS Press Release<br/> <input type="checkbox"/> FDA Talk Paper<br/> <input checked="" type="checkbox"/> CDER Q&amp;As<br/> <input type="checkbox"/> Other</p> |

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

|   |   |
|---|---|
| ❖ Exclusivity   |   |
| <ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>   | X No <input type="checkbox"/> Yes   |
| <ul style="list-style-type: none"> <li>NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>   | X No <input type="checkbox"/> Yes<br>If, yes, NDA/BLA # _____ and date exclusivity expires: _____   |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>  | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date exclusivity expires: _____                                       |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>  | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date exclusivity expires: _____                                       |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>   | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date exclusivity expires: _____                                       |
| <ul style="list-style-type: none"> <li>NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>   | X No <input type="checkbox"/> Yes<br>If yes, NDA # _____ and date 10-year limitation expires: _____   |
| Patent Information (NDAs only)  |   |
| <ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>   | X Verified<br><input type="checkbox"/> Not applicable because drug is an old antibiotic.  |
| <ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>  | 21 CFR 314.50(i)(1)(i)(A)<br><input type="checkbox"/> Verified<br><br>21 CFR 314.50(i)(1)<br><input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>  | <input type="checkbox"/> No paragraph III certification<br>Date patent will expire _____  |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] For each <b>paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</li> </ul> | <input type="checkbox"/> N/A (no paragraph IV certification)<br><input type="checkbox"/> Verified   |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If “Yes,” skip to question (4) below. If “No,” continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

*If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If “No,” continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

*If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If “No,” continue with question (5).*

|   |  |
|---|--|
| <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | <p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p> |
| <p><b>CONTENTS OF ACTION PACKAGE</b></p>  |  |
| <p>❖ Copy of this Action Package Checklist<sup>3</sup></p>  | <p>Yes</p>   |
| <p><b>Officer/Employee List</b></p>   |  |
| <p>• List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>  | <p>X Included</p>  |
| <p>Documentation of consent/non-consent by officers/employees</p>   | <p>X Included</p>  |
| <p><b>Action Letters</b></p>  |  |
| <p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>  | <p>1/27/12, 3/12/10, 10/18/10</p>                                  |
| <p><b>Labeling</b></p>  |  |
| <p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>   |  |
| <ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>  | <p>1/24/12</p>   |
| <ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>  | <p>5/4/09</p>  |
| <ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>  |  |

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.

|   |   |
|---|---|
| <ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>  | <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Medication Guide</li> <li><input type="checkbox"/> Patient Package Insert</li> <li><input checked="" type="checkbox"/> Instructions for Use</li> <li><input type="checkbox"/> Device Labeling</li> <li><input type="checkbox"/> None</li> </ul>  |
| <ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul> </li> </ul>  | <p>1/24/12</p>  |
| <ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul> </li> </ul>  | <p>7/28/11</p>  |
| <ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul> </li> </ul>  |   |
| <ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>   |   |
| <ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul> </li> </ul>  | <p>1/24/12</p>  |
| <ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i></li> </ul> </li> </ul> | <p>11/8/11, 2/3/10<br/>10/26/11, 9/15/10</p>  |
| <ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>  | <ul style="list-style-type: none"> <li><input type="checkbox"/> RPM</li> <li><input checked="" type="checkbox"/> DMEPA 10/26/11, 2/25/10</li> <li><input type="checkbox"/> DRISK</li> <li><input checked="" type="checkbox"/> DDMAC 1/4/12, 8/24/10,</li> <li><input type="checkbox"/> SEALD</li> <li><input type="checkbox"/> CSS</li> <li><input checked="" type="checkbox"/> Other reviews 12/21/11</li> </ul> |
| <p><b>Administrative / Regulatory Documents</b></p>   |   |
| <ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>  | <p>Not completed during first review cycle.</p>   |
| <ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>   | <p><input checked="" type="checkbox"/> Not a (b)(2)</p>   |
| <ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>  | <p><input checked="" type="checkbox"/> Not a (b)(2)</p>   |
| <ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>   | <p><input checked="" type="checkbox"/> Included 1/31/12</p>   |
| <ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents<br/><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>   |   |
| <ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul> </li> </ul>   | <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>  |
| <ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>• This application is on the AIP                     <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul> </li> </ul>   | <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p style="text-align: right;"><input type="checkbox"/> Not an AP action</p>  |
| <ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>February 10, 2010</u><br/>If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>   | <p><input checked="" type="checkbox"/> Included</p>   |

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

|  |  |
|--|--|
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>                                      | X Verified, statement is acceptable  |
| ❖ Outgoing communications <i>(letters (except action letters), emails, faxes, telecons)</i>  | 12/15/11, 12/7/11, 11/8/11, 11/2/11, 10/27/11, 10/20/11, 9/23/11, 3/1/11, 8/10/11, 6/3/11, 6/6/11, 5/11/11, 4/20/11, 3/30/11, 3/29/11, 2/22/11, 1/11/11, 12/1/10, 9/28/10, 6/24/10, 6/10/10, 4/20/10, 2/16/10, 10/17/09, 5/15/09 |
| ❖ Internal memoranda, telecons, etc.   | 7/28/10, 5/4/11  |
| ❖ Minutes of Meetings  |  |
| • Regulatory Briefing <i>(indicate date of mtg)</i>  | x No mtg   |
| • If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>   | x N/A or no mtg  |
| • Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>  | <input type="checkbox"/> No mtg  |
| • EOP2 meeting <i>(indicate date of mtg)</i>   | <input type="checkbox"/> No mtg  |
| • Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>   |  |
| ❖ Advisory Committee Meeting(s)  | X No AC meeting  |
| • Date(s) of Meeting(s)  |  |
| • 48-hour alert or minutes, if available <i>(do not include transcript)</i>  |  |
| <b>Decisional and Summary Memos</b>  |  |
| Office Director Decisional Memo <i>(indicate date for each review)</i>   | X None   |
| Division Director Summary Review <i>(indicate date for each review)</i>  | <input type="checkbox"/> None 1/27/12, 10/18/10  |
| Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>   | <input type="checkbox"/> None 9/17/10, 3/12/10   |
| PMR/PMC Development Templates <i>(indicate total number)</i>   | <input type="checkbox"/> None 1/25/12  |
| <b>Clinical Information<sup>5</sup></b>  |  |
| ❖ Clinical Reviews   |  |
| • Clinical Team Leader Review(s) <i>(indicate date for each review)</i>  |  |
| • Clinical review(s) <i>(indicate date for each review)</i>  | 12/12/11, 11/22/10, 9/15/10, 8/16/10, 7/1/10, 2/22/10, 12/17/09,   |
| • Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>  | <input checked="" type="checkbox"/> None   |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i> | 12/12/11   |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>  | X None   |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>   | X Not applicable   |

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iling reviews should be filed with the discipline reviews.

|   |   |
|---|---|
| ❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul> | 1/24/12<br>1/25/12<br><input type="checkbox"/> None<br>12/23/11               |
| ❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )   | <input type="checkbox"/> None requested 12/5/11,<br>12/29/09                  |
| <b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None   |   |
| ❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None   |
| Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None   |
| <b>Biostatistics</b> <input type="checkbox"/> None  |   |
| ❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )  | X None  |
| Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )  | X None  |
| Statistical Review(s) ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None 9/6/11, 2/3/10, 1/5/10                          |
| <b>Clinical Pharmacology</b> <input type="checkbox"/> None  |   |
| ❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )  | X None  |
| Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )  | X None  |
| Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None 12/5/11, 10/14/10,<br>9/29/10, 1/22/10, 8/19/09 |
| ❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )  | x None  |
| <b>Nonclinical</b> <input type="checkbox"/> None  |   |
| ❖ Pharmacology/Toxicology Discipline Reviews  |   |
| • ADP/T Review(s) ( <i>indicate date for each review</i> )  | X None  |
| • Supervisory Review(s) ( <i>indicate date for each review</i> )  | X None  |
| • Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None 12/16/11, 10/8/10,<br>3/1/10, 2/22/10           |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )   | X None  |
| ❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )   | <input type="checkbox"/> No carc 12/22/09                                     |
| ❖ ECAC/CAC report/memo of meeting   | <input type="checkbox"/> None 2/1/10<br>Included in P/T review, page          |
| ❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )  | X None requested  |

| <b>Product Quality</b> <input type="checkbox"/> None  |   |
|---|---|
| ❖ Product Quality Discipline Reviews  |   |
| • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>  | X None  |
| • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>   | X None  |
| • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>   | <input type="checkbox"/> None 1/4/12, 10/20/11, 10/19/11, 9/23/11, 9/22/11, 9/22/10, 7/22/10, 3/2/10, 2/8/10, 1/20/10, 10/17/09, 6/16/09,           |
| ❖ Microbiology Reviews<br>X NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i><br><input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i> | <input type="checkbox"/> Not needed<br>11/1/11, 7/22/10, 4/29/10, 3/1/10, 6/15/09   |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>  | x None  |
| ❖ Environmental Assessment (check one) (original and supplemental applications)   |   |
| X Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>  | 10/20/11  |
| <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>  |   |
| <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>  |   |
| ❖ Facilities Review/Inspection  |   |
| X NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup>)</i>                                 | Date completed: 11/14/11<br>X Acceptable<br><input type="checkbox"/> Withhold recommendation<br><input type="checkbox"/> Not applicable             |
| <input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>  | Date completed:<br><input type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation  |
| ❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>  | <input type="checkbox"/> Completed<br><input type="checkbox"/> Requested<br><input type="checkbox"/> Not yet requested<br>X Not needed (per review) |

..., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

**From:** [Dharia, Pooja](#)  
**To:** ["Ellis, Staci"](#)  
**Subject:** Bydureon + Byetta PMRs  
**Date:** Thursday, December 15, 2011 2:56:00 PM

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Hi Staci,

As discussed during the t-con, here is a list of the Bydureon PMRs.

For each of these studies, we will need a Final Protocol Submission date, a Study Completion Date, and a Final Report Submission Date, to be submitted within 14 days.

Bydureon:

1. A deferred randomized, double-blind, controlled pediatric study to evaluate the safety, efficacy, and pharmacokinetics of BYDUREON 2 mg daily for the treatment of type 2 diabetes mellitus (T2DM) in pediatric patients ages 10-17 years (inclusive).

This study does **not** need to be delayed until we have received and reviewed the results from the preclinical PMRs.

2. A case series registry which seeks to identify all possible cases of MTC which occur in North America during the fifteen year period after approval of Bydureon.
3. A randomized, double blind, placebo-controlled, event-driven cardiovascular outcomes trial in type 2 diabetic patients. The trial must also assess adverse events of interest including the long-term effects of BYDUREON on potential biomarkers of medullary thyroid carcinoma (MTC) (e.g. serum calcitonin) as well as the long-term effects on thyroid neoplasms, pancreatitis (including hemorrhagic and necrotizing forms), pancreatic cancer, injection site reactions (including nodules), allergic/hypersensitivity events, serious hypoglycemia, and renal disorders.
4. Cellular hyperplasia is a physiological process in which cells proliferate in response to a specific stimulus. Because the cells in hyperplastic tissue are typically normal in both appearance and organization, hyperplasia is generally thought to be reversible once the stimulus is removed. However, continued proliferation increases the chance of DNA mutations that can allow for the progression of hyperplasia to neoplasia. Although it is assumed that GLP-1 agonist-induced C-cell proliferation is reversible once treatment is discontinued, it is uncertain whether short-term exposure to exenatide extended-release increases the lifetime risk of Ccell tumors even after treatment is discontinued.

To address the question of reversibility of C-cell hyperplasia, you should conduct a 2-year mouse study consisting of a 6-month treatment period with 3 doses of exenatide extended-release yielding multiples of human exposures of 10-, 30-, and 100X, followed by a 1.5 year recovery period. Animals should be assessed for C-cell hyperplasia/neoplasia at 6-months and 2 years. Additionally, thyroids collected at the 6 month time point should be evaluated for GLP-1 receptor expression using a quantitative technique to determine whether there is a correlation between the level of GLP-1 receptor expression and the degree of Ccell proliferation.

5. It has been speculated that the sensitivity of GLP-1-induced C-cell hyperplasia is dependent on GLP-1 receptor density, with C-cells having higher expression levels of GLP-1 receptor being more susceptible to the proliferative effects of GLP-1 agonists.

Limited published reports indicate that human C-cells have a lower expression of GLP-1 receptor than rodents, thereby making humans less susceptible to GLP-1 agonist-induced C-cell proliferation. However, this hypothesis is based on a limited number of human thyroid samples. To complement the available information on human expression, C-cells from additional human thyroid biopsy samples should be assessed for GLP-1 receptor expression. These data should also be compared with the expression levels of GLP-1 receptor in mice after 6 months of treatment, which will be measured in the study for PMR #1.

GLP-1 receptor expression levels should be measured on C-cells from human thyroid biopsy samples with the following histopathology findings:

- a. Normal tissue
  - b. Non-neoplastic C-cell hyperplasia
  - c. Neoplastic C-Cell hyperplasia (microcarcinoma)
  - d. C-cell carcinoma

6. It is currently believed that GLP-1 agonist-induced C-cell proliferation is dependent on the GLP-1 receptor. However, this hypothesis should be verified in vivo.

A comparison of C-cell hyperplasia should be made between wild-type and GLP1 receptor knock-out mice after treatment with exenatide extended-release or vehicle for 3 months. To better ascertain the growth promoting pathways that are involved in the hyperplastic process, gene expression analysis should be conducted on C-cells that have been isolated through laser capture microdissection for each of the animals. The gene expression analysis should include a number of genes involved in growth promoting, growth inhibitory, and apoptotic pathways.

The following study for Byetta will also become a PMR:

7. A prospective observational cohort study to examine the incidence of pancreatic malignancy and thyroid neoplasm in patients with Type 2 diabetes mellitus initiated on Byetta compared to patients initiated on other anti-diabetic agents

Let me know if you have any questions.

Thanks,  
Pooja

Pooja Dharia, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
pooja.dharia@fda.hhs.gov  
(301) 796-5332

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/s/  
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POOJA DHARIA  
12/15/2011

**From:** [Dharia, Pooja](#)  
**To:** ["Ellis, Staci"](#)  
**Subject:** Bydureon REMS comments  
**Date:** Wednesday, December 07, 2011 1:19:00 PM  
**Attachments:** [rems-proposal-2011-12-05.doc](#)  
[rems-supporting 12-5-11.doc](#)

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Hi Staci,

Please find below comments on the proposed REMS for Bydureon. The tracked changes REMS and supporting document are also attached.

### **1. Communication Plan**

We recommend that the Direct Mail letter be eliminated from the REMS. We propose that the DHCP letter be sent twice, 6 months apart, via electronic mail (e-mail) within 60 days of approval or at the time of product launch, whichever comes first. Standard mail and facsimile should be employed to reach HCPs not reachable by email.

The DHCP should be sent to relevant professional organizations for distribution to their members. At the same time the letter is supplied to professional organizations, it should be sent to MedWatch. Please see below for a suggested list of professional societies:

Academy of Managed Care Pharmacy  
Ambulatory Pediatric Association  
American Academy of Family Physicians  
American Academy of Nurse Practitioners  
American Academy of Pediatrics  
American Academy of Physician Assistants  
American Association of Clinical Endocrinologists  
American Association of Colleges of Nursing  
American Association of Colleges of Pharmacy  
American Association of Critical-Care Nurses  
American Clinical Laboratory Association  
American College of Clinical Pharmacy  
American College of Emergency Physicians  
American College of Health Care Administrators  
American College of Nurse Practitioners  
American College of Physicians  
American Gastroenterological Association  
American Hospital Association  
American Medical Association  
American Nurses Association  
American Osteopathic Association  
American Pharmacists Association  
American Public Health Association  
American Society for Healthcare Risk Management  
American Society of Consultant Pharmacists  
American Society of Health-System Pharmacists  
Association of periOperative Registered Nurses  
Endocrine Nurses Society  
Federation of State Medical Boards  
Institute for Safe Medication Practices  
Interamerican College of Physicians and Surgeons  
Joint Commission

National Association of Emergency Medical Technicians  
National Association of Hispanic Nurses  
National Association of School Nurses  
National Black Nurses Association  
National Hispanic Medical Association  
National Medical Association  
National Pharmaceutical Association  
National Medical Association  
American Association of Diabetes Educators  
Alliance for Minority Medical Associations  
Asian Pacific Islander American Health Foundation  
Association of Asian Pacific Community Health  
Association of Minority Health Professional Schools  
Patient Safety Institute  
National Alliance for Hispanic Health  
National Black Women's Health Imperative  
National Congress of American Indians  
National Council of La Raza  
National Council of Negro Women  
Office of Minority Health  
Juvenile Diabetes Research Foundation  
HHS Office of Minority Health  
HHS Indian Health Service  
HHS HRSA  
HHS NIDDK Diabetes, Endocrinology, Metabolic Diseases  
HHS NIH Center for Minority Health and Health Disparities  
CMS  
CDC  
The Endocrine Society  
Lawson Wilkins Pediatric Endocrine Society  
Association for Preventionists in Infection Control  
Society for Healthcare Epidemiology in America  
American Diabetes Association

## **2. Timetable for Submission of Assessments**

We recommend that assessments be conducted at 1 and 2 years.

## **3. Information Needed for Assessment**

In addition to surveys to assess understanding, the assessment report should include the number and specialty of HCPs reached via email, the number and specialty of HCPs who opened the email, the names of professional organizations contacted to distribute the DHCP letter to their members, the names of the organizations who accepted and redistributed the letter, and the names of the professional organizations who declined to accept or redistribute the DHCP letter.

Additionally, the assessment report should include data and analysis establishing whether Bydureon is being used as first-line therapy.

## **4. General Comments**

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Bydureon with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word

document.

Let me know if you have any questions.

Thanks,  
Pooja

Pooja Dharia, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
pooja.dharia@fda.hhs.gov  
(301) 796-5332

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/s/  
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POOJA DHARIA  
12/07/2011



NDA 022200

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Amylin Pharmaceuticals, Inc.  
9360 Towne Centre Drive  
San Diego, California 92121-3030

Attention: Orville Kolterman, MD  
Sr. Vice President, Chief Medical Officer

Dear Dr. Kolterman:

Please refer to your New Drug Application (NDA) dated May 4, 2009, and received May 5, 2009, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Exenatide for Injectable Suspension, 2 mg. Please also refer to your complete Class 2 resubmission to this NDA, dated and received July 28, 2011.

We also refer to:

- Your initial proprietary name submission, dated November 5, 2009, for the proposed proprietary name Bydureon;
- Our initial correspondence dated February 3, 2010, finding this proposed proprietary name conditionally acceptable;
- Your submission dated June 29, 2010, confirming that the product characteristics for Bydureon remain unchanged;
- An email, dated August 10, 2011, from the Division of Metabolic and Endocrinology Products, requesting resubmission of your proprietary name for review as part of the Class 2 Complete Response;
- Your August 16, 2011, correspondence, received August 17, 2011, requesting re-review of your proposed proprietary name, Bydureon.

We have completed our review of the proposed proprietary name, Bydureon and have concluded that it is acceptable

The proposed proprietary name, Bydureon, will be re-reviewed 90 days prior to approval. If **any** of the proposed product characteristics as stated in your August 16, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manger in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Pooja Dharia at (301) 796-5332.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
11/08/2011

**From:** [Dharia, Pooja](#)  
**To:** ["Ellis, Staci";](#)  
**Subject:** Bydureon information request 11/2/11  
**Date:** Wednesday, November 02, 2011 10:38:51 AM

---

Hi Staci,

We have the following information requests for Bydureon:

- 1. In your Complete Response Safety Update 2011, you calculate the exposure-adjusted incidence rate of acute pancreatitis for both sitagliptin and pioglitazone. Please recalculate the incidence rates for sitagliptin and pioglitazone separately.**
- 2. In your Complete Response Safety Update 2011 Supplement, you analyzed pancreatitis events in completed, long-term, controlled studies of Byetta and Bydureon. Please clarify and justify the definition of "long-term" in the analysis.**

Thanks,  
Pooja

Pooja Dharia, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
[pooja.dharia@fda.hhs.gov](mailto:pooja.dharia@fda.hhs.gov)  
(301) 796-5332

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/s/  
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POOJA DHARIA  
11/02/2011

**From:** [Dharia, Pooja](#)  
**To:** ["Ellis, Staci";](#)  
**cc:** [Tossa, Margarita;](#)  
**Subject:** Bydureon carton and container comments  
**Date:** Thursday, October 27, 2011 12:51:04 PM  
**Attachments:** [carton and container comments.pdf](#)

---

Hi Staci,

Please find comments attached regarding the carton and container labeling for Bydureon.

For all future communication regarding carton and containers, please contact Margarita Tossa who is the OSE PM for Bydureon.

Thanks,  
Pooja

Pooja Dharia, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
[pooja.dharia@fda.hhs.gov](mailto:pooja.dharia@fda.hhs.gov)  
(301) 796-5332

10/27/11

**A. All Container Labels and Carton Labeling (trade and professional sample)**

1. We note the proprietary name is presented in all capital letters (i.e. BYDUREON) which decreases readability. Revise the proprietary name to appear in title case (i.e. Bydureon). Words set in upper and lower case, form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.
2. Ensure the presentation of the established name is at least half the size of the proprietary name in accordance to 21 CFR 201.10(g)(2), which requires that the established name shall be printed in letters that are at least half as large and a prominence commensurate to the proprietary name, taking into consideration all pertinent factors, including typography, layout, contrast and other printing features.

**B. Container (2 mg vial) Labels (Trade and Professional Sample)**

3. Relocate the 'Rx only' and 'Sterile' statements from the principal display panel to the lower right hand side of the label. As currently presented, the placement of the 'Rx only' and 'Sterile' statements next to the route of administration statement distracts from the important information 'Subcutaneous use only'.
4. Increase the prominence of 'Subcutaneous use only' by bolding the statement. As currently presented, this information is embedded in other information on the label. We had identified two medication error cases in which the patients administered Exetanide intramuscularly and intravenously instead of subcutaneously. Therefore, the clear presentation of 'Subcutaneous use only' statement may reduce the risk of medication errors associated with the wrong route of administration.
5. If space permits, include the 'Once-weekly' statement to the area above the proprietary name, similar to the presentation on the carton and lid labeling. Currently, the 'Once-weekly' statement does not appear on the vial labels. We had eleven medication error cases of wrong frequency of administration with another Exenatide formulation. Since your proposed product will also introduce a new frequency of administration in to the market place, this issue becomes even more important for patients who will be switching from the twice daily Byetta to the once-weekly Bydureon. Patients may not recognize that the new product, Bydureon has to be administered once weekly instead of twice daily. Therefore, the prominent presentation of this statement on all labels and labeling may reduce the risk of mediation errors associated with the wrong frequency of administration.

**C. Carton Labeling (trade and sample)**

Carton and container comments

10/27/11

6. Increase the prominence of the route of administration statement on the principal display panel by increasing the font size and bolding it. As currently presented, the statement 'Subcutaneous use only' lacks prominence.
7. Revise the color of the strength statement (i.e. 2 mg/vial) to appear in a color that provides more contrast with the white background. As currently presented the color (b) (4) against the white background lacks contrast and is difficult to read. We recommend you use the same font color to represent the product strength that you use for the other labels and labeling (i.e. black or green).

