

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202799Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 202799

SUPPL #

HFD #

Trade Name OMONTYS

Generic Name Peginestide

Applicant Name Affymax

Approval Date, If Known March 27, 2012

### 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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES  NO

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

5 years from the date of approval under 21 CFR 314.108(b)(2)

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?

N/A

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#

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:

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  NO

Investigation #2 YES  NO

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  NO

Investigation #2 YES  NO

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



Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the 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: Ebla Ali Ibrahim  
Title: Lead Regulatory Project Manager, Acting  
Date: March 5, 2012

Name of Office/Division Director signing form: Ann Farrell  
Title: Division 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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EBLA ALI IBRAHIM  
03/27/2012

ANN T FARRELL  
03/27/2012

## Ali Ibrahim, Ebla

---

**From:** Suggs, Courtney  
**Sent:** Tuesday, March 06, 2012 3:10 PM  
**To:** Ali Ibrahim, Ebla  
**Cc:** Greeley, George  
**Subject:** FW: Peginesatide (NDA 202-799)

**Attachments:** 1\_Pediatric\_Record.pdf

Hi Ebla,

Here is the confirmation of review I sent to Trinh after the PeRC meeting.

Thanks,  
Courtney

### Courtney M. Suggs, Pharm.D., MPH

LCDR, USPHS  
Regulatory Project Manager  
Pediatric and Maternal Health Staff  
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US Food and Drug Administration  
10903 New Hampshire Ave.  
Bldg 22, Room 6471  
Silver Spring, MD 20993  
Phone: (301) 796-2096  
Email: courtney.suggs@fda.hhs.gov

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**From:** Suggs, Courtney  
**Sent:** Thursday, February 09, 2012 11:07 AM  
**To:** Scott, Trinh  
**Cc:** Mathis, Lisa; Addy, Rosemary; Greeley, George; Lee, Catherine S.; Farrell, Ann T  
**Subject:**

Hi Trinh,

The email serves as confirmation of the review for the Peginesatide, NDA 202-799, conducted by the PeRC PREA Subcommittee on February 8, 2012.

The Division presented a partial waiver for patients ages birth to less than one year of age because studies are impossible or highly impracticable and a deferral for patients 1 year to less than 18 years of age because adult studies are completed and ready for approval for the treatment anemia associated with chronic renal failure in adult patient on dialysis.

The PeRC agreed with the Division to grant a partial waiver and deferral for this product.

***The PeRC also offers the following recommendations:***

- *The PeRC also recommends the Division review the timelines for submission of the deferred studies to see if they can be shortened.*

The pediatric record is attached for Peginesatide.



1\_Pediatric\_Record  
.pdf (64 KB)...

Thanks,

**Courtney M. Suggs, Pharm.D., MPH**

LCDR, USPHS

Regulatory Project Manager

Pediatric and Maternal Health Staff

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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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EBLA ALI IBRAHIM  
03/06/2012

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 202799 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: Division of Hematology Products PDUFA Goal Date: March 27, 2012 Stamp Date: 5/27/2011

Proprietary Name: Omontys

Established/Generic Name: Peginesatide

Dosage Form: Solution (for injection)

Applicant/Sponsor: Affymax, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** Treatment of anemia in adult patients for chronic renal failure on dialysis

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
  - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	__ yr. 0 mo.	__ yr. 12 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): Significant blood volume constraints exist in this age group with this condition, i.e., anemia associated with chronic kidney disease.

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric

patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Other	1 yr. __ mo.	18 yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: The sponsor requests a deferral for studies in pediatric patients (age <18) with CRF on dialysis. A proposed pediatric plan was submitted on October 21, 2010. The sponsor proposes to conduct the following studies:

- Study 1: Phase 2 open-label study to evaluate the safety, efficacy, and pharmacokinetics of AF37702 Injection for maintenance treatment of anemia in pediatric subjects with chronic kidney disease (CKD) on hemodialysis and already receiving ESA therapy. Proposed report submission 2016.
- Study 2: Phase 2 open-label follow-up study to evaluate the safety, tolerability and efficacy of AF37702 Injection for the maintenance treatment of anemia in pediatric subjects with CKD on hemodialysis. Proposed report submission 2017.
- Study 3: Phase 3 randomized, active-controlled, open-label, multicenter study to evaluate the efficacy and safety of AF37702 Injection for the maintenance treatment of anemia in pediatric subjects with CKD on dialysis. Proposed report submission 2025.
- Study 4: Phase 3 open-label follow-up extension study to evaluate the safety, tolerability and efficacy of AF37702 Injection for the maintenance treatment of anemia in pediatric subjects with CKD on dialysis. Proposed report submission 2026.