**D. Single-dose Kit Lid Label (trade and sample)**

8. Increase the prominence of 'Once-weekly' statement on the single-dose kit lid label. However, ensure this statement does not compete with prominence with the proprietary name.
9. Include the statement 'Discard unused portion' on the single-dose kit lid label. The statement 'Discard unused portion' can be placed immediately following the statement 'Inject immediately after mixing.'
10. Delete the statement (b) (4) . This information is not required, and it crowds the label.
11. Provide a single space between the '0.65' and 'mL' to appear as follows:

1 diluent syringe (0.65 mL).

As currently presented (0.65mL), there is no space between '0.65' and 'mL'.

**E. Diluent Syringe Label**

12. Increase the font size of the name 'Diluent'. As currently presented, 'Diluent' lacks prominence because it appears as the same font size as 'Bydureon'.
13. Revise the name 'BYDUREON' to appear in title case (i.e. Bydureon) and decrease the font size of Bydureon to appear smaller than the Name of the product, 'Diluent'. Additionally, delete 'suspension of' from the statement 'for suspension of Bydureon'. The revised statement should appear as follows:

Diluent  
for Bydureon

14. Include the contents of the Diluent on the syringe label. As currently presented, the ingredients of the Diluent do not appear on the label and it is not clear to patients and healthcare professionals what constitutes the Diluent.

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/s/  
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POOJA DHARIA  
10/27/2011

**From:** [Dharia, Pooja](#)  
**To:** ["Ellis, Staci";](#)  
**Subject:** Bydureon information request  
**Date:** Thursday, October 20, 2011 9:59:10 AM

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Hi Staci,

I have the following information requests for the Bydureon NDA:

**1. In pediatric study** [REDACTED] (b) (4)

[REDACTED]

**2. In pediatric study** [REDACTED] (b) (4)

[REDACTED] **To ensure adequate representation of younger pediatric patients, please require at least 30% of randomized subjects to be 10-14 years old.**

Thanks,  
Pooja

Pooja Dharia, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
[pooja.dharia@fda.hhs.gov](mailto:pooja.dharia@fda.hhs.gov)  
(301) 796-5332

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/s/  
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POOJA DHARIA  
10/20/2011



NDA 22-200

**INFORMATION REQUEST**

Amylin Pharmaceuticals, Inc.  
Orville Kolterman, M.D.  
Sr. Vice President, Research & Development  
9360 Towne Centre Drive, Suite 110  
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bydureon (exenatide extended release for injectable suspension).

We are reviewing the Biopharmaceutics and CMC section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Include test method TM-0216 (In vitro complete release at 37 °C) in your postapproval annual stability commitment for commercial scale exenatide QW (Section 3.2.P.8.2.3). This test should be conducted at the same time points as TM-0212 (In vitro initial release).
2. Provide the in vitro drug release method development report with detailed information/data.
3. You have used a buffered medium at pH 9.4 for the in vitro drug release study which is not physiologically relevant. Clarify why such medium was selected and provide any other drug release studies that you may have conducted in other media.
4. Clarify what is the discriminating capability of the proposed in vitro drug release (i.e., able to distinguish a good batch versus a bad batch). Provide the study report/data supporting your justification.
5. Clarify what is the impact of various microsphere size distribution (within your proposed acceptance criteria) on drug release.
6. The newly proposed drug release range at Day 31 of NLT  $\frac{(b)}{(4)}\%$  to NMT  $\frac{(b)}{(4)}\%$  violates the ICH Q6 a guideline where a maximum total variability of 20% is allowed for an extended release formulation without the support of IVIVC. Therefore, tighten the drug release range for this time point appropriately.

If you have any questions, call Khushboo Sharma, Regulatory Project Manager, at (301) 796-1270.

Sincerely,

*{See appended electronic signature page}*

Ali Al Hakim, Ph.D.  
Branch Chief, Branch VII  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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ALI H AL HAKIM  
09/23/2011



NDA 022200  
NDA 021919  
NDA 021773  
NDA 021773/S-002  
NDA 021773/S-029

## INFORMATION REQUEST

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Amylin Pharmaceuticals, Inc.  
Attention: Orville Kolterman, M.D.  
Sr. Vice President, Chief Medical Officer  
9360 Towne Centre Drive, Suite 110  
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your New Drug Applications (NDAs) and Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Byetta (exenatide) injection and Bydureon (exenatide extended-release for injectable suspension).

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b) (4)<sup>1</sup>. The pervasiveness and egregious nature of the violative practices by (b) (4) has led FDA to have significant concerns that the bioanalytical data generated at (b) (4) from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented (b) (4) and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by (b) (4) during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

<sup>1</sup> These violations include studies conducted by (b) (4) facility.

NDA 022200  
NDA 021919  
NDA 021773  
NDA 021773/S-002  
NDA 021773/S-029  
Page 2

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by [REDACTED] <sup>(b) (4)</sup> during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

**Please respond to this query within 30 days from the date of this letter.**

This information should be submitted as correspondence to each of the NDAs and sNDAs referenced above. In addition, please provide a desk copy to:

Office of New Drugs  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Room 6300  
Silver Spring, MD 20993-0002

If you have any questions, please call Pooja Dharia, Pharm.D., Regulatory Project Manager, at (301) 796-5332.

Sincerely,

*{See appended electronic signature page}*

Mary H. 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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JULIE C MARCHICK

09/01/2011

J. Marchick signing for M. Parks

# REQUEST FOR CONSULTATION

TO (Office/Division): IRT-QT  
IRT QT Review Group  
Devi Kozeli  
OND/ODEI/DCRP  
devi.kozeli@fda.hhs.gov  
WO22 RM4183/ Phone: X6-1128

FROM (Name, Office/Division, and Phone Number of Requestor):  
Pooja Dharia  
Regulatory Project Manager  
DMEP  
301-796-5332

DATE  
8/10/11

IND NO.  
IND 067092

NDA NO.  
NDA 022200

TYPE OF DOCUMENT  
class 2 resubmission

DATE OF DOCUMENT  
7/28/11

NAME OF DRUG  
Bydureon (exenatide  
extended-release for  
injectable suspension)

PRIORITY CONSIDERATION  
P - 6 month review

CLASSIFICATION OF DRUG  
treatment of type 2  
diabetes mellitus

DESIRED COMPLETION DATE  
11/14/11

NAME OF FIRM:

## 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 checked="" 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 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: Resubmission of NDA 022200 Bydureon from Amylin. Included in this resubmission are the clinical TQT study reports for BCB112 and BCB113.

#### Meetings

Planning Meeting 08/09/11  
Midcycle target: 10/28/2011  
Wrap Up target: 12/31/2011

#### Team Meetings

#### Labeling Meetings

Send labeling by 01/14/12  
Primary reviews due 01/04/12  
Secondary reviews due 01/07/12  
PDUFA Goal Date 01/28/12

TLs Reviewers  
Ilan Irony Valerie Pratt Clinical Reviewer  
Julie Marchick Pooja Dharia Regulatory Project Manager

EDR Location: \\CDSESUB1\EVSPROD\NDA022200\022200.enx  
Cover Letter: \\CDSESUB1\EVSPROD\NDA022200\0034\m1\us\cover.pdf dated 7/28/11

PLEASE NOTE: THERE IS AN OPEN TSI FOR THIS ISSUE—TSI# 906

SIGNATURE OF REQUESTOR

Pooja Dharia

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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POOJA DHARIA  
08/10/2011



**COMMENTS/SPECIAL INSTRUCTIONS:**

Resubmission for NDA 022200 Bydureon from Amylin.

We would like to request OSE review for the following:

1. PI, MG, IFU
2. REMS
3. DEpi: On February 16, 2010, the sponsor was informed of the following post-marketing requirement under FDAAA for BYDUREON:

*A medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of (exenatide for injectable suspension) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of BYDUREON (exenatide for injectable suspension).*

Additionally, the sponsor for VICTOZA (the only currently approved long-acting GLP-1 agonist) was required to conduct the following epidemiologic studies as post-marketing requirements:

*A five-year prospective epidemiological study using a large healthcare claims database to determine the incidence of thyroid cancer among patients with type 2 diabetes exposed to Victoza (liraglutide [rDNA origin]) Injection and patients with type 2 diabetes not exposed to Victoza (liraglutide [rDNA origin]) Injection, as well as the incidence of serious hypoglycemia, pancreatitis, hypersensitivity, and overall malignant neoplasms.*

The safety profiles of VICTOZA and BYDUREON are similar. Please comment on the need for, and the nature of, post-marketing required epidemiologic studies to further characterize the safety profile of BYDUREON, if it is approved.

Background

1. On May 20, 2010, the sponsor submitted a briefing document regarding their proposed Cancer registry.  
EDR link: <\\cdsesub1\EVSPROD\NDA022200\0023\m1\us\briefing-doc-2010-05-20.pdf>
2. On May 25, 2010, we held a teleconference with Amylin and issued meeting minutes on June 10, 2010.

| <u>Meetings</u>       |                    | <u>TLs</u>        | <u>Reviewers</u> |   |
|-----------------------|--------------------|-------------------|------------------|---|
| Planning Meeting      | 08/09/11           | Ilan Irony        | Valerie Pratt    | Clinical Reviewer                           |
| Midcycle              | target: 10/28/2011 | Jaya Vaidyanathan | Manoj Khurana    | Clinical Pharmacology Reviewer              |
| Wrap Up               | target: 12/31/2011 | Su Tran           | Olen Stephens    | Product Quality - CMC Reviewer              |
| Team Meetings         |                    | Patrick           |                  |   |
| Labeling Meetings     |                    | Marroum/Angelica  |                  |   |
| Send labeling by      | 01/14/12           | Dorantes          | Akm Kairuzzaman  | Product Quality - Biopharmaceutics Reviewer |
| Primary reviews due   | 01/04/12           | Todd Sahlroot     | Janice Derr      | Microbiology                                |
| Secondary reviews due | 01/07/12           | Karen Davis Bruno | Tim Hummer       | Stats                                       |
| PDUFA Goal Date       | 01/28/12           | Julie Marchick    | Pooja Dharia     | Non-Clinical Reviewer                       |
|                       |                    |                   |                  | Regulatory Project Manager                  |

EDR Location: <\\CDSESUB1\EVSPROD\NDA022200\022200.enx>  
 Cover Letter: <\\CDSESUB1\EVSPROD\NDA022200\0034\m1\us\cover.pdf>

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|--|--|
| SIGNATURE OF REQUESTER<br>Pooja Dharia | METHOD OF DELIVERY (Check one)<br><input type="checkbox"/> MAIL <span style="float: right;"><input type="checkbox"/> HAND</span> |
| SIGNATURE OF RECEIVER                  | SIGNATURE OF DELIVERER   |

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/s/  
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POOJA DHARIA  
08/10/2011

**From:** [Dharia, Pooja](#)  
**To:** ["Ellis, Staci";](#)  
**Subject:** Bydureon information request  
**Date:** Wednesday, August 10, 2011 1:46:05 PM  
**Attachments:** [Acknowledge Class 2 Resubmission NDA 022200.pdf](#)

---

Hi Staci,

Please find the acknowledgement attached for the Bydureon resubmission.

In addition, we have the following information requests:

**1. Please include the following information in a tabular format by site for study BCB108:**

- a. Number of subjects screened and randomized for each site by site**
- b. Number of subjects treated who prematurely discontinued for each site by site**
- c. Protocol violations reported at each site by site**

**2. Seven subjects were rescued from study BCB108. Please clarify the rescue method used in this study and its location in the protocol. Please also provide (or direct us to) narratives for the seven rescued subjects.**

**3. Please submit a revised pediatric development plan for Bydureon, including dates for protocol submission, study initiation, and study completion. We recommend you seek a deferral in subjects aged 10 - 16 (inclusive) and consider a PK substudy as part of the safety and efficacy study of 0.8 and 2 mg doses.**

For request #1, we are requesting a 1-week turnaround.

Thanks,  
Pooja

Pooja Dharia, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
[pooja.dharia@fda.hhs.gov](mailto:pooja.dharia@fda.hhs.gov)  
(301) 796-5332

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/s/  
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POOJA DHARIA  
08/10/2011

| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION  |   | <b>REQUEST FOR DDMAC LABELING REVIEW CONSULTATION</b><br><b>**Please send immediately following the Filing/Planning meeting**</b>  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
|---|---|--|---|---|----------|----------|--------------------|---------|--------------------|---------------|--|-------------------|--|------------------|----------|---------------------|----------|-----------------------|----------|-----------------|----------|---|--|--|-----|-----------|--|------------|---------------|-------------------|-------------------|---------------|--------------------------------|---------|---------------|--------------------------------|---------|--|--|------------------|-----------------|---|----------|--|--------------|---------------|-------------|-------|-------------------|------------|-----------------------|----------------|--------------|----------------------------|
| TO:<br><b>CDER-DDMAC-RPM</b>  |   | FROM: (Name/Title, Office/Division/Phone number of requestor)<br>Pooja Dharia, Pharm.D.<br>Regulatory Project manager<br>ODE II/DMEP<br>301-796-5332   |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| REQUEST DATE<br>8/10/11   | IND NO.<br>067092                                   | NDA/BLA NO.<br>022200  | TYPE OF DOCUMENTS<br>(PLEASE CHECK OFF BELOW)<br>NDA resubmission – 3 <sup>rd</sup> cycle     |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| NAME OF DRUG<br>Bydureon (exenatide extended-release for injectable suspension)   | PRIORITY CONSIDERATION<br>Priority – 6 month review | CLASSIFICATION OF DRUG<br>T2DM   | DESIRED COMPLETION DATE<br>(Generally 1 week before the wrap-up meeting)<br>November 14, 2011 |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| NAME OF FIRM:<br>Amylin   |   | PDUFA Date: 1/28/12  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| <b>TYPE OF LABEL TO REVIEW</b>  |   |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| <b>TYPE OF LABELING:</b><br>(Check all that apply)<br><input checked="" type="checkbox"/> PACKAGE INSERT (PI)<br><input type="checkbox"/> PATIENT PACKAGE INSERT (PPI)<br><input checked="" type="checkbox"/> CARTON/CONTAINER LABELING<br><input checked="" type="checkbox"/> MEDICATION GUIDE<br><input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)  |   | <b>TYPE OF APPLICATION/SUBMISSION</b><br><input checked="" type="checkbox"/> ORIGINAL NDA/BLA – 3 <sup>rd</sup> cycle<br><input type="checkbox"/> IND<br><input type="checkbox"/> EFFICACY SUPPLEMENT<br><input type="checkbox"/> SAFETY SUPPLEMENT<br><input type="checkbox"/> LABELING SUPPLEMENT<br><input type="checkbox"/> PLR CONVERSION |   | <b>REASON FOR LABELING CONSULT</b><br><input checked="" type="checkbox"/> INITIAL PROPOSED LABELING<br><input type="checkbox"/> LABELING REVISION |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| <b>EDR link to submission:</b><br>EDR Location: <a href="\\CDSESUB1\EVSPROD\NDA022200\022200.enx">\\CDSESUB1\EVSPROD\NDA022200\022200.enx</a><br>Cover Letter: <a href="\\CDSESUB1\EVSPROD\NDA022200\0034\m1\us\cover.pdf">\\CDSESUB1\EVSPROD\NDA022200\0034\m1\us\cover.pdf</a> dated 7/28/11  |   |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| <b>Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, “substantially complete” labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.</b>   |   |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| <b>COMMENTS/SPECIAL INSTRUCTIONS:</b>   |   |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| <table border="1"> <thead> <tr> <th colspan="2">Meetings</th> </tr> </thead> <tbody> <tr> <td>Planning Meeting</td> <td>08/09/11</td> </tr> <tr> <td>Midcycle</td> <td>target: 10/28/2011</td> </tr> <tr> <td>Wrap Up</td> <td>target: 12/31/2011</td> </tr> <tr> <td>Team Meetings</td> <td></td> </tr> <tr> <td>Labeling Meetings</td> <td></td> </tr> <tr> <td>Send labeling by</td> <td>01/14/12</td> </tr> <tr> <td>Primary reviews due</td> <td>01/04/12</td> </tr> <tr> <td>Secondary reviews due</td> <td>01/07/12</td> </tr> <tr> <td>PDUFA Goal Date</td> <td>01/28/12</td> </tr> </tbody> </table> |   | Meetings   |   | Planning Meeting  | 08/09/11 | Midcycle | target: 10/28/2011 | Wrap Up | target: 12/31/2011 | Team Meetings |  | Labeling Meetings |  | Send labeling by | 01/14/12 | Primary reviews due | 01/04/12 | Secondary reviews due | 01/07/12 | PDUFA Goal Date | 01/28/12 | <table border="1"> <thead> <tr> <th>TLs</th> <th colspan="2">Reviewers</th> </tr> </thead> <tbody> <tr> <td>Ilan Irony</td> <td>Valerie Pratt</td> <td>Clinical Reviewer</td> </tr> <tr> <td>Jaya Vaidyanathan</td> <td>Manoj Khurana</td> <td>Clinical Pharmacology Reviewer</td> </tr> <tr> <td>Su Tran</td> <td>Olen Stephens</td> <td>Product Quality - CMC Reviewer</td> </tr> <tr> <td>Patrick</td> <td></td> <td></td> </tr> <tr> <td>Marroum/Angelica</td> <td>Akm Kairuzzaman</td> <td>Product Quality - Biopharmaceutics Reviewer</td> </tr> <tr> <td>Dorantes</td> <td></td> <td>Microbiology</td> </tr> <tr> <td>Todd Sahlroot</td> <td>Janice Derr</td> <td>Stats</td> </tr> <tr> <td>Karen Davis Bruno</td> <td>Tim Hummer</td> <td>Non-Clinical Reviewer</td> </tr> <tr> <td>Julie Marchick</td> <td>Pooja Dharia</td> <td>Regulatory Project Manager</td> </tr> </tbody> </table> |  |  | TLs | Reviewers |  | Ilan Irony | Valerie Pratt | Clinical Reviewer | Jaya Vaidyanathan | Manoj Khurana | Clinical Pharmacology Reviewer | Su Tran | Olen Stephens | Product Quality - CMC Reviewer | Patrick |  |  | Marroum/Angelica | Akm Kairuzzaman | Product Quality - Biopharmaceutics Reviewer | Dorantes |  | Microbiology | Todd Sahlroot | Janice Derr | Stats | Karen Davis Bruno | Tim Hummer | Non-Clinical Reviewer | Julie Marchick | Pooja Dharia | Regulatory Project Manager |
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| Planning Meeting  | 08/09/11  |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| Midcycle  | target: 10/28/2011                                  |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| Wrap Up   | target: 12/31/2011                                  |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
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| Primary reviews due   | 01/04/12  |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| Secondary reviews due   | 01/07/12  |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| PDUFA Goal Date   | 01/28/12  |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| TLs   | Reviewers   |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| Ilan Irony  | Valerie Pratt                                       | Clinical Reviewer  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| Jaya Vaidyanathan   | Manoj Khurana                                       | Clinical Pharmacology Reviewer   |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| Su Tran   | Olen Stephens                                       | Product Quality - CMC Reviewer   |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| Patrick   |   |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| Marroum/Angelica  | Akm Kairuzzaman                                     | Product Quality - Biopharmaceutics Reviewer  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| Dorantes  |   | Microbiology   |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| Todd Sahlroot   | Janice Derr   | Stats  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| Karen Davis Bruno   | Tim Hummer  | Non-Clinical Reviewer  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| Julie Marchick  | Pooja Dharia  | Regulatory Project Manager   |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| SIGNATURE OF REQUESTER<br>Pooja Dharia  |   | METHOD OF DELIVERY (Check one)<br><input type="checkbox"/> eMAIL <input type="checkbox"/> HAND   |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |
| SIGNATURE OF RECEIVER   |   |  |   |   |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |   |  |  |     |           |  |            |               |                   |                   |               |                                |         |               |                                |         |  |  |                  |                 |   |          |  |              |               |             |       |                   |            |                       |                |              |                            |

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/s/  
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POOJA DHARIA  
08/10/2011



NDA 022200

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Amylin Pharmaceuticals, Inc.  
Orville Kolterman, M.D.  
Sr. Vice President, Research & Development  
9360 Towne Centre Drive, Suite 110  
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your new drug application (NDA) dated and received July 28, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BYDUREON (exenatide extended release for injectable suspension).

We consider this a complete, class 2 response to our October 18, 2010, action letter. Therefore, the user fee goal date is **January 28, 2012**.

If you have any questions, call Pooja Dharia, Pharm.D., Regulatory Project Manager, at (301) 796-5332.

Sincerely,

*{See appended electronic signature page}*

Pooja Dharia, Pharm.D.  
Regulatory Project Manager  
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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POOJA DHARIA  
08/10/2011

|  |   |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
|--|---|--|-------------------------------------|-------------------------------|----------------|-----------------|-------------|----------|---------------|----------|----------|--------------------|---------|--------------------|---------------|--|-------------------|--|------------------|----------|---------------------|----------|-----------------------|----------|-----------------|----------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION   |   | CMC MICRO & STERILITY ASSURANCE<br>REVIEW REQUEST  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| TO (Division/Office): <b>New Drug Microbiology Staff</b><br><br><b><i>E-mail to: CDER OPS IO MICRO</i></b><br><b><i>Paper mail to: WO Bldg 51, Room 4193</i></b>   |   | FROM:<br>Khushboo Sharma, ONDQA PM 301-796-1270<br><br>PROJECT MANAGER (if other than sender):   |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| REQUEST DATE<br>7/28/2011  | IND NO.   | NDA NO.<br>22-200  | TYPE OF DOCUMENT                    | DATE OF DOCUMENT<br>7/28/2011 |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| NAMES OF DRUG<br>Bydureon  | PRIORITY CONSIDERATION<br>Class II resubmission | PDUFA DATE<br>1/28/2012  | DESIRED COMPLETION DATE<br>1/4/2012 |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| NAME OF APPLICANT OR SPONSOR: Amylin   |   |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| <b>GENERAL PROVISIONS IN APPLICATION</b>   |   |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| <input type="checkbox"/> 30-DAY SAFETY REVIEW NEEDED <input type="checkbox"/> CBE-0 SUPPLEMENT<br>NDA FILING REVIEW NEEDED BY: 9/26/2011 (filing date) <input type="checkbox"/> CBE-30 SUPPLEMENT<br><input type="checkbox"/> BUNDLED <input type="checkbox"/> CHANGE IN DOSAGE, STRENGTH / POTENCY<br><input checked="" type="checkbox"/> DOCUMENT IN EDR   |   |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| COMMENTS / SPECIAL INSTRUCTIONS: Resubmission for NDA 22-200. Please review the sterility assurance (updated stability data etc.). EDR<br>Location: <a href="#">\\CDSESUB1\EVSPROD\NDA022200\0034</a><br>Bob Mello was the first cycle reviewer. See below schedule for timelines.   |   |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| <table> <tr> <td>Filing Meeting</td> <td>target: 8/27/11</td> </tr> <tr> <td>Filing Date</td> <td>09/26/11</td> </tr> <tr> <td>74-day letter</td> <td>10/10/11</td> </tr> <tr> <td>Midcycle</td> <td>target: 10/28/2011</td> </tr> <tr> <td>Wrap Up</td> <td>target: 12/31/2011</td> </tr> <tr> <td>Team Meetings</td> <td></td> </tr> <tr> <td>Labeling Meetings</td> <td></td> </tr> <tr> <td>Send labeling by</td> <td>01/14/12</td> </tr> <tr> <td>Primary reviews due</td> <td>01/04/12</td> </tr> <tr> <td>Secondary reviews due</td> <td>01/07/12</td> </tr> <tr> <td>PDUFA Goal Date</td> <td>01/28/12</td> </tr> </table> |   |  |                                     |                               | Filing Meeting | target: 8/27/11 | Filing Date | 09/26/11 | 74-day letter | 10/10/11 | Midcycle | target: 10/28/2011 | Wrap Up | target: 12/31/2011 | Team Meetings |  | Labeling Meetings |  | Send labeling by | 01/14/12 | Primary reviews due | 01/04/12 | Secondary reviews due | 01/07/12 | PDUFA Goal Date | 01/28/12 |
| Filing Meeting   | target: 8/27/11                                 |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| Filing Date  | 09/26/11  |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| 74-day letter  | 10/10/11  |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| Midcycle   | target: 10/28/2011                              |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| Wrap Up  | target: 12/31/2011                              |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| Team Meetings  |   |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| Labeling Meetings  |   |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| Send labeling by   | 01/14/12  |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| Primary reviews due  | 01/04/12  |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| Secondary reviews due  | 01/07/12  |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| PDUFA Goal Date  | 01/28/12  |  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
| SIGNATRE OF REQUESTER<br>Khushboo Sharma   |   | REVIEW REQUEST DELIVERED BY (Check one):<br>X DARRTS    EDR    X E-MAIL <input type="checkbox"/> MAIL    HAND  |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |
|  |   | DOCUMENTS FOR REVIEW DELIVERED BY (Check one):<br><br><input type="checkbox"/> EDR <input type="checkbox"/> E-MAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND |                                     |                               |                |                 |             |          |               |          |          |                    |         |                    |               |  |                   |  |                  |          |                     |          |                       |          |                 |          |

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/s/  
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KHUSHBOO SHARMA  
07/28/2011



NDA 022200

**DISPUTE APPEAL – DENIED**

Amylin Pharmaceuticals, Inc.  
Attention: Orville G. Kolterman, M.D.  
Senior Vice President, Chief Medical Officer  
9360 Towne Centre Drive, Suite 110  
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bydureon (exenatide extended-release for injectable suspension).

We also refer to your April 11, 2011, request for formal dispute resolution, received on April 11, 2011, to the Office of New Drugs. The request for dispute resolution concerns the decision by the Division of Metabolism and Endocrinology Products (DMEP) to issue a complete response (CR) letter on October 18, 2010. This formal dispute request follows your February 4, 2011, appeal to the Office of Drug Evaluation II (ODE II) and subsequent denial of your appeal on March 30, 2011, by Dr. Curtis Rosebraugh, Director, ODE II.

In the CR Letter of October 18, 2010, additional clinical data to address two clinical deficiencies were required prior to approval of Bydureon:

1. Conduct a thorough QT study (tQT) following treatment with exenatide at exposures comparable to those observed in patients with renal impairment taking Bydureon.
2. Submit Study LAR-108 along with the new tQT study to enable a more accurate evaluation of the efficacy of the to-be-marketed (TBM) formulation of Bydureon and to better inform labeling. This request arose from DMEP's conclusion that you had not demonstrated comparability between the clinical batches used in Study 2993LAR-105 (Study 105) and the TBM batches of Bydureon.

In your February 4, 2011, appeal to ODE II you argued that these additional data are not necessary for the Agency to reach a decision to approve Bydureon for treatment of patients with Type 2 diabetes mellitus. You also argued that it was inappropriate for DMEP to raise these issues in the second CR letter since they were not mentioned in the first CR letter issued on March 12, 2010.

In his letter of March 30, 2011, denying your first appeal, Dr. Rosebraugh agreed with DMEP that the additional clinical data requested in the second CR letter were "...necessary to allow adequate consideration, and perhaps resolution, of the issues, identified in the second CR letter and in my view are necessary before the drug product may be approved."

In your April 8, 2011, appeal to the Office of New Drugs, you requested a "...second, independent review of this matter."

I have carefully reviewed the materials you submitted in support of your appeal, the reviews and decision memoranda prepared by FDA staff, the two CR letters, Dr. Rosebraugh's appeal denied letter, and other pertinent material (e.g., the ICH E-14 guidance, selected references cited in your appeal). I have also consulted with staff in ODE II, the Office of Clinical Pharmacology (OCP), CDER's Interdisciplinary Review Team for QT Studies (IRT-QT), and Dr. Robert Temple, CDER Deputy Director for Clinical Science. Finally, I am aware that the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) recently recommended Bydureon for approval in the European Union. While the recommendation of another regulatory agency has no direct bearing on FDA's review and decision on Bydureon, for completeness I have reviewed materials provided to FDA by EMA under our confidentiality agreement that relate to their review of Bydureon.

I have completed my review of your request for formal dispute resolution and deny your appeal. The reasons for my decision are outlined below.

### Second CR Letter

First, I will address your assertions that DMEP was precluded from raising issues in the second CR letter that were not cited in the first CR letter. While I disagree with your assertion as a general matter (see below), I find this line of reasoning particularly flawed for this application given that you failed to provide important new safety information to the Agency in a timely manner (i.e., during the first review cycle for the Bydureon NDA) as required by regulation (21 CFR 314.50).

The fact that FDA did not require you to conduct a tQT for exenatide to support the safety of Bydureon did not relieve you of your obligation to submit those data once they became available. As detailed in the timeline included in Dr. Rosebraugh's appeal denied letter, Study GWCI, a tQT study of Byetta (the currently approved twice-daily formulation of exenatide) was completed in 2008 by Lilly, your marketing partner. That study was requested by HealthCanada as important safety data in support of the planned marketing application for Byetta in Canada, and was in progress at the time you met with DMEP on June 24, 2008, for a pre-NDA meeting for Bydureon. The minutes of the pre-NDA meeting show that you asked DMEP the following question:

*Given the absence of a signal of QT interval prolongation in the electrocardiogram data from Study 2993LAR-105, does the Agency agree that an additional QT study is not required to support the NDA submission of exenatide once weekly?*

In the background package for the pre-NDA meeting, and at the meeting, you did not disclose to DMEP that HealthCanada had requested a tQT study for exenatide and you did not disclose that a tQT of exenatide was underway. Based on the information available to them at that time, DMEP agreed that "...an additional QT study is not required at this time (emphasis added) for NDA 22-200. However, the final decision regarding cardiovascular (ECG) safety will be a review issue." I am confident that if DMEP had been aware that a tQT of exenatide was underway at the time of the pre-NDA meeting you would have been advised to submit those data as an important part of the safety assessment to the original NDA for Bydureon.

DMEP first became aware of Study GWCI on April 4, 2010, when HealthCanada contacted FDA to discuss safety concerns based on their review of the study results, which had been submitted by Lilly in support of the marketing application for Byetta. Of note, the results of Study GWCI were also submitted to EMA on March 4, 2010, as part of Lilly's original marketing application for Bydureon in

the European Union. In our review of the records it appears that your only communication to FDA about Study GWCI was through inclusion of this study in a table in the annual report for IND 057725, which was submitted on April 10, 2009. The results of Study GWCI were not included in the original submission of the Bydureon NDA on May 4, 2009, even though the study had been completed in July 2008, and were not included as part of the safety update in the resubmission of the Bydureon NDA on April 22, 2010, in response to the first CR letter.

I can think of no good explanation for your failure to inform DMEP of the data from Study GWCI in a timely manner so those data could be reviewed as part of the ongoing evaluation of the safety of Byetta and in the assessment of the safety of Bydureon, which results in significantly higher plasma concentrations of exenatide. For you to assert now that DMEP should be precluded from citing the need for an additional tQT study in the second CR letter based on their review of Study GWCI in the second review cycle is not logical, and is not consistent with FDA's requirement that all pertinent safety data be submitted for our review in support of marketing applications. While I disagree with your arguments regarding the ability of DMEP to raise QT safety issues in the second CR letter, I have focused my review of your appeal on the data from Study GWCI independent of the timing of its submission to the Agency.

On the more general matter regarding the ability of FDA to raise new issues in a second (or subsequent) CR letter that were not addressed in the first (or earlier) CR letter, when we issue a CR letter our goal is to provide a comprehensive list of deficiencies that prevent approval based on our review of the information submitted in a marketing application. Clearly, this goal does not preclude us from raising new deficiencies that arise from new information submitted to the application on a subsequent review cycle, which as described above is the case for your application. Also, I do not believe that we are precluded from raising important issues on a subsequent review cycle, even if we should have raised them in a prior review cycle. Application of such a standard implies that FDA should ignore important deficiencies in an application and grant approval rather than "correct" our error for not raising the issue earlier. While we try to be comprehensive in our review of applications, we cannot, and will not, ignore important issues in our approval decisions simply because of human error, subsequent reanalysis or reinterpretation of the data. While I acknowledge that such occurrences create an unexpected delay in approval, I also believe they are rare, which attests to our efforts to be comprehensive in our review. This also emphasizes the importance of sponsors making all pertinent data available for FDA review.

#### tQT study

As described in Dr. Rosebraugh's letter and the IRT-QT review, the results of GWCI did not reveal prolongation of the QT interval above the threshold for regulatory concern stated in the ICH E-14 guidance for the 10 mcg dose of exenatide tested. The first issue in dispute is how to interpret the data from GWCI in evaluating the safety of Bydureon, and whether a repeat tQT study at higher exenatide plasma exposures is required prior to approval.

You assert that when analyzed using the individual correction of QT (QTcI) there is no evidence of prolongation of the QT above the threshold for regulatory concern, even when the data are extrapolated to plasma exenatide levels of 500 pg/mL. You assert that the individual correction method is the preferred method used by the IRT-QT. You also assert that the data from GWCI, in combination with the extensive post-marketing experience with Byetta, where no serious adverse reactions related to QT prolongation (e.g., torsade de pointes) have been reported, and the absence of a signal of QT prolongation from ECGs obtained in the Byetta and Bydureon clinical trials, support a conclusion that

there is no clinically significant prolongation of the QT at the plasma exenatide levels achieved with Bydureon. You assert based on these interpretations of the available data that an additional tQT study is not needed prior to approval of Bydureon, and that confirmatory data can be obtained from your ongoing repeat tQT study as a post-marketing required study (PMR).

While it is true that individual correction of QT can be an important tool in evaluating the effect of a drug on the QT interval, our IRT-QT concluded that the baseline data available from Study GWCI are not adequate to construct a valid and reliable QTcI model. They recommend that baseline data from at least a whole day be collected prior to each period in a crossover study in order to construct a valid model for individual correction of QT. This approach allows collection of data across a range of heart rates and strengthens the validity of the QTcI correction. In study GWCI baseline data were collected at only one time point per subject per period. Therefore, the IRT-QT performed their primary analyses using Fredericia's correction (QTcF), which was pre-specified in the GWCI protocol as the primary correction method.

The IRT-QT analyses showed a positive and statistically significant concentration-QT relationship in study GWCI (slope 0.023,  $p=0.0003$ ). Based on the data from GWCI, the IRT-QT predicted values of  $\Delta\Delta\text{QTcF}$  of 9.6 (5.6, 13.5) and 14.1 (8.2, 20.0) at the geometric mean of steady-state  $C_{\text{max\_ss}}$  of 433 pg/mL with 2 mg QW Bydureon and the clinical exposure  $C_{\text{max\_ss}}$  of 650 pg/mL in patients with moderate renal impairment (assuming 50% increase in  $C_{\text{max\_ss}}$ ), respectively. While these predictions are based on modeling and a limited number of data points at higher exenatide concentrations, they are potentially relevant given the generally 2- to 3-fold higher plasma concentrations observed for Bydureon compared to Byetta and the 10-90% concentration range of 148 – 732 pg/mL observed in patients treated with Bydureon 2 mg QW in Study 105. The IRT-QT did acknowledge that there is some uncertainty regarding their analyses using QTcF since exenatide increases heart rate. The IRT-QT recommended that these uncertainties are best addressed by repeating the tQT study to cover at least exenatide concentrations seen with Bydureon.

The issue in dispute is whether the repeat tQT study should be performed prior to approval or can be submitted after review. I address my decision on this issue below in the section "Benefit/Risk."

### Comparability Assessment

The second issue in dispute is whether you have sufficiently established the comparability between the clinical batches (b) (4) scale produced at Alkermes facility) used in Study 105 and the TBM batches (b) (4) scale produced at Amylin facility) of Bydureon. This is a critical issue since Study 105 serves as the primary basis for determining the efficacy of Bydureon and is proposed for inclusion in the product label. You assert that you have established the comparability of the clinical and TBM batches and that no additional clinical trials are necessary to support approval and labeling.

Since the Office of New Drug Quality Assurance (ONDQA) rejected your attempt to establish comparability through an IV/IVc strategy, I focused my review on the comparative PK and clinical data from the extension of Study 105. I note that at the June 24, 2008, pre-NDA meeting DMEP advised you to conduct a separate randomized trial to evaluate comparability and expressed significant concerns regarding the ability of the proposed extension of Study 105 to adequately establish comparability. The Bydureon NDA did not include the requested stand-alone trial, instead you submitted the results from the extension of Study 105 as the primary basis of your claim of comparability between the clinical and TBM batches. In the extension of Study 105, patients stabilized on Bydureon 2 mg QW were randomized to receive the same weekly dose of Bydureon from

either the clinical or TBM batches. The extension study, therefore, tested the maintenance of efficacy from a stable pre-treatment baseline as compared to the main part of Study 105, which compared the treatment effect of Bydureon and Byetta in patients whose diabetes was not adequately controlled.

OCP analyzed the comparative PK data from the extension of Study 105 and concluded that you had failed to establish bioequivalence of the clinical and TBM batches. In their analysis they noted that the geometric least square (LS) mean ratio (90% CI) (TBM/clinical) for AUC<sub>0-168h</sub> and C<sub>ss</sub> were 0.68 (59-78%) and 0.75 (66-86%), respectively. These data do not meet our usual criteria for bioequivalence and demonstrate that the TBM batches result in significantly lower plasma exenatide concentrations than the clinical batches used in the main part of Study 105. This finding calls into question our ability to extrapolate the results of the head-to-head comparison of Bydureon QW to Byetta BID from Study 105 in order to describe the clinical effect of TBM Bydureon in the product label.

The results of main part of Study 105 showed that Bydureon was non-inferior to Byetta according to the pre-defined margin of 0.4% for HbA<sub>1c</sub>, and also that Bydureon was superior to Byetta based on the mean change from baseline for HbA<sub>1c</sub> of 1.9% for Bydureon and 1.5% for Byetta. These data would serve as the primary descriptor of the efficacy of Bydureon in the drug label, and would demonstrate a clinical advantage (i.e., superiority) of Bydureon QW over Byetta BID. Any claim of superiority must be supported by substantial evidence since such claims are of great importance to prescribers in determining what treatments to choose for their patients and also serve as the basis for promotional claims.

Unfortunately, the clinical endpoint data from the extension of Study 105 suggest that the TBM batches of Bydureon are less effective than the batches used in the main part of Study 105 (mean difference in change from baseline HbA<sub>1c</sub> = 0.2%, 95% CI 0.0 – 0.3). While you argue that these data also fall within the non-inferiority margin of 0.4% that you pre-specified, and therefore show the batches to be “comparable”, the non-inferiority margin was not agreed to by DMEP and has not been adequately validated for a study that evaluates the maintenance of treatment effect versus an active comparator from a stable on-treatment baseline. Further, the extension study only followed patients for 18 weeks, so we do not know if the difference between batches was stable at the end of the extension or may have continued to increase if the patients had been followed longer. These data call into question the true relative effect of TBM Bydureon to Byetta, which means that inclusion of the results of Study 105 in the package insert may represent an overestimation of the actual effect of TBM Bydureon and would not support a claim of superiority to Byetta.

### Benefit/Risk

In the end, the Agency’s decision on whether to approve a drug always involves an analysis of the benefits of the drug weighed against its risks. In the current case, while it is reasonable to conclude that TBM Bydureon is an effective drug, the available data are not adequate to inform a description of the benefit in the product label. Inclusion of the results of Study 105 in the product label would provide a misleading description of the benefit of Bydureon and, even if the label included caveats about the differences between the clinical and TBM batches, would likely lead prescribers to conclude, perhaps inappropriately, that Bydureon is more effective than Byetta.

On the safety side of the analysis, the data from Study GWCI provide a signal of a cardiovascular risk related to QT prolongation, a known marker for development of serious, and potentially lethal, ventricular arrhythmias. While I acknowledge that these data are not definitive, and are not supported

by other findings from the preclinical and clinical data for Byetta and Bydureon, they are of concern and must be carefully considered in weighing the benefits and risks for approval. If the effects predicted by modeling the data from GWCI are reflective of the true effects of higher plasma levels of exenatide they clearly exceed the threshold for regulatory and clinical concern. I agree with Dr. Rosebraugh's assessment that this would become an issue of the approvability of Bydureon, not just one of how to modify the label to warn prescribers of this risk.

In the absence of a clearly defined benefit of Bydureon over Byetta (beyond more convenient dosing) or a compelling demonstration that this product meets an unmet medical need for patients with Type 2 diabetes, I believe it is prudent to evaluate the QT signal further prior to approval. In reaching this conclusion, I am aware that the answer to this question can be obtained very soon since you have been working to complete the repeat tQT study since the second CR letter was issued in October, 2010. I can see no justification to proceed to approval of Bydureon at this point given that we will have the data from the repeat tQT study in the very near future. This conclusion is strengthened by the fact that the current data are not adequate to describe the relative benefit of Bydureon in the product label and my knowledge that you have completed another trial, Study 108, which directly addresses the needed comparison between TBM Bydureon and Byetta. Study 108 was submitted to the EMA and served as an important part of the data considered in their analysis of the benefits and risks of Bydureon. While I do not concur with CHMP's evaluation of the QT data for Bydureon and their acceptance of your proposal to complete the repeat tQT study after approval, the fact remains that they had the results of Study 108 in hand to help them to evaluate the benefits and risks of Bydureon and to inform their decision more fully.

For the reasons outlined above, I agree with DMEP and Dr. Rosebraugh that the second tQT study and the results of Study 108 are necessary to constitute a complete response to the Agency's second CR letter. These data will allow us to make a better informed decision on the benefits and risks and appropriate labeling, if approved, of Bydureon. While I recognize that this decision will be a disappointment to you and will delay marketing of Bydureon in the US, if the data from the repeat tQT study are not concerning and the data from Study 108 support a superiority claim (as you have reported in your summary data), you will benefit in the long run from a product label that clearly defines the benefit of Bydureon and removes a cloud regarding a risk of clinically significant prolongation of the QT.

I encourage you going forward to work with DMEP to reach agreement on the path for resubmission of the Bydureon NDA. I have spoken to the staff in DMEP and they are open to your submitting the results of Study 108 in advance of submission of the results of the second tQT study (I recognize that there was some confusion and disagreement on this point earlier). Submission of the full report of Study 108 by itself will not be considered a complete response to the second CR letter and will not restart the PDUFA clock. However, staff in DMEP could begin to review the data as time and other work commitments allow, which may lessen the amount of time needed to complete their review of your complete response to the CR letter once the data from the ongoing tQT study are submitted.

Questions regarding next steps in developing your complete response to the second CR letter should be directed to Dr. Pooja Dharia, Regulatory Health Project Manager in DMEP, 301-796-5332. If you wish to appeal this decision to the next level, your appeal should be directed to Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center's Dispute Resolution Project Manager, Amy Bertha. Any questions concerning your appeal should be addressed to Ms. Bertha at (301) 796-1647.

Sincerely,

*{See appended electronic signature page}*

John Jenkins, M.D.  
Director  
Office of New Drugs  
Center for Drug Evaluation and Research

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/s/  
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JOHN K JENKINS  
05/11/2011



NDA 022200

**FORMAL DISPUTE RESOLUTION –  
Appeal Denied**

Amylin Pharmaceuticals, Inc.  
Attention: Orville G. Kolterman, M.D.  
Senior Vice President, Chief Medical Officer  
9360 Towne Centre Drive, Suite 110  
San Diego, CA 92121

Dear Dr. Kolterman:

Reference is made to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bydureon (exenatide extended-release for injectable suspension).

Reference is also made to the complete response (CR) letters of March 12 and October 18, 2010, to you from Dr. Mary Parks, Director, Division of Metabolism and Endocrinology Products (DMEP, the Division), and to your February 3, 2011, Formal Dispute Resolution Request (FDRR), received February 4, 2011.

In the CR letter of October 18, 2010, two deficiencies were identified:

1. Conduct a thorough QT study (tQT) following treatment with exenatide at exposures comparable to those observed in renal-impaired patients taking Bydureon.
2. Submit Study 108 to enable a more accurate evaluation of the efficacy of Bydureon and to further inform labeling of the safety and effectiveness of Bydureon.

Neither the request for conduct of a tQT study nor the request for the submission of Study 108 was included in the first CR letter of March 12, 2010, but arose after DMEP was made aware of, and reviewed the data from Study H80-EW-GWCI, a tQT study of Byetta required by HealthCanada.

Your FDRR asks that we consider whether the pending new drug application for Bydureon should be approved without the need for additional clinical data. In support of this request, you have asked that we consider two issues:

**Issue 1 – tQT Study**

You contend that the tQT study of Byetta, H80-EW-GWCI (henceforth referred to as GWCI), did not show a clinically meaningful QT prolongation effect. This study was performed at the request of HealthCanada and explored the effects of the non-extended-release form of exenatide, Byetta, on QT interval. Both parties in dispute agree that the results for Byetta itself were not

concerning. However, since Bydureon is an extended-release formulation of exenatide that achieves higher serum levels than Byetta, the agency did extrapolation predictions revealing that there could potentially be QT prolongation at the expected higher exposures occurring with Bydureon administration. You contend that to the extent GWCI raises any new questions based on extrapolations, they can be reasonably addressed through a postmarket study. Inherent in your request to perform the tQT study postmarketing is the presupposition that the results of a tQT study, should they demonstrate levels indicated by modeling, would not be prohibitive to marketing.

## **Issue 2 – Comparability of Batch Sizes**

You contend that you have met your burden under the SUPAC-MR guidance<sup>1</sup> to show comparability between an investigational-scale batch of Bydureon and a commercial-scale batch of Bydureon manufactured at a different site. While you acknowledge that pharmacokinetic bioequivalence was not met, you feel that several lines of evidence demonstrate that there are adequate data contained within the NDA to support comparability.

You also question whether the Agency can raise issues in a second-cycle CR letter that were not originally identified in a first-cycle CR letter. This question affects both Issue 1 and Issue 2, and I will comment on it in relation to each issue.

I have reviewed the information you provided in support of your conclusions and your requested action as well as internal documents. I have been briefed on the application and the issues in dispute by staff from DMEP, Office of Biostatistics, and Office of Clinical Pharmacology, and I have consulted with Dr. Robert Temple, Deputy Center Director for Clinical Science. I also met with you and the appropriate reviewers on March 4, 2011, to discuss the issues underlying the dispute.