† Note: *Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-*

marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

*pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

{See appended electronic signature page}

*Trinh Scott*

Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Ali Ibrahim, Ebla**

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**From:** Ali Ibrahim, Ebla  
**Sent:** Tuesday, March 13, 2012 3:26 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** RE: NDA 202799 - Revised IFU Pre-Filled Syringe  
**Attachments:** NDA 202799 Revised IFU Pre-filled syringe.doc

Hello,

Please find attached the Revised IFU for the Pre-filled syringe. Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

---

**From:** Ingolia, Diane [mailto:Diane\_Ingolia@Affymax.com]  
**Sent:** Tuesday, March 13, 2012 12:37 PM  
**To:** Ali Ibrahim, Ebla  
**Cc:** Conroy, Christine  
**Subject:** RE: NDA 202799 - Revised IFU  
**Importance:** High

Hi Ebla,

Did FDA have any comments on the Instructions for Use (IFU) for the pre-filled syringes? Should comments made on the IFU for the vials be applied to the IFU for the pre-filled syringes?

Kind regards,

Diane

Diane Ingolia, Ph.D.  
Executive Director, Regulatory Affairs  
Affymax, Inc.  
4001 Miranda Avenue

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 202799 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Omontys Established/Proper Name: Peginesatide Dosage Form: Solution (for Injection)		Applicant: Affymax Inc. Agent for Applicant (if applicable):
RPM: Trinh Scott/Ebla Ali Ibrahim		Division: Division of Hematology Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)            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><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>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><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> 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>	
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>March 27, 2012</u></li> </ul>		<input checked="" type="checkbox"/> 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 checked="" type="checkbox"/> None

<sup>1</sup> 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.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? 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>	<input type="checkbox"/> Received
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC       </p> <p>         NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)          Subpart I <input type="checkbox"/> Approval based on animal studies       </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request       </p> <p>         BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)          Subpart H <input type="checkbox"/> Approval based on animal studies       </p> <p>         REMS: <input checked="" type="checkbox"/> MedGuide  <input checked="" type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required       </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>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<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>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>3</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>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes 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? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes 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>	<input checked="" type="checkbox"/> Verified <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) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <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 Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each 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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <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>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	March 27, 2012
<b>Officer/Employee List</b>	
❖ 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> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP, March 27, 2012
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<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>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	May 27, 2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</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>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<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>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	May 27, 2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</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>• Most-recent draft labeling</li> </ul>	
<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>• 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.</li> </ul> </li> </ul>	August 29, 2011 August 25, 2011
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA December 23, 2011 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) February 24, 2012 <input checked="" type="checkbox"/> ODPD (DDMAC) January 31, 2012, DDTCP - March 7, 2012  <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	August 10, 2011 - RPM Review
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <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>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<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>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<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 8, 2012</u> 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>	<input checked="" type="checkbox"/> Included

<sup>5</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>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	June 10, July 6, 14, 22, 25, 27, August 19, September 14, 16, 27, October 3, 14, 28, November 2, 17, December 15, 2011, January 9, February 3, 8, 13, 24, 27, March 9, 13, 2012
❖ Internal memoranda, telecons, etc.	January 31, 2012
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg January 13, 2012
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg October 21, 2010
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg February 23, 2007
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	February 1, 2007
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	December 7, 2011
• 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>	<input type="checkbox"/> None March 27, 2012
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None March 23, 2012
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None March 10, 2012
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 6
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	March 9, 2012
• Clinical review(s) <i>(indicate date for each review)</i>	February 6, 2012
• 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 OR 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>	See Page 14 of the Clinical Review, February 6, 2012
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None DCRP - November 15, 2011
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