After careful review and consideration, I conclude that, overall, the issues surrounding your request for not providing any additional clinical data prior to NDA approval do not have merit. I agree with DMEP that additional clinical data are necessary to fully define the risks and benefits of Bydureon to determine if approval is warranted, and if approval is eventually deemed appropriate, to allow for adequate labeling. I will summarize the basis for my conclusions below.

In order to discuss the issues raised above, I have constructed a timeline and brief synopsis of events for reference.

**April 28, 2005:** Byetta, the non-extended release form of exenatide, approved. (NDA 021773)

**May 1, 2007:** Quality and Clinical Pharmacology End-of-Phase 2 (EOP2) meeting held regarding Bydureon. Amylin informed that

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<sup>1</sup> Guidance for Industry, *SUPAC-MR: Modified Release Solid Oral Dosage Forms* available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070640.pdf>.

physico-chemical characterization and in vitro drug-release testing would be insufficient to support comparability between investigational and commercial products. (IND 067092)

**June 24, 2008:** Pre-NDA meeting. Amylin advised to conduct a bioequivalence study or submit a biowaiver based on an IV/IVc strategy. Amylin also advised that IV/IVc would be difficult with an injectable formulation. DMEP recommended a separate randomized trial for clinical bridging to establish comparability. (IND 067092)

Based on bridging to Byetta and limited information provided by sponsor from Study 105, an additional QT study was not required for submission of Bydureon, but the final decision regarding cardiovascular safety was determined to be a review issue.

**April 23, 2008-July 21, 2008:** Study GWCI, exenatide thorough QT study conducted for HealthCanada. GWCI was not conducted under a United States IND.<sup>2</sup>

**October 29, 2008:** Amylin notified that biowaiver request denied. (IND 067092)

**November 17, 2008:** Comments to Amylin regarding protocol for comparability extension of Study 105. Amylin advised that if bioequivalence is not demonstrated based on AUC, the efficacy results from the extension of Study 105 might not be sufficient. (IND 067092)

**April 10, 2009:** Study GWCI listed in table in Annual Report for IND 057725 (Byetta). Study summary not submitted.

**May 4, 2009:** NDA 022200 for Bydureon submitted. Study GWCI not included in application.

**March 12, 2010:** First CR letter citing concerns of product quality and need for a Risk Evaluation Strategy (REMS).

**April 4, 2010:** HealthCanada initiated discussion with DMEP regarding their concerns of the results of GWCI. This is the first time DMEP is made aware of GWCI results.

**April 13, 2010:** Amylin contacted and informed that completed results of GWCI must be submitted.

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<sup>2</sup> E-mail, Dr. Kolterman, October 14, 2010.

**April 22, 2010:** Amylin resubmits Bydureon application. Results of GWCI are not included.

**May 20, 2010:** Data for GWCI submitted.

**October 18, 2010:** Second CR letter noting QT and comparability concerns.

### **Discussion of Issue 1**

A thorough QT/QTc study (tQT) is intended to determine whether a drug has a threshold pharmacologic effect on cardiac repolarization as detected by QT/QTc prolongation and is very sensitive at determining this threshold.<sup>3</sup> As is noted in our guidance, a tQT study may be required for already approved drugs if there is a significantly higher exposure (i.e., C<sub>max</sub> or AUC). Therefore, it is well within our purview to require further study of QT prolongation potential, even of already approved drugs, if we have a concern caused by new data or a new formulation. The main question to be addressed in your dispute is the nature and validity of the concern, and if there is uncertainty, how much risk are we willing to tolerate until that concern is fully addressed, i.e., should the drug be approved with the risk fully defined pre- or post-approval? This question cannot be viewed in isolation and must be considered in the context of the patient population for which the drug is indicated and the state of our knowledge regarding our ability to make QT prolongation predictions.

While we want to identify possible QT effects for all drugs, in this case it is especially important as there is evidence that diabetes itself is a risk factor for QT interval prolongation, which some speculate may further increase cardiovascular morbidity and mortality in this patient population.<sup>4,5</sup> There is evidence to support this supposition as QT interval prolongation has been demonstrated to be an independent predictor of cardiac death in the diabetic population.<sup>6,7</sup> Therefore, since diabetic populations are at increased risk for cardiovascular disease and have prolonged QT intervals compared to non-diabetic populations, one could postulate that drugs increasing the QT interval beyond an already increased baseline may increase the already high cardiovascular mortality rates associated with diabetes.<sup>8</sup> Identifying possible QT effects of drugs is also complicated as our knowledge of mechanisms of QT prolongation is still evolving. For example, there was early speculation that larger molecules (peptides) may not enter cardiac cells

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<sup>3</sup> Guidance for Industry, *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf>.

<sup>4</sup> Li, W, et al.: Patients with metabolic syndrome have prolonged corrected QT interval (QTc). *Clin Cardiol.* 2009 Dec;32(12):E93-9.

<sup>5</sup> VanHoose L, et al: Electrocardiographic changes with the onset of diabetes and the impact of aerobic exercise training in the Zucker Diabetic Fatty (ZDF) rat. *Cardiovasc Diabetol.* 2010 Sep 22;9:56.

<sup>6</sup> Rana BS, QT interval abnormalities are often present at diagnosis in diabetes and are better predictors of cardiac death than ankle brachial pressure index and autonomic function tests. *Heart.* 2005 Jan; 91(1):44-50.

<sup>7</sup> Dekker, JM. Association between QT interval and coronary heart disease in middle-aged and elderly men. The Zutphen Study. *Circulation* 1994;90; 779-785.

<sup>8</sup> Chugh, SS. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease, the Oregon sudden unexpected death study. *Circulation.* 2009 Feb 10; 119(5):663-70.

and therefore would not affect ion channels, thus having no potential for QT prolongation. However, recently it has been shown that peptides can prolong QTc intervals due to cell surface interactions.<sup>9</sup> We also know that other methods of QT prolongation, such as drug-induced human ether-a-go-go-related gene (hERG) trafficking defects, do not require direct block of hERG and may not be discovered in nonclinical analysis.<sup>10</sup> Also, other gene variants with cardiac repolarization effects continue to be discovered.<sup>11</sup> Therefore, there is always the potential that we may encounter a QT prolongation safety issue that is clinically apparent (perhaps at a critical dose threshold) that was not expressed by nonclinical testing or predicted by our current state of knowledge.

As part of the background for your argument regarding potential QT changes, you note that DMEP had not noted QT prolongation for exenatide (in the form of Byetta), which was approved prior to our requirement for a tQT study for new antidiabetic therapies. Based on no demonstrative signal with Byetta, DMEP had not required a thorough QT study for Bydureon at the time of application submission. You also argue that DMEP had not cited any deficiencies related to analysis of ECG data in the original CR letter. This is an incomplete summary, however, as noted in the timeline above, you were in possession of results of GWCI well in advance of submitting your Bydureon NDA. An NDA is required to include all pertinent knowledge of the safety and efficacy of the subject drug (21 CFR 314.50). I can think of no justification as to why you would not have included Study GWCI with your submission as this is pertinent safety information, and indeed was concerning to HealthCanada. Placing a line listing in an annual report for Byetta is not adequate notification to DMEP of this study. Whether QT concerns were identified as a deficiency in the first CR letter becomes moot as you clearly did not supply DMEP with all relevant safety information.

You contend that “Study GWCI does not hold weight” because your analysis using the individualized correction (QTcI) formula, which you feel is the most appropriate correction, reveals a non-significant slope. In your analysis using QTcI and extrapolation, concentrations of 500 pg/mL are predicted to have placebo-corrected QTcI of 3.95 ms. However, our Interdisciplinary Review Team for QT Studies (QT Team) did not agree with using QTcI as the correction formula as they felt it was not reliable due to sparse baseline sampling. As such, their analysis was performed using Fridericia’s corrections (QTcF) which revealed a significantly positive slope (slope: 0.023, p-value: 0.0003) and predicted values for QTcF of 9.58 (5.6, 13.5) and 14.1 (8.16, 20.0) for steady-state C<sub>max</sub> concentrations of 433 pg/mL and 650 pg/mL, respectively. Both of these serum levels are easily obtainable with dosing of Bydureon. There is no dispute regarding the results of the different correction formulae, but rather upon which is appropriate to draw conclusions. Therefore, extrapolation results based upon QTcI do not reveal potentially clinically important QT prolongation, while results based upon QTcF may.

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<sup>9</sup> Qu, Y, et al: BeKm-1, a Peptide Inhibitor of hERG Potassium Currents, Prolongs QTc Intervals in Isolated Rabbit Heart. *J Pharmacol Exp Ther.* 2010 Dec 23. [Epub ahead of print]

<sup>10</sup> Dennis, A, et al: hERG channel trafficking: novel targets in drug-induced long QT syndrome. *Biochem Soc Trans.* 2007 Nov; 35(pt 5):1060-3.

<sup>11</sup> Chugh, SS. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease, the Oregon sudden unexpected death study. *Circulation.* 2009 Feb 10; 119(5):663-70.

You note that HealthCanada approved Byetta on January 13, 2011. I note that, upon approval, the following was included in the label regarding QT prolongation and their concern (bolded):

*QT Interval:* Exenatide 10 µg s.c. was associated with a small but statistically significant QTc interval prolongation. The magnitude of the observed effect differed for the three heart rate correction methods used (individual-specific method (QTcI), Fridericia method (QTcF), study population-specific method (QTcP)). A maximum mean increase of 2.44 (90% CI 0.40, 4.47) ms (QTcI); 5.81 (90% CI 3.62, 8.00) ms (QTcF); and 6.34 (90% CI 4.12, 8.56) ms (QTcP) was observed at 2 hours post-dosing. The QTc prolongation effect (QTcF) shows a positive correlation with exenatide plasma concentration and a negative correlation with plasma glucose. The optimal heart rate correction for the type of data available in this study is not known.

**Care should be observed in patients with risk factors for Torsades de Pointes (e.g., congenital long QT syndrome, cardiac disease, electrolyte abnormalities).**

I think most would agree that there is no perfect QT correction formula, and all have their inherent limitations. Further compounding these limitations in your case is the acknowledgment that the observed positive exposure-response correlation is based on extrapolation of only a few data points. Therefore, results of extrapolations made upon an imperfect formula must be viewed with caution and indeed this has been acknowledged by the QT Team in their struggle to determine if this finding is clinically relevant.

As you state, there are further data that must be considered. There was not a nonclinical signal for QT prolongation with exenatide including lack of effect on hERG potassium currents both in vitro and in in-vivo non-human studies. There also did not seem to be a signal of concern in the ECGs collected during the Bydureon clinical exposure in Study 105, and there were not any cases of torsades de pointe. However, caution needs to be exercised in relying too heavily upon this result as Study 105 was small (N=148) and torsades de pointe is a very rare event and our experience is that even very arrhythmogenic drugs may not exhibit a case in large, closely monitored, clinical programs.

I will now summarize and discuss how I integrate the facts above into my determination. I think one could draw some reassurance from a nonclinical program where QT prolongation was not identified. There also is an extensive history of use with Byetta without any indication to date of QT prolongation-associated arrhythmias, albeit at exposures expected to be two to three times less than with Bydureon. Finally, we have Study 105, where there did not seem to be an indication of QT interval prolongation, but this was a small trial. Against this backdrop, we have Study GWCI, where the concern was expressed based on extrapolation (mathematical prediction) using sparse data points and an imperfect QT interval correction.

In my mind this comes down to the difference between thinking there may not be a problem, and knowing that there is not a problem. That is where risk tolerance acts as the fulcrum to balance uncertainties versus the potential advances in disease therapy that a drug may offer, all of which must be viewed under the prism of seriousness of the risk under consideration and baseline attributable risk of the population. The question with Bydureon is in regard to potential cardiac effects. Remembering that QT prolongation is an independent risk factor for cardiovascular

mortality in the diabetic population, any drug that increases an already abnormal baseline QT interval may increase mortality rates. Considering that cardiovascular disease is the principal cause of death in the diabetes population with multifold increases compared to non-diabetic populations, this could potentially mean a large population impact (attributable risk). Presently there are many categories of drug therapies available to treat diabetes, and multiple drugs within each category, none of which have demonstrated QT interval prolongation. In light of this, for a high stakes risk that may have an increase in an already high attributable risk, it is only prudent to have very low risk tolerance, particularly when we know the question can be answered definitively in a timely fashion. If we grant your request for approval with post-approval evaluation, and there is a clinically significant increase in the QT interval, which may be an approvability issue, we will have placed a large number of patients in jeopardy for what arguably is only an advantage of a convenient dosing interval. I believe that would be irresponsible when there should only be a slight delay until the results of the requested tQT study will definitely prove the issue one way or the other. Pivotal in this decision is that I believe that if Bydureon were to express the QT interval prolongation noted in the extrapolations of GWCI, it would be an approvability issue, not just a labeling issue.

It is possible that the tQT study evaluating higher exenatide levels will not demonstrate an elevation of risk that would affect approvability. I believe once-a-week dosing would be something appreciated by both patients and physicians. It should never, however, be lost in this discussion that exenatide is presently available to those diabetic patients who would benefit from its use and at doses that we have assurance are safe. We know that dose does make a difference. One example is that of propoxyphene where an increase in dose from 600 mg a day to 900 mg a day resulted in clinically worrisome QT interval prolongations leading to market withdrawal. Another example, while not specific for QT interval prolongation but illustrating dose importance, is that of long-acting beta-agonists. Long-acting beta-agonists increase serious asthma-related outcomes in a dose-related fashion. This is illustrated by formoterol, where a mere doubling of the dose, while numerically improving forced expiratory volume in one second (FEV1), led to serious asthma-related outcomes in clinical trials. This increase in risk, despite improvements in FEV1 compared to lower doses, prohibited marketing of the higher dose.

As such, should dose-related concerns arise of the nature discussed above, I feel they should be carefully and thoroughly evaluated, and without a compelling reason for approval now, this should occur before marketing. Finally, you do bear responsibility that this issue has delayed approval, as you did not bring this concern to the attention of DMEP in a timely fashion, despite the fact that you had study GWCI in hand at the time of original application submission. Had DMEP been aware of this in 2008, the tQT study we are now demanding would have already been performed and the results available whether they be exculpatory or inculpatory.

## **Discussion of Issue 2**

The effectiveness of Bydureon was assessed in Study 105, a comparative efficacy and safety trial between Byetta 10 mcg twice daily and exenatide 2 mg once weekly. Therefore, the results of Study 105 serve to provide the data for appropriate labeling for Bydureon. During development, there were two different production scales for Bydureon, a (b) (4) batch used in a Phase 2 study (104) and a (b) (4) batch (henceforth referred to as 'investigational' Bydureon) used

for Study 105, both produced by Alkermes. The Bydureon product for marketing (henceforth referred to as 'commercial' Bydureon) was a (b) (4) batch produced by Amylin at a different site. As outlined above in the timeline, there were numerous discussions between Amylin and the review team regarding the data necessary to bridge the investigational and commercial Bydureon batches to demonstrate comparability. It is important (required) that the commercial and investigational Bydureon products are comparable, as a bridge must be established between the two that allows reliance upon the results of Study 105 for labeling purposes.

You contend that you have met the burden of comparability as outlined under the SUPAC-MR guidance document and that you have demonstrated comparability using three different analytical methods. You state that the physicochemical comparability study revealed acceptable criteria for the investigational and commercial product. You also claim that you validated an IV/IVc approach that, while not predictive for C<sub>max</sub>, demonstrated bioequivalence on the Area Under the Curve (AUC) parameter that you are using as supportive data. Finally, to support comparability, you evaluated a clinical endpoint as an extension to Study 105 (henceforth known as Study 105c). The primary statistical analysis used for Study 105c was a non-inferiority assessment of the change in HbA<sub>1c</sub>% in subjects at the end of Study 105 who were then re-randomized between the investigational- and commercial-scale Bydureon products. You claim that non-inferiority was achieved in this comparison with a non-inferiority margin of less than 0.4 HbA<sub>1c</sub>% as is recommended in our guidance.<sup>12</sup> The primary efficacy analysis for Study 105 was after a 30-week assessment period, whereas the primary endpoint for Study 105c was after an 18-week exposure period (approximately 60% of the evaluation time of Study 105).

You state that you have a validated model to meet the Agency's predictability requirements which demonstrates bioequivalence on the AUC parameter of Amylin/Alkermes ratio = 0.89. However, this is a prediction from a failed IV/IVc approach. However, you were informed at the May 1, 2007, EOP2 meeting that physico-chemical characterization and IV/IVc approach would be insufficient to support comparability and that a bioequivalence study would be necessary to bridge the investigational and commercial Bydureon products. I will therefore limit my discussion to the results of Study 105c.

For Study 105c, you claim that the AUC<sub>0-168h</sub> (pg.h/mL) ratios comparing commercial to investigational products was 0.85 with a 90% CI of 76-94%. We have not been able to reproduce these results and have determined that ratio to be 0.68 with a 90% CI 59-78%. Therefore, we cannot rely on this parameter as a measure of comparability and must determine if there were similar efficacy results for Study 105c in order to conclude that this decrease in exposure is not clinically important. At our face-to-face meeting of March 4, 2011, there did not seem to be much dispute from you regarding these facts, and most of the discussion focused upon the efficacy results of 105c.

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<sup>12</sup> Guidance for Industry, *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071624.pdf>.

Study 105 demonstrated that investigational Bydureon was non-inferior to Byetta, and perhaps even superior. For this study, you choose a non-inferiority (NI) margin of 0.4 HbA1c%. The Agency guidance for diabetes mellitus<sup>13</sup> states that we typically accept a non-inferiority (NI) margin of 0.3 or 0.4 HbA1c% provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials. While not stated explicitly in this guidance, DMEP expects the trial to occur in subjects with a wide range of HbA1c in need of additional therapy for their diabetes (why else would you add an additional agent?). DMEP's experience indicates that greater treatment differences between drugs with known differences, or between drug and placebo, occur in subjects with higher baseline HbA1c. This in part forms the basis for their recommendations for an NI margin. Smaller treatment differences between drugs with known differences, or between a drug and placebo, occur in subjects with lower baseline HbA1c. This is relevant to Study 105c, because if a true difference exists, then an NI trial may have reduced ability to demonstrate this difference if the baseline HbA1c values are too low, the duration of the trial too short, or both.

This effect was demonstrated in Study 105, as patients with baseline HbA1c  $\geq 9.0$  had significantly greater reductions in HbA1c in the Bydureon group than did the Byetta group ( $p < 0.001$ ), while patients with baseline HbA1c  $< 9.0$  had a fairly similar HbA1c response in the Bydureon group compared to the Byetta group ( $p = 0.191$ ). To put it another way, if the groups compared at randomization already have low HbA1c and are followed for less time, there is 'less play' to demonstrate inferiority. If there is attenuation of effect at lower baseline HbA1c levels, only enrolling subjects with lower baseline HbA1c and following them for a shorter period of time could attenuate a true difference, thus biasing a non-inferiority study toward a finding of no difference. Study 105c was really an evaluation of 'maintenance' of HbA1c control more so than a proper non-inferiority trial of treatment effect in a population that needed additional therapy. In my view, the NI margin stated in the guidance is not applicable as it is in reference to trials that are designed to evaluate incremental gains of effect, not incremental loss of effect. At the pre-NDA meeting of June 24, 2008, the agency recommended you conduct a dedicated clinical trial rather than an extension trial partially for these reasons. That is because, if you were to conduct an extension trial in a group of closely controlled diabetic subjects, an NI margin of 0.4 % may not be appropriate. My review of the meeting minutes demonstrate that DMEP expressed they would not agree to an NI margin of 0.4 % and that they would instead be evaluating the difference between treatment groups with adjusted means and the similarity of data would be a review issue.

In Study 105c, the baseline average HbA1c was 6.8 mg/dL, compared to 8.3 for Study 105 and of 18-weeks duration compared to 30 weeks for Study 105, approximately 60% of the evaluation time. The commercial product appeared to be inferior to the investigational product with a mean treatment difference of 0.2 mg/dL with 95% CI of 0.0 to 0.3 in the direction of inferiority despite being underpowered and of shorter duration. The 0.2 mg/dL difference was nearly statistically significant (despite being underpowered) at a p-value of 0.062 in the face of having only approximately 70% of the subjects included in study 105. Had Study 105c been conducted

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<sup>13</sup> Guidance for Industry, *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071624.pdf>.

longer, the slopes of the incremental loss of effect lines indicate that an even greater treatment difference would be expected. Therefore, there is concerning evidence of inferiority of the commercial Bydureon compared to the investigation Bydureon. It is clear to me that I cannot conclude that investigational and commercial Bydureon are comparable. Therefore, there is no bridge that would allow results from Study 105 to be placed in the label as it would misrepresent the efficacy results that could be expected from commercial Bydureon. I agree with DMEP that evidence of the efficacy of commercial drug product is necessary for accurate labeling. Fortunately, you have completed (but not submitted) Study 108, which compares commercial Bydureon to Byetta and should be able to provide us with this information.

Upon submission of Study GWCI, with further evaluation of the data, taking into account the new safety concerns, DMEP recognized that Study 105 could not be used for accurate labeling which led to their request for further evidence to support comparability. This demonstrates that reviews are not static and that the totality of the data must be considered when new information is presented.

You bear the responsibility for these delays with your failure to submit the data from Study GWCI. I find your explanation at the face-to-face meeting that you did not submit GWCI because you did not feel it raised any safety issue perplexing. We want all pertinent data upon which to make safety decisions. You were relying upon the cardiac safety of Byetta in your submission for Bydureon, so it should be obvious that the tQT study of Byetta is important information. Further, if, as you stated at the meeting, GWCI supported the cardiac safety of Byetta and by extension Bydureon, then it would be in your interest to present us with these data to support your safety assertions. If GWCI had been submitted in the first-cycle application, these issues would have been addressed in a more timely fashion that would have benefited you.

### **Summary**

While there are data to suggest that there may not be clinically important QT prolongation with Bydureon, there also is a tQT study with extrapolation data indicating that there may be clinically significant QT prolongation. The data indicating there may be QT prolongation, admittedly, should be viewed with caution. While a reasonable person may think that there is not clinically important QT prolongation with a yet-to-be approved drug, this is not the same as knowing that there is not clinically important QT prolongation. In that void of knowledge, comes the amount of risk that is tolerable, and that amount of risk is dependent upon many factors, some of which include the advantages of the drug, available therapies, the disease being treated, the population for intended use, and any unique risks in this population. I believe that in the case of a diabetic medication for use to reduce serum glucose, where there are multiple categories of drugs and multiple drugs within each category (including for this example lower doses of exenatide), that the tolerable risk due to lack of knowledge regarding a potential cardiac risk, a deficiency that can be easily remediated, should be exceeding low. I am aware that you are presently enrolling patients into a pilot tQT study with intention to conduct a definitive tQT study to address this safety issue. You also have complete trial results from Study 108 which may allow for accurate and appropriate labeling and also may be necessary for fully informed risk/benefit calculations in the event that the tQT study does show prolongation. These two pieces of information are necessary to allow adequate consideration, and perhaps resolution of

the issues, identified in the second CR letter and in my view are necessary before the drug product may be approved.

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. This appeal should be sent through the Center's Dispute Resolution Project Manager, Ms. Amy Bertha, with a copy to NDA 022200. Any questions concerning your appeal should be addressed to Ms. Bertha at (301) 796-1647. Questions regarding next steps with the review division as recommended in this response should be directed to Dr. Pooja Dharia, Regulatory Project Manager, 301-796-5332.

Sincerely,

*{See appended electronic signature page}*

Curtis J. Rosebraugh, M.D., M.P.H.  
Director  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CURTIS J ROSEBRAUGH  
03/30/2011



IND 067092  
NDA 022200

## ADVICE/INFORMATION REQUEST

Amylin Pharmaceuticals, Inc.  
Orville Kolterman, M.D.  
Sr. Vice President, Research & Development  
9360 Towne Centre Drive, Suite 110  
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for exenatide long acting release (LAR). In addition, please refer to your new drug application (NDA) dated and received May 4, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BYDUREON (exenatide for injectable suspension).

On October 18, 2010, NDA 022200 received a Complete Response letter citing the need to conduct a tQT study following treatment with exenatide at exposures comparable to those observed in renal impaired patients taking Bydureon as well as the submission of a completed Study LAR-108 titled, "A Randomized, Open-Label, Parallel-Group, Comparator-Controlled, Multicenter Study to Evaluate the Glycemic Effects, Safety, and Tolerability of Exenatide Once Weekly in Subjects with Type 2 Diabetes Mellitus. To satisfy these deficiencies, we reiterate that the results from your tQT study must be submitted in conjunction with StudyLAR-108 to be considered a complete response.

We also refer to the teleconference between representatives of your firm and the FDA on November 23, 2010. The purpose of the meeting was to discuss your thorough QT protocol design rationale which was submitted on October 29, 2010. We also refer to your amendment submitted on December 8, 2010 entitled "A Randomized, Three-period, Placebo- and Positive-controlled, Double-blind, Crossover Study to Assess the Electrophysiological Effects of Exenatide at Therapeutic and Supratherapeutic Concentrations on the 12-lead Electrocardiogram QT Interval in Healthy Subjects."

We have the following comments and recommendations:

1. The rationale for dose selection appears to be reasonable.
2. The selected ECG/PK sampling time points appear to be reasonable.
3. When using moxifloxacin as the positive control, in addition to demonstrating the baseline-corrected mean difference of moxifloxacin and placebo on QTc greater than 5 ms as

evidenced by the largest lower bound of the two-sided 90% CI for the  $\Delta\Delta QTc > 5$  ms, you also need to display that the time-course of  $\Delta\Delta QTc$  follows expected moxifloxacin concentration time course.

4. Categorical analyses should summarize the number of subjects as well as the number of observations with QTc intervals  $> 450$  ms,  $> 480$  ms, and  $> 500$  ms and change from baseline in QTc  $> 30$  ms and  $> 60$  ms.
5. The concentration-QT analysis plan appears to be reasonable. In most cases, a linear mixed effects modeling approach may be used to quantify the relationship between plasma concentrations (of the parent drug and/or metabolite(s)) and  $\Delta\Delta QTc$  (time-matched drug-placebo difference in QTc interval, baseline-adjusted). Based upon this relationship, the predicted population average  $\Delta\Delta QTc$  and its corresponding upper 95% 1-sided confidence interval bound may be computed at appropriate concentrations, e.g., the mean maximum plasma concentrations under therapeutic and suprathreshold doses or other concentrations of interest. In addition to the above analysis, there may be merit in considering alternate dependent variables such as QTc or  $\Delta QTc$  (baseline-adjusted) to derive the  $\Delta\Delta QTc$  endpoint.

We encourage the exploration of the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response relationship. Therefore, diagnostic evaluation is expected as part of the application of the method recommended here. Additional exploratory analyses (via graphical displays and/or model fitting) include accounting for a delayed effect and the justification for the choice of pharmacodynamic model (linear versus nonlinear).

6. We are also interested in the effects of extended-release exenatide on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.
7. When you submit your 'thorough QT study' report, please include the following items:
  - a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
  - b. Electronic copy of the study report
  - c. Electronic or hard copy of the clinical protocol
  - d. Electronic or hard copy of the Investigator's Brochure
  - e. Annotated CRF
  - f. A data definition file which describes the contents of the electronic data sets
  - g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
  - h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate HR, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a

specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)

- i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
  - j. Narrative summaries and case report forms for any
    - i. Deaths
    - ii. Serious adverse events
    - iii. Episodes of ventricular tachycardia or fibrillation
    - iv. Episodes of syncope
    - v. Episodes of seizure
    - vi. Adverse events resulting in the subject discontinuing from the study
  - k. ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))
  - l. A completed Highlights of Clinical Pharmacology Table
8. Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at [www.cardiac-safety.org/library](http://www.cardiac-safety.org/library).

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include: (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

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

Sincerely,  
*{See appended electronic signature page}*  
Mary H. 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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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY H PARKS  
01/11/2011

# REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Cardio-Renal Products**  
**Devi Kozelli**  
**OND/ODEI/DCRP**  
**devi.kozeli@fda.hhs.gov**  
**WO22 RM4183/ Phone: X6-1128**

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

DATE  
11/8/10

IND NO.  
67,092

NDA NO.  
22-200

TYPE OF DOCUMENT  
Original

DATE OF DOCUMENT  
October 29, 2010

NAME OF DRUG  
**Bydureon**

PRIORITY CONSIDERATION  
**Standard**

CLASSIFICATION OF DRUG  
**Anti-diabetic agent**

DESIRED COMPLETION DATE  
**ASAP**

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

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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

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

COMMENTS / SPECIAL INSTRUCTIONS: In preparation to our upcoming teleconference with Amylin regarding their QT prolongation deficiency, the sponsor has submitted a (1) study design rationale and (2) a protocol summary for their proposed study (BCB 112). The documents can be found in the edr (10/29/10) at the following locations.

Cover letter: <\\cdsesub5\EVSPROD\IND067092\0224\m1\us\cover.pdf>

Study Rationale: <\\cdsesub5\EVSPROD\IND067092\0224\m1\us\draft-protocol-sum-bcb112.pdf>

BCB112 Protocol Summary: <\\cdsesub5\EVSPROD\IND067092\0224\m1\us\protocol-sum-rationale.pdf>

PLEASE NOTE: THERE IS AN OPEN TSI FOR THIS ISSUE—**TSI# 906**

SIGNATURE OF REQUESTOR  
**Reference ID: 2861766**

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/s/  
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JOHN M BISHAI  
11/09/2010

## **Bishai, John**

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**From:** Bishai, John  
**Sent:** Tuesday, September 28, 2010 2:37 PM  
**To:** 'Ellis, Staci'  
**Subject:** NDA 22200 Bydureon-REMS comments

**Attachments:** NDA 022200 Bydureon REMS Review Comments.doc

Hello Staci,

We have reviewed your proposed REMS which was submitted as part of your Class 2 resubmission dated April 22, 2010. Below, please find our comments. For convenience, attached please a duplicate copy of our comments in MS Word.

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

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  
Tel: 301.796.1311  
Fax: 301.796.9712



NDA 022200  
Bydureon REMS Review

### **REMS COMMENTS**

#### **1. REMS Goals:**

Revise REMS goals as follows:

- To inform providers about the risk of acute pancreatitis (including necrotizing pancreatitis) and the potential risk of medullary thyroid carcinoma associated with Bydureon.
- To educate patients about the serious risks associated with Bydureon.

#### **2. Medication Guide**

A. Comments on the content of the Medication Guide will be provided separately.

#### **3. Communication Plan:**

Revise the Communication Plan as follows. All revisions should be made to the REMS and the REMS Supporting Document.

A. A definite time period, including initiation date and end date, is needed in the communication plan

for all communication activities. Currently you propose the DHCP letter to be sent out within 60 days of product launch, with no parameters for a launch date. We recommend sending the letter within a set timeframe, for example, within 60 days of approval of Bydureon or in conjunction with product launch, whichever is sooner.

- B. Broaden the intended audience of the communication plan to include all endocrinologists. Provide more detail about how the intended audience will be derived (which databases, numbers of healthcare professionals by specialty, etc...) for the healthcare professionals that are likely to prescribe Bydureon as well as all endocrinologists.
- C. Any new prescribers of Bydureon should also be targeted in the communication plan. Revise the dissemination strategy to identify and reach new prescribers regardless of use or specialty for 3 years after product launch. These details should be included in the REMS and the REMS Supporting Document.
- D. The follow-up Direct Mailer and Highlighted Information for Prescribers should be updated if labeling changes for the risks outlined in the REMS are approved. Include this information in the Supporting Document.
- E. DHCP Letter
  - a. See letter with suggested track changes in Appendix B (*see attachment*).
  - b. Submit the revised DHCP Letter.
- F. Direct Mail Letter
  - a. See letter with suggested track changes in Appendix C (*see attachment*).
  - b. Submit the revised Direct Mail Letter.
- G. Highlighted Information for Prescribers
  - a. Include information about the medullary thyroid cancer disease registry in the brochure, including contact information for further information about the registry.
  - b. Incorporate relevant revisions from the DHCP Letter into the Highlighted Information for Prescribers.
  - c. Submit the revised Highlighted Information for Prescribers.
- H. REMS specific link on Bydureon website
  - a. The goals listed on the website should reflect the goals in the approved REMS.

#### **4. Timetable for Assessment of the REMS:**

- A. Proposed Timetable: We recommend the following language, which is from the draft guidance, "*Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*":

Amylin Pharmaceuticals, Inc. will submit REMS Assessments to FDA at 1 year, 2 years, 3 years, and 7 years from the date of the initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Amylin Pharmaceuticals, Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

#### **REMS Supporting Document**

- 1. Revise the Supporting Document to be consistent with the REMS.

## **General Comments**

1. Submit the revised Proposed REMS with appended materials and the REMS Supporting Document. Provide a track changes and clean version of all revised materials and documents.
2. **Format Request:** Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.
3. We note that the surveys and methodologies for REMS assessment have not been submitted and your intent to submit them to FDA at least 90 days before you plan to conduct the evaluation. The submission should be coded "REMS Correspondence".
  - A. We remind you to submit final methodology and instruments that were used to evaluate the effectiveness of the REMS with your required assessments.

## **APPENDIX A: PROPOSED REMS**

### **NDA 22-220 BYDUREON (exenatide extended release for injectable suspension)**

Amylin Pharmaceuticals, Inc.

9360 Town Centre Drive, San Diego, CA 92121

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

#### **I. GOALS**

- To inform providers about the risk of acute pancreatitis (including necrotizing pancreatitis) and the potential risk of medullary thyroid carcinoma associated with Bydureon.
- To educate patients about the serious risks associated with Bydureon.

#### **II. REMS ELEMENTS**

##### **A. Medication Guide**

A Medication Guide will be enclosed with each BYDUREON prescription in accordance with 21 CFR 208.24. The Medication Guide is appended.

##### **B. Communication Plan**

In accordance with FDCA 505-1(e)(3), Amylin Pharmaceuticals will implement the following elements of a communication plan:

**1. A Dear HCP (DHCP) Letter** will be mailed within 60 days of product approval or at the time of product launch whichever is sooner. The letter will also be available via a link from the BYDUREON website and through the medical information department. The intended audience for this letter is HCPs who are likely to prescribe BYDUREON. Amylin has identified this audience as HCPs who have written at least one BYETTA prescription within the last 12 months, which includes physicians, nurse practitioners, and physicians' assistants predominantly in the specialties of endocrinology, internal medicine, and family practice. In addition, all endocrinology specialists and retail pharmacists will receive the letter.

Please see the appended Dear Healthcare Professional Letter.

**2. A Direct Mail Letter**

(b) (4)

Please see the appended Direct Mail Letter.

**3. The Highlighted Information for Prescribers** will be provided by Amylin/Lilly representatives during the first discussion of BYDUREON with all HCPs detailed during the first six months after launch. The Highlighted Information for Prescribers will also be

(b) (4)

Please see the appended Highlighted Information for Prescribers.

Any newly identified prescribers of Bydureon (through three years after product launch) will be informed on the contents of the communication plan.

All components of the communication plan will be updated to reflect any changes in labeling for the risks outlined above.

Amylin and Lilly will make the REMS, the DHCP letter, the Medication Guide, the Highlighted Information for Prescribers, and professional labeling available via a REMS-specific link from the BYDUREON website as well as through the medical information department. The Medication Guide, the Highlighted Information for Prescribers and professional labeling will also be available via hard copy from Amylin and Lilly representatives and through Amylin's call center.

Please see the appended BYDUREON REMS landing page screen shot.

**C. Elements to Assure Safe Use**

Elements to Assure Safe Use are not required.

**D. Implementation System**

An Implementation System is not required.

**E. Timetable for Submission of Assessments**

Amylin Pharmaceuticals, Inc. will submit REMS Assessments to FDA at 1 year, 2 years, 3 years, and 7 years from the date of the initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Amylin Pharmaceuticals, Inc. will submit each assessment

so that it will be received by the FDA on or before the due date.

## APPENDIX B: DEAR HEALTHCARE PROVIDER LETTER

Month, 2010

### IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Amylin Pharmaceuticals, Inc. and Eli Lilly and Company are writing to inform you of important safety information about BYDUREON™ (exenatide extended-release for injectable suspension), a once weekly GLP-1 receptor agonist for the treatment of type 2 diabetes. The U.S. Food and Drug Administration (FDA) has approved BYDUREON as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of BYDUREON outweigh the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis. (b) (4)

There is a Boxed Warning for BYDUREON:

#### **WARNING: RISK OF THYROID C-CELL TUMORS**

Exenatide extended-release caused an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether exenatide extended-release causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

#### **Potential Risk of Medullary Thyroid Carcinoma**

- Patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation.
- Routine monitoring of serum calcitonin (a biomarker of MTC) or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with BYDUREON. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin testing for MTC and a high background incidence of thyroid disease.

#### **Risk of Acute Pancreatitis**

- Based on postmarketing data exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis.
- After initiation of BYDUREON, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be

accompanied by vomiting).

- If pancreatitis is suspected, BYDUREON should promptly be discontinued, confirmatory tests should be performed, and appropriate management should be initiated.
- If pancreatitis is confirmed, BYDUREON should not be restarted.
- [REDACTED] (b) (4) in patients with a history of pancreatitis.

### **Appropriate Patient Selection for BYDUREON**

- BYDUREON is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- BYDUREON is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- BYDUREON has not been studied in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis while using BYDUREON. [REDACTED] (b) (4) in patients with a history of pancreatitis.
- BYDUREON should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- BYDUREON has not been studied in combination with insulin and concurrent use is not recommended.
- BYDUREON should not be used in patients with a history of severe hypersensitivity to exenatide or any product components.

### **Important Information Regarding a Medullary Thyroid Carcinoma Disease Registry**

[REDACTED] (b) (4)  
Amylin is establishing a medullary thyroid carcinoma (MTC) case series registry to systematically monitor the annual incidence of MTC in the United States. This study will be designed to identify if there is any increased risk of MTC related to the introduction of BYDUREON into the marketplace and will also characterize patient medical histories related to diabetes and use of BYDUREON.

If you have any questions about the MTC registry, please call 1-877-700-7365 or visit

[REDACTED] (b) (4)

### **Adverse Events**

[REDACTED] (b) (4)

[REDACTED]

Please contact our Medical Information department at 1-877-700-7365 if you have any questions about the information in this letter or the safe and effective use of BYDUREON.

Sincerely,

Lisa Porter, M.D.  
Vice President, Clinical Development  
Amylin Pharmaceuticals, Inc.

(b) (4)

A large rectangular grey box redacting the right side of the page, covering the name and contact information of the recipient.

Enclosure: BYDUREON® (exenatide extended-release for injectable suspension) Full Prescribing Information (version)

**This letter has been reviewed and approved by the FDA as part of the Bydureon REMS.**

**APPENDIX C: DIRECT MAIL LETTER**

(b) (4)



**This letter has been reviewed and approved by the FDA as part of the Bydureon REMS.**

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/s/

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JOHN M BISHAI  
09/28/2010

## 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  
**August 23, 2010**

IND NO.

NDA NO.  
**22-200**

TYPE OF DOCUMENT  
**PI Label Review**

DATE OF DOCUMENT  
**April 22, 2010**

NAME OF DRUG  
**Bydureon**

PRIORITY CONSIDERATION  
**Standard**

CLASSIFICATION OF DRUG  
**Anti-diabetic agent**

DESIRED COMPLETION DATE  
**August 25, 2010**

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

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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): |
| <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"/> BIOAVAILABILTY 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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COMMENTS / SPECIAL INSTRUCTIONS: Please review the PI which can be found in the DMEP eRoom.  
[http://erom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0\\_11e65](http://erom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_11e65)

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

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Application  
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Submission  
Type/Number

Submitter Name

Product Name

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NDA-22200

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ORIG-1

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AMYLIN  
PHARMACEUTICA  
LS INC

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Bydureon (exenatide LAR)

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/s/  
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JOHN M BISHAI  
08/24/2010



NDA 022200

**MEETING MINUTES**

Amylin Pharmaceuticals, Inc.  
Attention: Orville Kolterman, M.D.  
Sr. Vice President, Research & Development  
9360 Towne Centre Drive, Suite 110  
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your new drug application (NDA) dated and received May 4, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BYDUREON (exenatide for injectable suspension).

We also refer to the teleconference between representatives of your firm and the FDA on November 23, 2010. The purpose of the meeting was to discuss your thorough QT protocol design rationale which was submitted on October 29, 2010.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1131.

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

Enclosure



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type C

**Meeting Date and Time:** November 23, 2010 at 1:00 PM

**Application Number:** NDA 022200

**Product Name:** BYDUREON (exenatide for injectable suspension).

**Sponsor/Applicant Name:** Amylin Pharmaceuticals

**Meeting Chair:** Mary Parks, M.D.

**Meeting Recorder:** John Bishai, Ph.D.

**FDA ATTENDEES**

|                                  |  |
|----------------------------------|--|
| Mary Parks, M.D.                 | Division Director (DMEP)                     |
| Amy Egan, M.D., M.P.H.           | Deputy Director for Safety                   |
| Ilan Irony, M.D.                 | Diabetes Clinical Team Leader                |
| Lina AlJuburi, Pharm.D.          | Chief, Project Management Staff              |
| John Bishai, Ph.D.               | Regulatory Project Manager                   |
| Sally Choe, Ph. D.               | Team Leader, Office of Clinical Pharmacology |
| Jaya Vaidynathan, Ph.D.          | Reviewer, Office of Clinical Pharmacology    |
| Christine Garnett, Ph.D.         | Team Leader, Office of Clinical Pharmacology |
| Suchitra Balakrishnan, MD, Ph.D. | Clinical Reviewer, QT-IRT                    |
| Nitin Mehrotra, Ph.D.            | Clinical Pharmacology Reviewer, QT-IRT       |

**SPONSOR ATTENDEES**

Amylin

|                         |                               |
|-------------------------|-------------------------------|
| Orville Kolterman, M.D. | Sr. VP, Chief Medical Officer |
| Christian Weyer, M.D.   | Sr. VP, R&D                   |

|                    |  |
|--------------------|--|
| Lisa Porter, M.D.  | VP, R&D ExenatideOne   |
| Mark Fineman       | Sr. Director, R&D Strategic Relations                                    |
| Larry Shen         | Sr. Director, Corporate Analytics  |
| Brenda Cirincione  | Director, Medical Research   |
| Leigh MacConell    | Director, Medical Research   |
| Denis Roy          | Sr. Director, NDS  |
| Sean Zhao, M.D.    | VP, Global Safety  |
| Mark Longer, Ph.D. | Sr. Director, Regulatory CMC (Acting Regulatory Affairs Department Head) |
| Staci Ellis        | Director, Regulatory Affairs   |

Lilly

|                                |  |
|--------------------------------|--|
| Michael Cobas Meyer, M.D., MBA | Senior Director, Global Patient Safety - Diabetes and Autoimmune Therapeutic Areas |
| Malcolm Mitchell, M.D.,        | Sr. Director, Exploratory Medicine   |
| Prajakti Kothare, Ph.D.        | Research Advisor - PK/PD   |
| Theresa Wright, M.D.           | Sr. Director, Global Patient Safety  |
| Helle Linnebjerg, M.D.         | Research Advisor, Exploratory Medicine   |
| Kati Broderick, Pharm.D.       | Director, Global Regulatory Affairs  |

Consultant

(b) (4)

## 1.0 BACKGROUND

On October 18, 2010, a Complete Response Letter was issued to NDA 022200. One of the deficiencies cited was the need to conduct a tQT study following treatment with exenatide at exposures comparable to those observed in renal impaired patients taking Bydureon. To better understand the study details, Amylin requested, via electronic mail, a teleconference to discuss Amylin's proposed QT study which was submitted to the Agency on October 29, 2010. During the teleconference, the following points were agreed upon.

1. The protocol as proposed is acceptable. However, please see the discussion section for more specific comments.
2. The administration of exenatide in the form of an IV infusion is acceptable
3. Patient population as detailed in your protocol is acceptable
4. A specific heart rate correction method i.e. the primary endpoint does not have to be pre-specified as long as a selection method is pre-specified and implemented.
5. A PK/PD model may be implemented to explore issues relating to possible confounders.

## 2. DISCUSSION

### 2.1. QT Protocol

#### Discussion:

Before we conveyed comments regarding the proposed draft Thorough QT Study, we inquired about any experience obtained with the intravenous use of exenatide. You informed us that Amylin has used exenatide as an intravenous infusion in three earlier trials of exenatide, without any safety concern.

1. The supratherapeutic target of 500 pg/mL is expected to cover the steady state exposures possible with exenatide once weekly formulation in patients with moderate renal impairment. However, according to the proposed design, the PK samples would be collected over relatively constant target concentrations of 300 and 500 pg/mL. Thus, the average increase in concentration is only 1.7 fold which may not be adequate to characterize exposure-response relationship. We recommend you collect additional sampling points early in the infusion cycle (between the start of the infusion until the time the 300 pg/mL target exenatide concentration is reached or after stopping the infusion once 500 pg/mL target is reached) to obtain a wide range of exposures and corresponding ECGs.
2. You propose to collect multiple (N=11) PK and ECG sample points over 12 h once a target steady state concentration is reached and is stable at approximately 300 and 500 pg/mL. Eleven sampling time points over a period of 12 h at relatively constant concentrations may not be needed. Rather, as stated above, we recommend that you assess PK and ECG at lower exenatide concentrations for adequate characterization of the exposure-response relationship.
3. We have concerns about your plan to replace subjects who withdraw from the study. Subject replacement will violate the randomization principle. Efforts should be made to enroll and retain the subjects for the entire study period. If the reasons for withdrawal are related to the treatment, then replacing subjects could bias the results. In addition, having to adjust enrollment due to withdrawals during the trial may pose logistical problems and may affect

the integrity of the trial. You might need to consider enrolling more subjects based on the anticipated dropout rate if possible.

4. When using moxifloxacin as the positive control, we want to see that (1) the baseline corrected mean difference of moxifloxacin and placebo on QTc should be greater than 5 ms as evidenced by the largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTc} > 5$  ms and (2) QTc profile of moxifloxacin over time is adequately demonstrated (time-course of  $\Delta\Delta\text{QTc}$  follows expected moxifloxacin concentration- time course). To perform this task (1), you will benefit by examining only a few time points where the maximum moxifloxacin effect will occur. For instance, a few time points near  $T_{\text{max}}$  (between 1 hr to 4 hr after dose). We agree with your plan to adjust multiple endpoints for moxifloxacin.
5. Categorical analyses should summarize the number of subjects as well as the number of observations with QTc intervals  $> 450$  ms,  $> 480$  ms, and  $> 500$  ms and change from baseline in QTc  $> 30$  ms and  $> 60$  ms.
6. In most cases, a linear mixed effects modeling approach may be used to quantify the relationship between plasma concentrations (of the parent drug and/or metabolite(s)) and  $\Delta\Delta\text{QTc}$  (time-matched drug-placebo difference in QTc interval, baseline-adjusted). Based upon this relationship, the predicted population average  $\Delta\Delta\text{QTc}$  and its corresponding upper 95% 1-sided confidence interval bound may be computed at appropriate concentrations, e.g., the mean maximum plasma concentrations under therapeutic and suprathreshold doses or other concentrations of interest. In addition to the above analysis, there may be merit in considering alternate dependent variables such as QTc or  $\Delta\text{QTc}$  (baseline-adjusted) to derive the  $\Delta\Delta\text{QTc}$  endpoint.

We encourage the exploration of the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response relationship. Therefore, diagnostic evaluation is expected as part of the application of the method recommended here. Additional exploratory analyses (via graphical displays and/or model fitting) include accounting for a delayed effect and the justification for the choice of pharmacodynamic model (linear versus nonlinear).

7. We recommend that you incorporate the following elements into your assessment of the ECGs recorded during this study:
  - a. Pre-specify the lead for interval measurements
  - b. Baseline and on-treatment ECGs should be based on the same lead
8. We are also interested in the effects of exenatide on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.
9. When you submit your ‘thorough QT study’ report, please include the following items:
  - a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
  - b. Electronic copy of the study report
  - c. Electronic or hard copy of the clinical protocol
  - d. Electronic or hard copy of the Investigator’s Brochure

- e. Annotated CRF
  - f. A data definition file which describes the contents of the electronic data sets
  - g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
  - h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate HR, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
  - i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
  - j. Narrative summaries and case report forms for any
    - i. Deaths
    - ii. Serious adverse events
    - iii. Episodes of ventricular tachycardia or fibrillation
    - iv. Episodes of syncope
    - v. Episodes of seizure
    - vi. Adverse events resulting in the subject discontinuing from the study
  - k. ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))
  - l. A completed Highlights of Clinical Pharmacology Table
10. Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at [www.cardiac-safety.org/library](http://www.cardiac-safety.org/library).

## 2.2 Additional Comments

(b) (4), a consultant to Amylin, asked FDA whether ECG data accompanying trough levels from several controlled clinical trials addressed QT prolongation concerns, particularly in light of new analyses being conducted on the GWCI study. FDA said that it would not be able to comment on the re-analysis of GWCI in light of the information submitted to FDA via email by Dr. Kolterman and Ms Stacie Ellis (see attached emails) which conveys some uncertainty on what data from GWCI can actually be relied upon. FDA also informed Amylin that any new analyses of GWCI submitted as a response to the CR letter will likely require a clinical audit by the Division of Scientific Investigation.

*Post-meeting request: FDA is requesting that Amylin submit the information regarding GWCI programming errors and plans for re-analyses by (b) (4) be submitted officially to the INDs and NDAs of both Byetta and Bydureon.*

**Bishai, John**

---

**From:** Ellis, Staci [Staci.Ellis@amylin.com]  
**Sent:** Friday, October 29, 2010 3:49 PM  
**To:** Bishai, John  
**Cc:** Parks, Mary H  
**Subject:** IND 57,725 Byetta GWCI Info: For Tuesday's Tcon  
**Importance:** High  
**Attachments:** QT data correction correspondence\_10 29\_v2\_formatted.docx; emfalert.txt

Hello John,

We need to alert you to a programming error that we have discovered in the GWCI study report (tQT study for BYETTA). When this error is corrected, the slope of the concentration QTcF relationship is reduced and no longer achieves statistical significance. The details around both the nature of the error and the manner in which it was discovered are outlined below.

As we were preparing to run additional analyses on the relationship between exenatide concentrations and QT interval in support of the design of a proposed tQT study, we began by re-running the previous analyses. These analyses were originally run by a CRO (b) (4), so we needed to ensure we were using the same programming to conduct our additional analyses. On Tuesday of this week (October 26) we found that we could not replicate the results for derived variables based on a "double delta" (placebo- and baseline-adjusted) calculation. Realizing that we could not replicate the original results, we did a thorough review of the datasets and on Thursday (October 28) identified an error in the derived dataset named "decg.sas7bdat dataset"; specifically in the variable "Value\_DD" (value\_dd=value\_c – mean placebo change from baseline; reference IND 57,725; Serial 0386, 14 June 2010). As a result, the regression analysis of  $\Delta\Delta\text{QTc}$  and plasma exenatide concentration has been revised (see attachment). The attachment provides additional detail and displays both the original and corrected data plots.

We felt it was important to provide this to you prior to our teleconference next Tuesday so that we are all working with the same set of correct information. To that end, I would very much appreciate you forwarding this e-mail and the attached document to all agency participants in next Tuesday's meeting. In addition, I'm cc'ing Dr. Parks given the timing of this information in proximity to the scheduled meeting.

We look forward to speaking with you next Tuesday.

Regards,

Staci

<<...>>

**AMYLIN PHARMACEUTICALS, INC**  
**Exenatide Once Weekly**  
**NDA 022-200**

**Summary of Dataset Correction and Resulting Reanalyses**

**29 October 2010**

This document is the property of Amylin Pharmaceuticals, Inc and is confidential and proprietary.

In response to the Agency's Complete Response Letter dated 18 October 2010, the Sponsor initiated additional analyses to evaluate the QTc data from Study H8O-EW-GWCI (GWCI; thorough QT study with BYETTA). This activity was undertaken to gain further insight into the relationship between QTc and plasma exenatide concentrations to guide the design of the additional thorough QT study requested by the Agency. During the data assembly process for these additional analyses, a programming error was identified in the calculation of the derived variables associated with the time-matched, baseline-adjusted, drug-placebo difference in QTc ( $\Delta\Delta\text{QTcF}$ ,  $\Delta\Delta\text{QTcI}$ ,  $\Delta\Delta\text{QTcP}$ ). Double delta should be calculated by subtracting the mean placebo response of the specific patient at the time point relative to dosing from the corresponding exenatide value. Further investigation of this finding concluded that only these derived variables were affected, all source data and change from baseline QTc variables ( $\Delta\text{QTcF}$ ,  $\Delta\text{QTcI}$ ,  $\Delta\text{QTcP}$ ) are correct. However, the corrected slope for the concentration QTcF relationship is now 0.009 (-0.002, 0.021) and the relationship is no longer significant ( $p = 0.121$ ). The main conclusion in Section 7.2.1 of the GWCI clinical study report was not affected. That is, for both QTcF and QTcI (the heart rate correction method that best fits the data), the upper limit of the 90% two-sided confidence interval for the mean difference between exenatide and placebo was less than 10 msec at all time points ([Appendix A](#)). Therefore, Study GWCI remains a negative thorough QT study.

The regression analysis between  $\Delta\Delta\text{QTcF}$  and plasma exenatide concentration (described in the GWCI report [IND 57,725, Serial 0383, on 15 April 2010) was re-evaluated using the corrected data variables. Originally, the slope (95% CI) was 0.02 (0.01, 0.03), with  $p < 0.001$ . As mentioned above, the corrected slope (95% CI) is 0.009 (-0.002, 0.021) and the relationship is no longer found to be significant ( $p = 0.121$ ). With respect to the regression analysis of  $\Delta\Delta\text{QTcI}$ , described in the expert opinion written by Dr. (b) (4) (first sent via e-mail to Dr. Rosebraugh on 07 October 2010), the slope did not change; however, the confidence interval for the slope was slightly wider, in part due to the revision of the 90% CI to 95% CI. The p-value remained greater than 0.05. The corrected slope and 95% confidence interval are 0.003 (-0.008, 0.013) with a p-value of 0.628. The original and the revised figures for  $\Delta\Delta\text{QTcF}$  and  $\Delta\Delta\text{QTcI}$  are included in [Appendix B](#), Figures A, B, C and D.

Of note, both raw ECG data (ecg.xpt) and the derived ECG data (decg.xpt) from Study GWCI were submitted to the FDA on 14 June 2010. This programming error affected only derived data decg.xpt. The raw ECG data was not affected. We are in the process of amending the GWCI clinical study report to reflect these changes. The amended study report will be submitted to the Agency upon completion.

**Appendix A. Table GWCI 7.2. Statistical Comparison of Mean Changes from Predose in QTc Intervals Between 10 µg Exenatide and Placebo (Source: H8O-EW-GWCI Main Report)**

**Table GWCI.7.2. Statistical Comparison of Mean Changes from Predose in QTc Intervals Between 10 µg Exenatide and Placebo**

| Parameter<br>(msec)             | Time<br>(h) | Least Squares Mean Change from Predose |                   | Least Squares Mean<br>Difference (90% CI)<br>Exenatide - Placebo |
|---------------------------------|-------------|--|-------------------|--|
|                                 |             | 10 µg Exenatide<br>(N=62)              | Placebo<br>(N=62) |  |
| QTcF <sup>a</sup>               | 1           | 3.58                                   | -0.36             | 3.93 (1.74, 6.13)  |
|                                 | 2           | 5.32                                   | -0.49             | 5.81 (3.62, 8.00)  |
|                                 | 3           | 4.46                                   | 0.44              | 4.02 (1.82, 6.22)  |
|                                 | 4           | 2.65                                   | 0.95              | 1.70 (-0.49, 3.90)   |
|                                 | 5.5         | 0.55                                   | -0.70             | 1.25 (-0.94, 3.45)   |
|                                 | 10          | -3.18                                  | -4.45             | 1.27 (-0.92, 3.47)   |
| QTcI <sup>b</sup>               | 1           | 0.73                                   | -0.32             | 1.06 (-0.98, 3.09)   |
|                                 | 2           | 2.41                                   | -0.03             | 2.44 (0.40, 4.47)  |
|                                 | 3           | 1.42                                   | 0.99              | 0.43 (-1.61, 2.47)   |
|                                 | 4           | -0.23                                  | 1.21              | -1.44 (-3.48, 0.59)  |
|                                 | 5.5         | -3.34                                  | -2.72             | -0.62 (-2.65, 1.41)  |
|                                 | 10          | -4.26                                  | -4.85             | 0.59 (-1.44, 2.63)   |
| QTcP <sup>a</sup>               | 1           | 3.99                                   | -0.35             | 4.34 (2.12, 6.56)  |
|                                 | 2           | 5.80                                   | -0.54             | 6.34 (4.12, 8.56)  |
|                                 | 3           | 4.93                                   | 0.39              | 4.53 (2.31, 6.76)  |
|                                 | 4           | 3.09                                   | 0.94              | 2.15 (-0.07, 4.37)   |
|                                 | 5.5         | 1.23                                   | -0.17             | 1.40 (-0.82, 3.62)   |
|                                 | 10          | -2.87                                  | -4.23             | 1.37 (-0.85, 3.59)   |
| Model based<br>QTc <sup>c</sup> | 1           | 0.67                                   | -0.46             | 1.14 (-1.12, 3.39)   |
|                                 | 2           | 1.82                                   | -0.27             | 2.09 (-0.24, 4.43)   |
|                                 | 3           | 1.08                                   | 0.70              | 0.38 (-1.95, 2.71)   |
|                                 | 4           | -0.30                                  | 1.16              | -1.46 (-3.74, 0.82)  |
|                                 | 5.5         | -4.70                                  | -4.84             | 0.14 (-2.00, 2.29)   |
|                                 | 10          | -5.10                                  | -5.97             | 0.87 (-1.27, 3.01)   |

Abbreviations: CI = confidence interval; N = number of subjects studied; QTcF = Fridericia QT correction; QTcI = individual QT correction; QTcP = population QT correction.

<sup>a</sup> ANOVA model: Change in QTc = TIME + TREATMENT + TREATMENT\*TIME with random effects for SUBJECT, SUBJECT\*TIME + SUBJECT\*TREATMENT.

<sup>b</sup> ANOVA model: Change in QTc = SEQUENCE + TIME + TREATMENT + TREATMENT\*TIME with random effects for SUBJECT, SUBJECT\*TIME + SUBJECT\*TREATMENT.

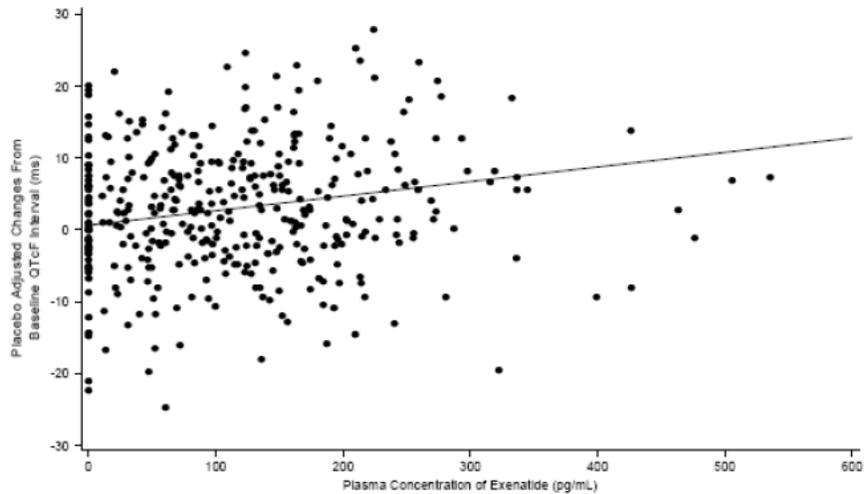
<sup>c</sup> ANCOVA model: Change in QT = Change in RR + TIME + TREATMENT + TREATMENT\*TIME with random effects for SUBJECT, SUBJECT\*TIME + SUBJECT\*TREATMENT.

Least squares means estimated at change in RR=0 at each timepoint for model based correction.



**Appendix B. Original (Figures A and C) and Revised Regression (Figures B and D) of  $\Delta\Delta$ QTcF and  $\Delta\Delta$ QTcI versus Plasma Exenatide Concentration**

A



Slope (95% CI) from linear mixed effects model = 0.02 (0.01, 0.03) [p-value <0.001]

— Regression line from linear mixed effects model

Predicted  $\Delta\Delta$ QTcF (90% PI) = 4.82 (3.12, 6.52) at observed geometric mean  $C_{max}$ : 208 pg/mL

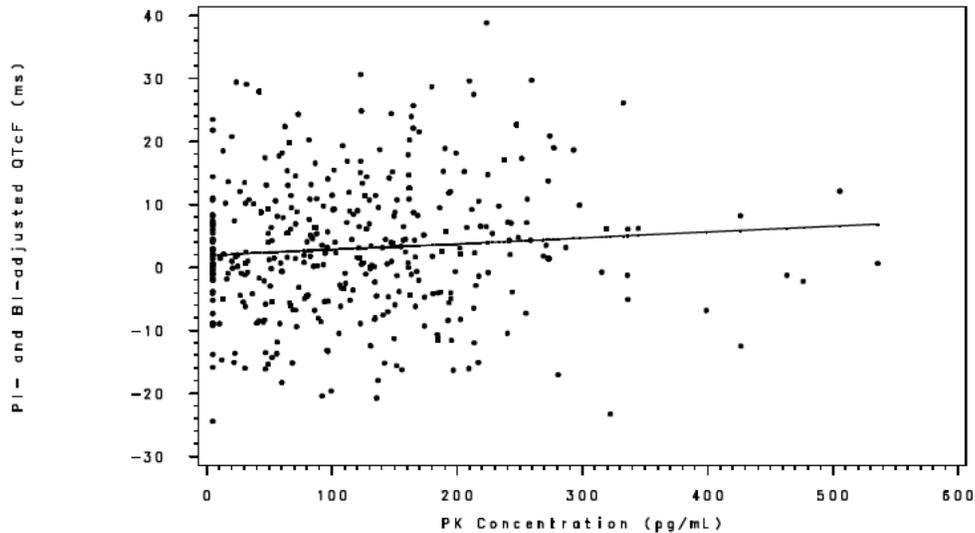
Predicted  $\Delta\Delta$ QTcF (90% PI) = 11.50 (8.86, 14.14) at observed maximum  $C_{max}$ : 536 pg/mL

**Figure GWCI.7.4. Scatterplot of changes from predose in QTcF interval versus plasma exenatide concentrations following a single 10 µg dose.**

Source: Study H8O-EW-GWCI Clinical Study Report, submitted to IND 57,725, Serial 0383, Section 7.3.

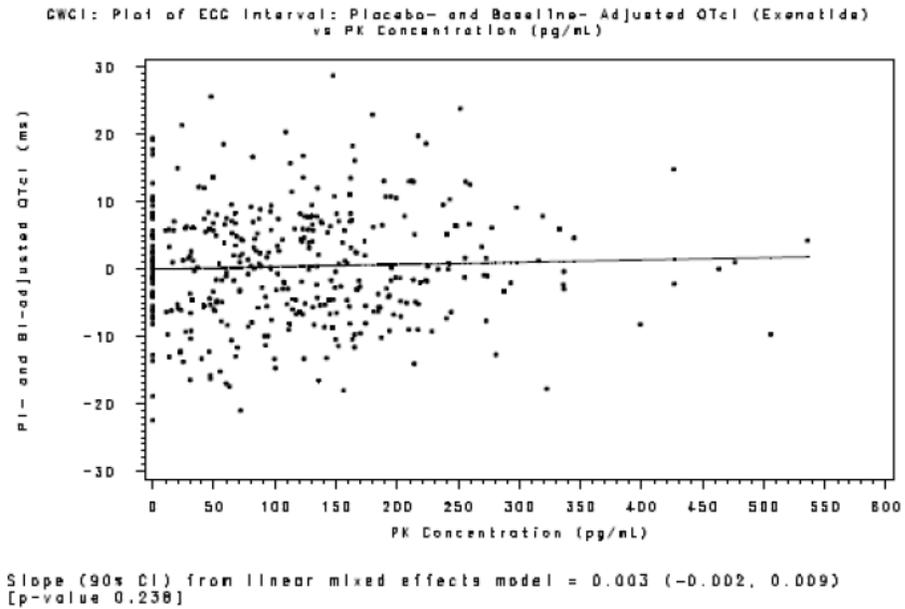
B

GWCI: Plot of ECG Interval: Placebo- and Baseline- Adjusted QTcF (Exenatide) vs PK Concentration (pg/mL)



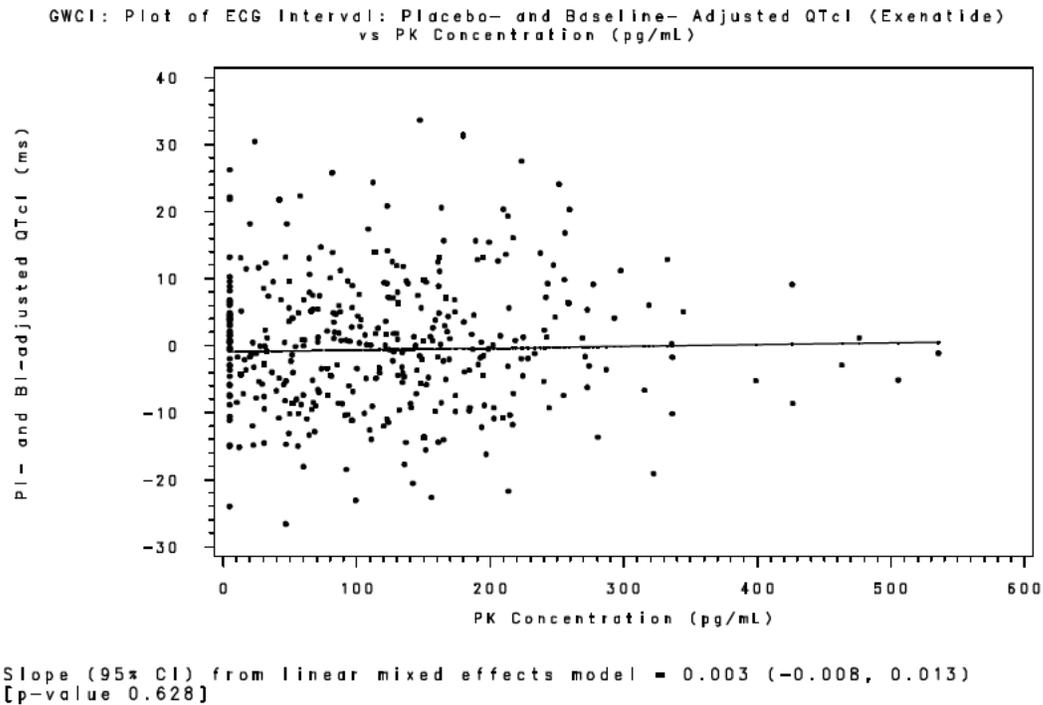
Slope (95% CI) from linear mixed effects model = 0.009 (-0.002, 0.021)  
[p-value 0.121]

C



Source: Expert Opinion – Evaluation of Methods for Heart Rate Correction in the Byetta Thorough QT/QTc study (Study H80-EW-GWCI) from Dr. (b) (4) (sent via e-mail to Dr. Rosebraugh on 07 October 2010).

D



## Bishai, John

---

**From:** Kolterman, Orville [Orville.Kolterman@amylin.com]  
**Sent:** Friday, November 05, 2010 10:39 AM  
**To:** Parks, Mary H  
**Subject:** Re: BYDUREON Follow Up

Your understanding is correct.

Thanks.

Orville

Sent from my iPhone...  
Typos occur frequently!

On Nov 5, 2010, at 3:14 AM, "Parks, Mary H" <Mary.Parks@fda.hhs.gov> wrote:

> Dr. Kolterman,  
>  
> I have forwarded your email below to the IRT review staff.  
>  
> Just so that I am understanding your email correctly - the information you provided to us on 10/29/10 (please see attached email from Staci Ellis) is no longer valid for review by IRT staff? They are currently reviewing this in preparation for the rescheduled meeting. If the information from that email is no longer appropriate, I will ask that they halt their review and await updated information from Amylin.  
>  
> Thank you.  
> Mary  
>  
>  
>  
> \_\_\_\_\_  
> From: Kolterman, Orville [mailto:Orville.Kolterman@amylin.com]  
> Sent: Thursday, November 04, 2010 6:17 PM  
> To: Parks, Mary H  
> Cc: Bishai, John; Ellis, Staci  
> Subject: BYDUREON Follow Up  
> Importance: High  
>  
> Dear Dr. Parks,  
>  
> I'm writing to you and cc'ing John since we understand he is currently out of the office.  
>  
> As a follow-up to our e-mail from last Friday, we have continued our evaluation of Study GWCI. Review of derived datasets and associated statistical analyses used for modeling data from this study have revealed additional challenges, which notably impact extrapolation of concentration-QTc data; therefore, we recommend that the revised plots of concentration vs. ••QTcF and ••QTcI provided to you on Friday 29 October not be used.  
>  
> We find the analytical issues in GWCI to be quite disconcerting and are taking it very seriously. We apologize for the confusion this has created and are taking the following steps to address the issues:  
>  
> \* The derived datasets including those for ECG, PK, and glucose concentrations will be rebuilt, re-validated and analyzed, and submitted to the Agency with an amended CSR for GWCI, based on verified data.  
> \* We have engaged an independent 3rd party CRO ([REDACTED] (b) (4)) to begin with the raw data to derive the datasets and re-run all analyses related to ECGs for GWCI using the original Statistical Analysis Plan.  
> \* Amylin and Eli Lilly will also re-derive the datasets and re-run analyses related to

ECGs per the original Statistical Analysis Plan for GWCI to serve as a confirmation of the CRO's work.

> We will provide an update to the Agency next week as well as an estimated date for completion of the amended CSR.

>

> We believe the additional tQT study with exenatide will help confirm that the true effect of exenatide at higher concentrations is similar to that observed in DURATION-1. We are fully prepared to engage in a discussion with you and the IRT to align on a study design for BCB112 so we can move this study forward, and we are currently working with John to reschedule the teleconference with the IRT that was originally scheduled for Tuesday 02 November.

>

> Given that (a) the purpose and scope of BCB112 are not impacted by the issues with replicating analytical output from GWCI, (b) the study design of BCB112 is not based on results of GWCI, and (c) BCB112 will provide important data, we would like to confirm that we are still on track for a teleconference to discuss the study design before the Thanksgiving holiday break.

>

> Request for Agency Feedback

> For concentration-QT analyses of Study GWCI, a linear mixed effects model was implemented in SAS using QTcF as the dependent variable and exenatide concentrations as the independent variable, with a random effect term applied on the intercept. Additional retrospective/exploratory analyses suggest that application of the random effect terms on the slope or slope and intercept may cause minor numerical changes in the slope estimate with no major differences in overlay plots of observed vs. regressed lines.

>

> Can the IRT share with the Sponsor the model used for review of concentration-QT analyses of Study GWCI (either the specific modeling code or specifics on how fixed and random effects were constructed within the model)? This would help the Sponsor better understand the inferences drawn by the IRT from the model. We would welcome a brief conversation or a written response, whichever is more efficient for the Agency.

>

> Thank you for taking the time to engage with us on this issue via email. I understand that you will forward this to the IRT so they will remain informed in real time as well. Again, we apologize for any confusion this new information may bring to the table, but feel it should not affect the timing of the BCB112 study design discussion. We look forward to a robust discussion with your team and the IRT in the next couple of weeks.

>

> Regards,

>

> Orville

>

> Orville G. Kolterman, MD

> Sr. Vice-President, Chief Medical Officer

> Phone: 858-642-7153

> Cell: (b) (6)

> okolterman@amylin.com

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> <IND 57,725 Byetta GWCI Info: For Tuesday's Tcon.eml>

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/s/  
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JOHN M BISHAI  
12/01/2010

## MEMORANDUM OF INTERNAL MEETING MINUTES

**MEETING DATE:** July 27, 2010  
**TIME:** 1:00 to 2:00 PM  
**LOCATION:** 3266 WO Bldg. 22  
**APPLICATION:** NDA 022200  
**DRUG NAME:** Bydureon (exenatide extended-release for injectable suspension)  
**TYPE OF MEETING:** Midcycle Review

### ATTENDEES:

Curtis Rosebraugh  
Mary Parks  
Amy Egan  
Ilan Irony  
Valerie Pratt  
Karen Davis-Bruno  
Jaya Vaidyanathan  
Olen Stephens  
Linda Galgay

Robert Mello  
Lina Aljuburi  
John Bishai  
Margarita Tossa  
Lanh Green  
Diane Wysowski  
Kendra Worthy

### BACKGROUND:

On March 23, 2010, a Complete Response (CR) letter was issued to Amylin for NDA 022200 Bydureon, citing Microbiology and REMS deficiencies. On April 22, 2010, the Agency received Amylin's resubmission with an action goal date set for October 22, 2010. The current meeting on the agenda was the midcycle review, a 21<sup>st</sup> century milestone meeting.

### MEETING OBJECTIVES:

- Discuss pending/completed reviews
- Discuss the REMS components
- Discuss the PMRs
- Labeling

### DISCUSSION POINTS:

Microbiology completed their review and is recommending approval. Currently, all reviews are complete with the exception of clinical who is waiting for the completion of the QT prolongation review by the QT Interdisciplinary Review Team (QT IRT) (expected mid-August).

A comparison was made to the recently approved Victoza (liraglutide) and Byetta (exenatide-monotherapy), both products have a REMS and several PMRs. The REMS elements include a (1) Medication Guide and (2) a Communication plan. Concerning PMRs, Victoza has been associated with nonclinical thyroid tumor findings and its sponsor, Novo Nordisk is

required to do a medullary thyroid cancer (MTC) case-series registry targeted at discerning the risk of developing medullary thyroid cancer (MTC) associated with Victoza. In addition, both Byetta and Victoza have epidemiological PMRs focusing on the incidence rate of pancreatitis, pancreatic malignancy, and thyroid neoplasms in GLP-1 agonist exposed versus non-exposed patients. A discussion was held explaining the origin of the respective safety signals and the limitations of these PMR studies. Last, the group also discussed the importance of the nonclinical PMRs as a means to better understand the product's mechanism of action. In summary, the purpose of the meeting was to hold a discussion between the OND review team and OSE on usefulness or lack thereof of the recently completed PMR studies for Byetta and their applicability to this particular application as well as the applicability of the MTC case-series registry that is planned for Victoza and other approved GLP-1 analogues

#### **DECISIONS (AGREEMENTS) REACHED:**

1. A REMS consisting of a Medication Guide and a Communication Plan is still recommended.
2. All parties agreed on the importance of a well designed MTC case-series registry. DMEP would like to have a registry that identifies if a GLP-1 analogue was used at MTC case registration or as early as possible in the case identification process rather than at case interview, which would take longer. However, unless cases are interviewed in a systematic and comprehensive way, information on risk factors other than GLP-1 use would not be known. (b) (4)  
DEPI expects to send the evaluation of the revised MTC case-series protocol (from (b) (4)) to DMEP soon.
3. It was decided that an epidemiological study to better estimate the rates of pancreatitis, pancreatic malignancy, and thyroid tumors was not necessary. DEPI suggested that it might be more useful to monitor such events via a planned clinical trial (i.e. cardiovascular outcomes trial). AERS data will provide case reports, but not incidence rates, relative risks, or very good etiologic data given the high rates of pancreatitis expected in diabetes patients due to obesity and pre-existing subclinical gallstone disease. Cancer outcomes (in addition to MTC) would require a long-term follow-up study to determine increased risks associated with chronic GLP-1 use (not discussed at meeting).
4. Nonclinical PMRs focusing on the RET oncogene will be recommended.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22200

-----  
ORIG-1

-----  
AMYLIN  
PHARMACEUTICA  
LS INC

-----  
Bydureon (exenatide LAR)

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/s/  
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JOHN M BISHAI  
07/28/2010

## Bishai, John

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**From:** Bishai, John  
**Sent:** Thursday, June 24, 2010 1:49 PM  
**To:** 'Ellis, Staci'  
**Subject:** NDA 22-200 Amylin's Bydureon: Instructions for Use Comments

Hello Staci,

In addition to reviewing your May 20, 2010 Class 2 resubmission, we have reviewed your November 3, 2009 submission which provided the instruction for use (IFU) for Bydureon (NDA 22-200). After reviewing your submission we had the following comments to both, your IFU and your products' lid label.

### **Instructions for Use:**

#### 1) Mixing the Medicine and Filling the Syringe:

- a) In step 3a, provide a description of what the patient is doing by pressing the plunger. For example, add the statement "This pushes the diluent into the vial the statement should read:
  - (a) With your thumb, push down the plunger until it stops. This pushes the diluent into the vial. The plunger may feel like it is springing back a little.
  - (b) In step 3e, clarify this step by adding wording to indicate that the vial will be upside down in this step. For example add the statement "upside down" the statement should read:
    1. Now, hold the vial upside down so the syringe is pointing up and the plunger is pointing down towards the ground. With your thumb, push in the plunger until it stops, and keep holding it in place.
  - (c) In step 3i, revise the statement so that it is clear that the patient will remove the orange connector from the syringe. The statement should read:
    1. With one the other hand, twist the orange connector to remove it from the syringe. Be careful not to push in the plunger.

#### 2) Injecting the Medicine

- i) Include as statement or step between step 4d and 4e to instruct the patient to clean the injection site with an alcohol swab prior to injecting the medication.

#### 3) Common Questions and Answers

- i) At the end of questions 2, indicate the steps which relate to the questions, in a similar manner that was done at the end of questions 4 and 5. The statement should read:

(This question relates to steps 3a through 3d shown on pages 18 through 20).

### **Lid Label:**

Under the description of the kit contents, the description of the needles provided is vague. Include the needle gauge and length in the description of the needles supplied with the kit. We understand that the Applicant is trying to minimize the risk of patients using a different needle with this product. However, the needle gauge and length is typically included on kit labeling. The Applicant could include the measurements of the needle and a statement that informs healthcare practitioner and patients this product should not be used with other needles. For example, 2 needles ([gauge and length] Bydureon should only be used with these custom needles).

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

Regards,  
John

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22200

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ORIG-1

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AMYLIN  
PHARMACEUTICA  
LS INC

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Bydureon (exenatide LAR)

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/s/  
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JOHN M BISHAI  
06/24/2010

## REQUEST FOR CONSULTATION

TO (*Office/Division*): Division of Cardio-Renal Products  
Devi Kozelli  
OND/ODEI/DCRP  
devi.kozeli@fda.hhs.gov  
WO22 RM4183/ Phone: X6-1128

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

DATE  
6/23/10

IND NO.  
57,725

NDA NO.  
21-773; 21-  
919;22-200

TYPE OF DOCUMENT  
Original

DATE OF DOCUMENT  
November 20, 2009 May  
13, 2010,

NAME OF DRUG  
Byetta (exenatide); Bydureon

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-diabetic agent

DESIRED COMPLETION DATE  
ASAP

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 ( <i>SPECIFY BELOW</i> ): |
| <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 ( <i>SPECIFY BELOW</i> ): |
| <input type="checkbox"/> OTHER ( <i>SPECIFY BELOW</i> ): |  |

#### 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 ( <i>List below</i> )  | <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:** Based on the results of a thorough QT study showing some prolongation of the PR and QT intervals, and increases in heart rate, DMEP is interested in looking at post-marketing data regarding arrhythmia-related adverse events. Please perform a search of the AERS database for arrhythmia-related SMQs reported in association with the use of Byetta, including but not limited to Conduction Defects, Tachyarrhythmias, and Torsade de Pointes/QT Prolongation.

#### Background:

We had a call w/ HealthCanada yesterday to discuss their concern regarding QT prolongation w/ Byetta based on a TQT study they required of the company. The company conducted a single-dose, placebo and positive-controlled study which revealed prolongation of the QT interval, PR interval and increases in heart rate. This study was not conducted under a US IND, so the company never submitted the results to FDA. They did report such a study in their annual report as per regulations. Apparently other foreign regulatory agencies have not received this study

report either. As background, Byetta was approved in 2004 prior to FDA requirement for TQT of all NMEs. With Bydureon, the QT group was consulted and based on review of clinical trial data/experience, it was determined that this NDA would not need to conduct a TQT study. We provided the attached documents to Christine Garnet, who was part of the QT group and also consulted for us on Bydureon. Limitations of the study included the fact that it was a single dose study and suprathapeutic doses could not be achieved.

Direct link to edr: \\Cdsub1\evsprod\NDA021773\021773.enx  
\\Cdsub1\evsprod\NDA021919\021919.enx

Upon opening the edr, you will find a response to our information request, summary tables, and CRFs. Please use the links below to access the document.

Cover letter: <\\cdsub1\EVSPROD\IND057725\0384\m1\us\cover.pdf>

Response: <\\cdsub1\EVSPROD\IND057725\0384\m1\us\fda-response-qt-gwci.pdf>

Annotated CRFs: <\\cdsub1\EVSPROD\IND057725\0384\m5\datasets\gwci\tabulations\legacy\blankcrf.pdf>

In addition, below we have provided Health Canada's review of a QT study which will shortly be submitted to the Division,

|  |  |
|--|--|
| SIGNATURE OF REQUESTOR                 | METHOD OF DELIVERY (Check one)<br><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  |

33 pages have been withheld immediately following this page as b4 (CCI/TS)

| Application Type/Number | Submission Type/Number | Submitter Name                    | Product Name                      |
|-------------------------|------------------------|-----------------------------------|-----------------------------------|
| IND-21773               | ORIG-1                 | FALKO JAMES<br>MICHAEL MD         | TRITIATED GLUCOSE 3H-3<br>GLUCOSE |
| NDA-22200               | ORIG-1                 | AMYLIN<br>PHARMACEUTICA<br>LS INC | Bydureon (exenatide LAR)          |
| IND-57725               | ORIG-1                 | AMYLIN                            | BYETTA (EXENATIDE<br>INJECTION)   |

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/s/

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JOHN M BISHAI  
06/23/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022200

MEETING MINUTES

Amylin Pharmaceuticals, Inc.  
Attention: Orville Kolterman, M.D.  
Sr. Vice President, Research & Development  
9360 Towne Centre Drive, Suite 110  
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your Investigational New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BYDUREON (exenatide for injectable suspension).

We also refer to the telecon between representatives of your firm and the FDA on May 25, 2010. The purpose of the meeting was to discuss your cancer registry.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Enclosure:

MEETING MINUTES

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type C  
**Meeting Category:** NDA  
**Meeting Date and Time:** May 25, 2010 @ 1:00 pm  
**Application Number:** NDA 022200  
**Product Name:** BYDUREON (exenatide for injectable suspension)  
**Indication:** Treatment of Type II Diabetes  
**Sponsor/Applicant Name:** Amylin Pharmaceuticals, Inc.

### FDA ATTENDEES

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

Mary Parks, M.D. Director  
Amy Egan, M.D., M.P.H. Deputy Director for Safety  
John Bishai, Ph.D. Regulatory Project Manager

#### Office of Surveillance and Epidemiology (OSE)

Diane Wysowski, Ph.D. Epidemiologist/ Division of Epidemiology

### SPONSOR ATTENDEES

#### Amylin Attendees:

Orville Kolterman, MD, Sr. VP, Research and Development  
Lisa Porter, MD, Vice President, Research and Development, Exenatide One  
Made Wenten, PhD, Sr. Scientist, Health Outcomes  
Dana Lee, PharmD, Director, Pharmacovigilance  
Mark Longer, PhD, Acting Head of Regulatory Affairs  
Staci Ellis, Director, Regulatory Affairs

#### Eli Lilly Attendees:

Michael Cobas Meyer, MD, Sr. Director, Global Patient Safety, Diabetes and Autoimmune Therapeutic Areas  
Kwame Appenteng, MPH., PhD, Visiting Scientist, Global Pharmacoepidemiology Global Patient Safety  
Becky Noel, DrPH, MSPH, Global Patient Safety  
Kati Broderick, PharmD., Global Regulatory Lead, Exenatide One

Questions:

1. Does the Agency agree that a (b) (4) is the preferred approach for conducting this registry? If so, can the Agency provide guidance on how to facilitate a (b) (4)? How will Amylin and Lilly be able to provide input to the design of the protocol?

**Response:** The Agency agrees with (b) (4) for conducting the registry. We suggest that (b) (4) vendor with experience in conducting cancer registries. It is possible that design considerations from your proposed protocol could be incorporated into a finalized protocol for (b) (4). To that end, it would be important for you to submit a protocol for our review that highlights those design features you consider critical to the success of the study and your rationale. You should incorporate as much detail as possible, including:

- sample size and power calculations;
- the expected participation rate of state registries, including sensitivity analyses showing various participation rates;
- the expected range of patient participation rates and the resulting sample sizes;
- sensitivity analyses showing various assumptions for participation rates, relative risks, and latency periods for the development of MTC;
- the availability of identified data from state registries (i.e., the number of registries from which patient level data can be gathered);
- average lag time between diagnosis of MTC and reporting to the cancer registry;
- back-up plan in areas where a population-based registry is unable or unwilling to participate (e.g., comprehensive cancer center registries may be invited to participate);
- proposed methods for increasing participation of patient interviews;
- financial incentives to registries, patients and/or HCPs for participation;
- number of telephone call back attempts to a patient that will be made before the patient is counted as a non-respondent;
- obtaining proxy information from HCPs and names of relatives if the patient is deceased or unavailable for interview;
- the availability of tumor information (histology, grade, outcome, treatment modality) from the state registries;
- obtaining medical record validation of all cases with DM diagnoses and especially those with GLP-1 agonist exposure and a sample of those without DM diagnoses or GLP-1 exposure;
- provision for the establishment of a registry data monitoring committee;
- description of the data monitoring committee;
- possibility of conducting a nested case-control study within the cohort should a signal be detected during the course of the registry;

- description of the controls that would be used in a case-control study should the need arise for one;
- source of incidence rates to be used for comparison;
- method to ensure that the characteristics of patient participants is not different from non-participants;
- timelines for submission of interim data;
- name of the proposed contractor and staff credentials;
- anticipated exposure to BYDUREON (sales);
- methods for handling patients diagnosed with MTC at death;
- conducting a National Death Index search for patients diagnosed with MTC who died to obtain cause of death information as needed (Note that certain personal identifiers are required to conduct NDI searches);
- characterization of drug exposure status (e.g., ever BYDUREON use, use in the past five years, current use, dose, duration of use, use and duration of other GLP-1 agonists, etc.);
- collection of covariate information (alcohol use, smoking history, BMI, occupational exposures, nuclear/radiation exposures, etc.);
- publication of results.

Any MTC cases with exposure to GLP-1 agonists derived from other sources including case reports in the medical literature or voluntary reporting should be noted as not ascertained through the registry.

2. What does the Agency see as the next steps toward actuating [REDACTED] (b) (4)?

**Response:** We recommend that you work with [REDACTED] (b) (4)

3. Does the study synopsis provided above fulfill the Agency's expectations for this case series registry? Are there components the Agency feels are critical or important that are missing from this synopsis?

**Response:** Please see response to Question 1 above.

4. Amylin and Lilly propose to report [REDACTED] (b) (4). Does the Agency concur with this proposal?

**Response:** Data should also include:

- The number of patients enrolled in the study compared to the number of MTC cases reported in the NAACR database.
- The lag time between the date of cancer diagnoses and inclusion of data into the databases and the timeliness of subject interviews after diagnosis.

- **Demographic characteristics of all identified cases of MTC, such as tumor histology, topography, morphology, and method of diagnosis.**
  - **A comparison of those cases included in the case-series registry to those who are not included (within the originating registry and the overall NAACCR database).**
  - **Descriptive statistics including potential risk factors including drug exposures, radiation exposure, lifestyle factors, environmental exposures and other characteristics (FH of MEN syndromes or FMTC history).**
  - **For patients with DM, a characterization of GLP-1 receptor agonist exposure by drug, dose and duration prior to the diagnosis of MTC.**
  - **An evaluation of the effectiveness of the surveillance program in meeting the objective of successfully obtaining data for a substantial proportion of the incident cases of MTC in adults in the US, including proposals for correction should the registry be accruing insufficient numbers of cases.**
5. What additional steps, if any, are required to fulfill this postmarketing requirement?

**Response: It is not necessary for us to reach agreement on a final protocol before an action is taken on your NDA. Prior to an action, you will be asked to provide timelines for the final protocol submission, the study completion date, and the final study report submission. Please allow sufficient time for your final protocol submission so that your protocol can be reviewed and commented on and modified (if necessary). Your protocol must be acceptable to the division and to OSE before it is considered final.**

**General Comments to the Sponsor:**

- If any sampling of MTC cases is to be carried out, it should be based on accepted statistical methods and practices. However, because the exposure and outcome are rare, even missing one case of MTC with GLP-1 agonist exposure may be a problem in determining the incidence of MTC associated with GLP-1 agonist exposure.
- All patients who stated that they had DM and especially those answering that they took a GLP-1 agonist should be in the subset having medical record validation. In addition, a scientific sample of patients who stated that they did not have DM and did not take a GLP-1 agonist should have medical record validation.
- Because MTC cases with GLP-1 agonist exposure may be ascertained through passive reporting (voluntarily submitted reports) or case reports published in the medical literature, we suggest that the ascertainment methods for each MTC case found associated with a GLP-1 agonist be clearly stated.

| Application Type/Number | Submission Type/Number | Submitter Name                    | Product Name             |
|-------------------------|------------------------|-----------------------------------|--------------------------|
| NDA-22200               | GI-1                   | AMYLIN<br>PHARMACEUTICA<br>LS INC | Bydureon (exenatide LAR) |

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/s/

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MARY H PARKS  
06/10/2010

## REQUEST FOR CONSULTATION

TO (Division/Office):

**Mail: OSE**

Margarita Tossa

Margarita.Tossa@fda.hhs.gov

Office of Safety and Epidemiology

WO22 RM3461 phone:6-4053

FROM:

John Bishai Ph.D.

Regulatory Project Manager

DMEP, HFD-510, phone #: 6-1311

|   |                   |                        |  |  |
|---|-------------------|------------------------|--|--|
| DATE<br>5/24/10   | IND NO.<br>67,092 | NDA NO.<br>022200      | TYPE OF DOCUMENT<br>Original             | DATE OF DOCUMENT                         |
| NAME OF DRUG<br><b>BYDUREON (exenatide for injectable suspension)</b> |                   | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG<br>GLP-1 analogue | DESIRED COMPLETION DATE<br>July 19, 2010 |

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

#### II. BIOMETRICS

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

#### IV. DRUG EXPERIENCE

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

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We request a feasibility study to determine whether case series registry approach is going to be able to help us assess the thyroid cancer risk. Specifically, the feasibility study will help determine whether long-acting GLP-1's are associated with an increase in the incidence of MTC.

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

| Application Type/Number | Submission Type/Number | Submitter Name                   | Product Name                       |
|-------------------------|------------------------|----------------------------------|------------------------------------|
| NDA-22200               | ORIG-1                 | AMYLIN<br>PHARMACEUTICALS<br>INC | Bydureon (exenatide LAR)           |
| SAFETY-894              | ORIG-1                 | FOOD AND DRUG<br>ADMINISTRATION  | GLUCAGON-LIKE-PEPTIDE I<br>(GLP-1) |

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/s/

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JOHN M BISHAI  
05/24/2010



NDA 022200

**ACKNOWLEDGE CLASS 2 RESPONSE**

Amylin Pharmaceuticals, Inc.  
Attention: Orville Kolterman, M.D.  
Sr. Vice President, Research & Development  
9360 Towne Centre Drive, Suite 110  
San Diego, CA 92121

Dear Dr. Kolterman:

We acknowledge receipt of your April 22, 2010 resubmission to your new drug application for BYDUREON (exenatide for injectable suspension).

We consider this a complete, class 2 response to our March 12, 2010 action letter. Therefore, the user fee goal date is **October 22, 2010**.

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22200

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ORIG-1

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AMYLIN  
PHARMACEUTICA  
LS INC

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Bydureon (exenatide LAR)

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/s/  
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JOHN M BISHAI  
05/05/2010



NDA 022200

**REMS NOTIFICATION LETTER**

Amylin Pharmaceuticals, Inc.  
Attention: Orville Kolterman, M.D.  
Sr. Vice President, Research & Development  
9360 Towne Centre Drive, Suite 110  
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your New Drug Application (NDA) submitted May 4, 2009, under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BYDUREON (exenatide for injectable suspension).

We also refer to your November 3, 2009, submission which contained your proposed Medication Guide.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for BYDUREON (exenatide for injectable suspension) to ensure that the benefits of the drug outweigh the risks of medullary thyroid carcinoma and acute pancreatitis, including necrotizing and hemorrhagic pancreatitis.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that BYDUREON (exenatide for injectable suspension) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of BYDUREON (exenatide for injectable suspension). FDA has determined that BYDUREON (exenatide for injectable suspension) is a product that has serious risks (relative to benefits) of which patients should be made aware because information

concerning the risks could affect patients' decisions to use, or continue to use (exenatide for injectable suspension). Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed BYDUREON (exenatide for injectable suspension).

**Communication Plan:** We have determined that a communication plan targeted to healthcare providers who are likely to prescribe BYDUREON (exenatide for injectable suspension) for three years from the date of product launch will support implementation of the elements of your REMS. The communication plan must provide for the dissemination of information about labeling, with emphasis on important product WARNINGS AND PRECAUTIONS including the potential risk of medullary thyroid tumors and the risk of pancreatitis, including necrotizing and hemorrhagic pancreatitis, and also appropriate patient selection.

The communication plan must include, at minimum, the following:

1. Dear Healthcare Provider Letters (DHCP) that contain the FDA-approved labeling and address the potential risk of medullary thyroid tumors, the risk of pancreatitis, appropriate patient selection, and provide detailed information on your medullary thyroid cancer registry. Your Dear Healthcare Provider Letter should be mailed within 60 days of product launch. If the details of your medullary thyroid cancer registry are not known at that time, then a separate Dear Healthcare Provider letter will need to be issued once the registry becomes operational.
2. A Direct Mail Letter containing the information included in the Dear Healthcare Provider Letter, but sent annually for the next three years to all prescribers who are likely to prescribe BYDUREON (exenatide for injectable suspension).
3. Highlighted Information for Prescribers to be distributed by Amylin representatives during the first discussion of the product with all healthcare providers visited during the first six months after product launch. This information will also need to be sent with the Direct Mail Letter.
4. A description of the intended audience for the communication plan, stating specifically the types and specialties of healthcare providers to which the letters will be directed. This should be inclusive of prescribers who are likely to prescribe BYDUREON (exenatide for injectable suspension).
5. All the above components of the communication plan as well as the professional labeling must be available via a REMS specific link on the BYDUREON (exenatide for injectable suspension) website. The Medication Guide, the Highlighted Information for Prescribers, and the professional labeling must also be available via hardcopy from Amylin sales specialists, through Amylin's medical information department, and by calling the Amylin customer service line.

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than at 1 year, 2 years, and 3 years, and in the 7<sup>th</sup> year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for (exenatide for injectable suspension). Additionally, all relevant proposed REMS materials including communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include, but is not limited to, the following:

- A. Evaluation of patients’ understanding of the serious risks of BYDUREON (exenatide for injectable suspension)
- B. Evaluation of healthcare providers’ understanding of the serious risks of BYDUREON (exenatide for injectable suspension).
- C. An assessment of healthcare providers’ awareness of:
  - a. appropriate patient population characteristics,
  - b. the potential risk for medullary thyroid carcinoma, and
  - c. the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis
- D. Evaluation of healthcare providers’ identification and treatment of:
  - a. medullary thyroid carcinoma after initiation of BYDUREON (exenatide for injectable suspension)
  - b. acute pancreatitis after initiation of BYDUREON (exenatide for injectable suspension)
- E. Evaluation of the extent to which the elements of the REMS are meeting the goals of the REMS and whether modifications to the elements or goals are needed

- F. An assessment of the number of BYDUREON (exenatide for injectable suspension) prescribers identified to receive the DHCP letter and the number of DHCP letters mailed
- G. An assessment of the percentage of targeted prescribers who are presented with the Highlighted Information for Prescribers via sales specialists or medical information department

Before we can continue our evaluation of this NDA, you will need to submit the proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend that you use one of the following two statements depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

Prominently identify the proposed REMS submission and subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022200  
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022200  
PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of medullary thyroid carcinoma.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

As described in our phone call dated February 16, 2010, we have determined that, if this application is approved, you will be required to conduct a postmarketing study of BYDUREON (exenatide for injectable suspension) to assess the signal of a serious risk of medullary thyroid carcinoma. Specifically, we have determined that, if NDA 22-200 is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to conduct the following:

1. A medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of (exenatide for injectable suspension) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of BYDUREON (exenatide for injectable suspension).

We will continue discussion of your proposed postmarketing study, as needed.

Any additional specific details of this required postmarketing study and any other required or agreed upon postmarketing studies or clinical trials, including schedule milestones and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

**IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT JOHN BISHAI, PH.D.,  
REGULATORY PROJECT MANAGER, AT (301) 796-1311.**

Sincerely,

*{See appended electronic signature page}*

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

## **APPENDIX A: REMS TEMPLATE**

*If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.*

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name

Address

Contact Information

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

#### **I. GOAL(S):**

List the goals and objectives of the REMS.

#### **II. REMS ELEMENTS:**

##### **A. Medication Guide or PPI**

*If a Medication Guide is included in the proposed REMS, include the following:*

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

##### **B. Communication Plan**

*If a Communication Plan is included in the proposed REMS, include the following:*

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

##### **C. Elements To Assure Safe Use**

*If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:*

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

#### **D. Implementation System**

*If an Implementation System is included in the proposed REMS, include the following:*

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

#### **E. Timetable for Submission of Assessments**

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than at 1 year, at 2 years, at 3 years, and in the 7<sup>th</sup> year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, at 1 year, at 2 years, at 3 years and in the 7th year from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

## **APPENDIX B: SUPPORTING DOCUMENT**

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
  - a. Additional Potential Elements
    - i. Medication Guide
    - ii. Patient Package Insert
    - iii. Communication Plan
  - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
  - c. Implementation System
  - d. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22200

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ORIG-1

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AMYLIN  
PHARMACEUTICA  
LS INC

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EXENATIDE LAR

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/s/  
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MARY H PARKS  
02/16/2010



NDA 022200

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Amylin Pharmaceuticals, Inc.  
9360 Towne Centre Drive  
San Diego, CA 92121-3030

Attention: Orville Kolterman, M.D.  
Senior Vice President Liaison, Research & Development

Dear Dr. Kolterman:

Please refer to your New Drug Application (NDA) dated May 4, 2009, received May 5, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exenatide for Injectable Suspension, 2 mg.

We also refer to your November 5, 2009, correspondence, received November 5, 2009, requesting review of your proposed proprietary name, Bydureon. We have completed our review of the proposed proprietary name, Bydureon and have concluded that it is acceptable.

The proposed proprietary name, Bydureon, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 5, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager John Bishai at (301) 796-1311.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22200

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ORIG-1

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AMYLIN  
PHARMACEUTICA  
LS INC

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/s/  
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CAROL A HOLQUIST  
02/03/2010



NDA 22-200

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 May 4, 2009, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bydureon (exenatide once weekly) injection.

To facilitate our review of the cardiovascular risk of exenatide, we request that you submit the following data regarding major adverse cardiovascular events (MACE).

Submit the requested no later than October 5, 2009, to ensure that there is sufficient time for review.

Please provide information and analyses regarding MACE events as follows:

I. Analysis population(s):

A. The main analysis population should include the 12 long-term, randomized, controlled clinical trials of Byetta that were originally included in the NDA submission.

B. You should also tabulate the occurrence of these MACE endpoints from the 5 long-term, uncontrolled trials of Byetta that were originally included in the NDA submission (i.e. 2993-112E, -113E, -115E, -117, and -119).

C. You should also assess the incidence of cardiovascular event terms in exenatide LAR studies 2993LAR-105 and -104.

II. Endpoints: Use the following two endpoints, which will be referred to hereafter as "standardized MedDRA query (SMQ) MACE" and "Custom MACE". We acknowledge that there may be many opinions about what precise terms should be included in these endpoints, but these are the terms we want you to use. For nonfatal events, use MedDRA Preferred Terms as they were originally assigned in your NDA submission. Do not use post hoc adjudication for nonfatal events. Adjudication of cardiovascular deaths is acceptable. Do not add or subtract Preferred Terms from either endpoint.

“SMQ MACE”: Use a composite endpoint of cardiovascular death, and all Preferred Terms in the Standardised MedDRA Queries for “Myocardial Infarction” and “Central Nervous System Haemorrhages and Cerebrovascular Accidents”.

“Custom MACE”: Use a composite endpoint of cardiovascular death and the following MedDRA Preferred Terms:

- Acute myocardial infarction
- Basilar artery thrombosis
- Brain stem infarction
- Brain stem stroke
- Brain stem thrombosis
- Carotid arterial embolus
- Carotid artery thrombosis
- Cerebellar infarction
- Cerebral artery embolism
- Cerebral artery thrombosis
- Cerebral infarction
- Cerebral thrombosis
- Cerebrovascular accident
- Coronary artery thrombosis
- Embolic cerebral infarction
- Embolic stroke
- Hemorrhagic cerebral infarction
- Hemorrhagic stroke
- Hemorrhagic transformation stroke
- Ischemic cerebral infarction
- Ischemic stroke
- Lacunar infarction
- Lateral medullary syndrome
- Moyamoya disease
- Myocardial infarction
- Papillary muscle infarction
- Postprocedural myocardial infarction
- Postprocedural stroke
- Silent myocardial infarction
- Stroke in evolution
- Thalamic infarction
- Thrombotic cerebral infarction
- Thrombotic stroke
- Wallenberg syndrome

III. Analyses: For the statistical analysis of SMQ MACE and custom MACE, apply the same statistical methods that you used in the NDA submission (as described in Part 4 of the Statistical

Analysis Plan for Exenatide Cardiovascular Risk Meta Analysis) using the analysis populations described under section I. of this document.

In addition, please provide by-study summaries of the outcomes used in the analysis of cardiovascular risk.

If you have any questions, call John Bishai, Ph.D., Regulatory Project Manager, at 301-796-1280.

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22200

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ORIG-1

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AMYLIN  
PHARMACEUTICA  
LS INC

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EXENATIDE LAR

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/s/  
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MARY H PARKS  
10/17/2009

## REQUEST FOR CONSULTATION

TO (Office/Division): Division of Cardio-Renal Products  
Devi Kozelli  
OND/ODEI/DCRP  
devi.kozeli@fda.hhs.gov  
WO22 RM4183/ Phone: X6-1128

FROM (Name, Office/Division, and Phone Number of Requestor): Division of  
Metabolism and Endocrinology Products  
John Bishai, Project Manager (6-1311)

DATE  
August 28, 2009

IND NO.  
67,092

NDA NO.  
22,200

TYPE OF DOCUMENT  
NDA submission

DATE OF DOCUMENT  
May 4, 2009

NAME OF DRUG  
Bydureon (exenatide once  
weekly)

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-Diabetic

DESIRED COMPLETION DATE  
September 30, 2009

NAME OF FIRM: Amylin

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input checked="" 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:

We request a review of Amylin's proposed cardiovascular risk meta-analysis for Bydureon. The relevant documents in questions are in the edr:

#### Study Report Body:

\\CDSESUB1\EVSPROD\NDA022200\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes\5353-rep-analys-data-more-one-stud\cv-analysis\cv-analysis.pdf

#### Analysis Data set:

\\CDSESUB1\EVSPROD\NDA022200\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes\5353-rep-analys-data-more-one-stud\cv-analysis\cv-analysis.pdf

Analysis Data Definition:

\\CDSESUB1\EVSPROD\NDA022200\0001\m5\datasets\cv-analysis\analysis\define.pdf

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

| Linked Applications | Submission Type/Number | Sponsor Name                               | Drug Name / Subject    |
|---------------------|------------------------|--|------------------------|
| -----<br>NDA 22200  | -----<br>ORIG 1        | -----<br>AMYLIN<br>PHARMACEUTICA<br>LS INC | -----<br>EXENATIDE LAR |

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/s/  
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JOHN M BISHAI  
08/28/2009



**NDA 22-200**

**FILING COMMUNICATION**

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) dated May 4, 2009, received May 5, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for BYDUREON (exenatide for injectable suspension), 2 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 5, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 22, 2009.

During our filing review of your application, we identified the following potential review issues:

1. Bacterial endotoxin and sterility test methods were cited as USP<85> and USP<71>, respectively. Actual test methods and their associated validation reports were not provided. Please provide copies of the current test procedures for bacterial endotoxin testing and sterility testing of the drug product and the drug product diluent used at release and during stability. Also, please submit copies of the bacterial endotoxin test and sterility test assay validation reports (REST080763 and REST080762, respectively).

2. At the End-of-Phase-2 meeting, you only discussed the stability plan to establish Lonza and Mallinckrodt “as drug substance suppliers for exenatide LAR drug product.” Your current proposal in the NDA to have [REDACTED] (b) (4)
3. Provide the location in the NDA of the following information that was discussed at the End-of-phase-2 meeting: comparative chemical and physical characterization and comparative bioassay testing of exenatide manufactured by Lonza and Mallinckrodt.
4. Confirm that the full CMC documentation on the noncompendial excipient [REDACTED] (b) (4) polymer (poly-D,L-lactide-co-glycolide, 50:50) is in the Drug Master File [REDACTED] (b) (4).
5. Clarify the USP testing that was conducted to qualify the product-contact components of the container closure systems used to package the exenatide product and the diluent. Provide the results of these USP tests.
6. Provide the testing conditions and analytical method description for the extractables study (potential leachables) discussed in 3.2.P.2.4.2.1.
7. Although the Division acknowledges our prior agreement to receive the final, audited study report for your 2-year rat carcinogenicity study (REST060229) as a post-marketing commitment, recent safety data have suggested a potential link between GLP-1 receptor agonists and rodent thyroid C-cell tumors. In order to further assess this signal with your product, this final study report will need to be reviewed in order to determine if this NDA can be approved. We request the submission of your final study report and SAS dataset for analysis *within 60 days of receipt of this request*. Failure to do so may result in an unfavorable final recommendation for this NDA.
8. The cardiovascular meta-analysis indicates that several Byetta clinical trials have been completed since the original NDA. As you are bridging the exenatide LAR NDA to the exenatide NDA(s), please submit an updated Integrated Analysis of Safety of the completed, controlled, phase 2/3 trials of Byetta and exenatide LAR with the following adverse events of interest. Please compare incidence rates reported with exenatide, exenatide LAR, and all exenatide combined to the corresponding incidence rates reported with active comparators or placebo, where applicable.
  - Deaths, serious adverse events, and discontinuations due to adverse events.
  - Thyroid neoplasms: Please provide a written analysis of thyroid neoplasms to supplement the narratives that were already submitted with the NDA. If additional cases were identified after the September 30, 2008 cutoff, please include them and their narratives in this analysis. Please also include a discussion of thyroid neoplasms identified in exenatide postmarketing reports, as was discussed at the pre-NDA meeting.
  - Pancreatitis and/or elevated amylase/lipase: For serum amylase/lipase, please break the analysis down by >3x ULN, 5x ULN, and 10x ULN.

- Renal failure: including summary analyses of mean and median changes from baseline, shift analyses, and outlier analyses (e.g., proportion of patients with serum creatinine >1.5x the baseline value)
  - Cardiovascular events
9. Please submit this information by the 120-day safety update due date. Please include revised datasets where applicable, specifically including datasets of all amylase, lipase, and calcitonin measurements.
10. We do not have comments on the cardiovascular meta-analysis at the present time, but comments may be forthcoming as our reviews continue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver and partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

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

Sincerely,  
*{See appended electronic signature page}*

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  
7/17/2009 11:32:17 AM



NDA 22-200

**NDA ACKNOWLEDGMENT**

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:

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

Name of Drug Product: BYDUREON (exenatide for injectable suspension), 2 mg  
Date of Application: May 4, 2008  
Date of Receipt: May 5, 2008  
Our Reference Number: NDA 22-200

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 4, 2009, in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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  
5/15/2009 01:42:49 PM

**For Consulting Center Use Only:**

**Date Received:** \_\_\_\_\_

**Assigned to:** \_\_\_\_\_

**Date Assigned:** \_\_\_\_\_

**Assigned by:** \_\_\_\_\_

**Completed date:** \_\_\_\_\_

**Reviewer Initials:** \_\_\_\_\_

**Supervisory Concurrence:** \_\_\_\_\_

## Intercenter Request for Consultative or Collaborative Review Form

**To (Consulting Center):**

Center: CDRH via Office of Combination Products  
Division: Division Of General, Restorative And Neurological Devices  
Mail Code: HF\_- HFZ-410  
Consulting Reviewer Name: Anthony Watson/Pauline Fogarty  
Building/Room #: CORP Room# 350E  
Phone #: (240) 276-3737  
Fax #: (240) 276-3602  
Email Address: pauline.fogarty@fda.hhs.gov  
RPM/CSO Name and Mail Code:

**From (Originating Center):**

Center: CDER  
Division: Division of Metabolic and Endocrine Products  
Mail Code: HFD-510  
Requesting Reviewer Name: John Bishai  
Building/Room #: WO 22/ 3239  
Phone#: 301-796-1311  
Fax #:  
Email Address: john.bishai@fda.hhs.gov  
RPM/CSO Name and Mail Code: HFD-510  
Requesting Reviewer's Concurring Supervisor's Name: Lina Aljuburi

**Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.**

Date of Request: 5/14/09

Submission/Application Number: NDA 22-200

Type of Product:  Drug-device combination  Drug-biologic combination  Device-biologic combination  
 Drug-device-biologic combination  Not a combination product

Submission Receipt Date: May 5, 2009

Name of Product: BYDUREON (exenatide for injectable suspension)

Requested Completion Date: **January 5, 2010**

Submission Type: NDA

Official Submission Due Date: January 15, 2009

Name of Firm: Amylin Pharmaceuticals

Intended Use: Commercial

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):  
Please check the quality and safety of the pen. The NDA document can be found in the EDR (see link below). The document can be found in the EDR (see link below). This particular NDA was previously IND 67,092.  
Direct link to edr: \\Cdsub1\evsprod\NDA022200\022200.enx

Documents to be returned to Requesting Reviewer?    π Yes     π No

**Complete description of the request.** Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review     π Collaborative Review

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/s/

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John M Bishai

5/14/2009 03:43:53 PM

## REQUEST FOR CONSULTATION

TO (Office/Division): IRT QT Review Group  
Devi Kozelli  
OND/ODEI/DCRP  
devi.kozeli@fda.hhs.gov  
WO22 RM4183/ Phone: X6-1128

FROM (Name, Office/Division, and Phone Number of Requestor): John Bishai  
Division of Metabolism and Endocrinology Products,  
301-796-1311

DATE  
5/14/2009

IND NO.  
67,092

NDA NO.  
22-200

TYPE OF DOCUMENT  
Clinical Information  
Amendment - QT  
Protocol

DATE OF DOCUMENT  
May 5, 2009

NAME OF DRUG  
BYDUREON (exenatide for  
injectable suspension)

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-diabetic agent

DESIRED COMPLETION DATE  
January 5, 2010

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 clinical study reports for NDA 22-341. The document can be found in the EDR (see link below). The document can be found in the EDR (see link below). This particular NDA was previously IND 67,092.

Direct link to edr: \\Cdsub1\evsprod\NDA022200\022200.enx

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

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PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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John M Bishai  
5/14/2009 03:40:03 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  
5/14/2009

IND NO.  
67,092

NDA NO.  
22-200

TYPE OF DOCUMENT  
RMP Review

DATE OF DOCUMENT  
May 5, 2009

NAME OF DRUG  
BYDUREON (exenatide for  
injectable suspension)

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-diabetic agent

DESIRED COMPLETION DATE  
January 5, 2010

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 RMP for NDA 22-341. The document can be found in the EDR (see link below). This particular NDA was previously IND 67,092.  
Direct link to edr: \\Cdsub1\evsprod\NDA022200\022200.enx

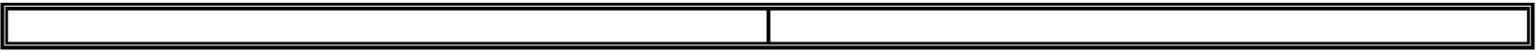
SIGNATURE OF REQUESTOR

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  
5/14/2009 03:36:48 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  
5/14/2009

IND NO.  
67,092

NDA NO.  
22-200

TYPE OF DOCUMENT  
Patient Labeling Review

DATE OF DOCUMENT  
May 5, 2009

NAME OF DRUG  
**BYDUREON (exenatide for  
injectable suspension)**

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
Anti-diabetic agent

DESIRED COMPLETION DATE  
January 5, 2010

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:** This is a request for a Patient labeling review (ie PPI, User Manuals, etc.) . The document can be found in the EDR (see link below). This particular NDA was previously IND 67,092.  
Direct link to edr: \\Cdsesub1\evsprod\NDA022200\022200.enx

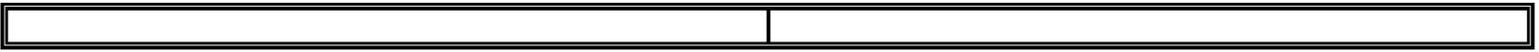
SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

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/s/

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John M Bishai

5/14/2009 03:32:29 PM

## REQUEST FOR CONSULTATION

TO (Office/Division): CDER/OPS  
**Jim McVey**  
 james.mcvey@fda.hhs.gov  
 Microbiologist  
 New Drug Microbiology  
 WO51 Room # 4162 phone: x615723

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

|   |                   |                                    |   |  |
|---|-------------------|------------------------------------|---|--|
| DATE<br>5/14/2009   | IND NO.<br>67,092 | NDA NO.<br>22-200                  | TYPE OF DOCUMENT<br>Original NDA              | DATE OF DOCUMENT<br>May 5, 2009            |
| NAME OF DRUG<br><b>BYDUREON (exenatide for injectable suspension)</b> |                   | PRIORITY CONSIDERATION<br>Standard | CLASSIFICATION OF DRUG<br>Anti-diabetic agent | DESIRED COMPLETION DATE<br>January 5, 2010 |

NAME OF FIRM: Amylin Pharmaceuticals

### REASON FOR REQUEST

#### I. GENERAL

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

#### II. BIOMETRICS

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

#### III. BIOPHARMACEUTICS

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

#### IV. DRUG SAFETY

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

#### V. SCIENTIFIC INVESTIGATIONS

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

**COMMENTS / SPECIAL INSTRUCTIONS:** This a micro request to check the sterility of the product. The document can be found in the EDR (see link below). This particular NDA was previously IND 67,092.  
 Direct link to edr: \\Cdsub1\evsprod\NDA022200\022200.enx

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

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PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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John M Bishai  
5/14/2009 03:28:50 PM