<ul style="list-style-type: none"> <li>❖ 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> </li> </ul>	Original - May 27, 2011; Final Version - March 23, 2012 March 22, 2012, AP letter March 27, 2012 <input type="checkbox"/> None Final Review DRISK- March 26, 2012
<ul style="list-style-type: none"> <li>❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)</li> </ul>	<input type="checkbox"/> None requested DSI Review Summary - December 16, 2011 DSI Letters - December 7, November 28, 2011
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<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	
<ul style="list-style-type: none"> <li>❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None February 7, 2012
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None February 6, 2012
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None February 7, 2012
<ul style="list-style-type: none"> <li>❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)</li> </ul>	<input type="checkbox"/> None December 22, 2012
<b>Nonclinical</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Pharmacology/Toxicology Discipline Reviews</li> </ul>	
<ul style="list-style-type: none"> <li>• ADP/T Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None February 27, 2012
<ul style="list-style-type: none"> <li>• Supervisory Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None February 27, 2012
<ul style="list-style-type: none"> <li>• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None February 2, 2012
<ul style="list-style-type: none"> <li>❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> No carc December 8, 2011
<ul style="list-style-type: none"> <li>❖ ECAC/CAC report/memo of meeting</li> </ul>	<input type="checkbox"/> None November 17, 2011 Included in P/T review, page77
<ul style="list-style-type: none"> <li>❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)</li> </ul>	<input checked="" type="checkbox"/> 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>	<input type="checkbox"/> None	March 8, 2012
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None	March 6, 2012
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None	ONDQA - January 31, 2012, Biopharm - January 18, 2012
❖ Microbiology Reviews		
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed	February 1, 2012
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		
	<input type="checkbox"/> None	Stats - January 17, 2012
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See page 125 of the CMC Review	
<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		
<input checked="" type="checkbox"/> 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>7</sup>)</i>	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <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: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation	
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		
	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)	

<sup>7</sup> I.e., 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.

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/s/  
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EBLA ALI IBRAHIM  
03/28/2012

Palo Alto, CA 94304  
Phone: 650-812-8746

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---

**From:** Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]  
**Sent:** Friday, March 09, 2012 12:06 PM  
**To:** Ali Ibrahim, Ebla; Ingolia, Diane  
**Cc:** Conroy, Christine  
**Subject:** RE: NDA 202799 - Revised IFU

Hello,

Please find attached FDA's revised IFU document. Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

---

Ebla  
09, 2012 1:00 PM

ne  
J2799 - Revised PI, Revised Med guide, REMS document, Revised DHCP Letter  
I

Hello,

Please find attached the following documents:

1. minor changes to the PI
2. FDA's revision to the Med guide
3. REMS document (not in track change because everything in your version has been changed)
4. and FDA's revision to the DHCP letter

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within 7 days.

## **LS**

Revise the goals for the Omontys REMS as follows:

- To inform healthcare professionals that OMONTYS Injection is indicated only for use in the treatment of patients with anemia of chronic renal failure on dialysis.
- To inform healthcare professionals of the serious risk associated with the use of OMONTYS Injection including potentially fatal cardiovascular and/or thromboembolic adverse events, and the increased risk of these events in non-dialysis patients.

## **ICATION GUIDE**

Although we agree that there should be a Medication Guide for Omontys, the Medication Guide should not be included as an element of the Omontys REMS.

## **MUNICATION PLAN**

The DHCP letter should be sent twice, 12 months apart, with the first dissemination within 60 days of product approval or at the time of product launch, whichever is sooner, and again after 12 months via electronic mail (email) to the nephrology prescribing community. Standard mail and facsimile should be employed to reach HCPs not reachable by email.

Any new prescribers of Omontys should also be targeted in the communication plan. Revise the dissemination strategy to identify and reach new prescribers regardless of use or specialty for 18 months after product launch. These details should be included in the REMS and the REMS Supporting Document.

The DHCP should be sent to relevant professional organizations for distribution to their members.

We ask that you compile the list of recipients for the letter as indicated in the draft REMS.

The letter should be available for 2 years following approval of the Omontys REMS on a dedicated REMS website.

Any new prescribers of Omontys should also be targeted in the communication plan. Revise the dissemination strategy to identify and reach new prescribers regardless of use or specialty for 18 months after product launch. These details should be included in the REMS and the REMS Supporting Document.

## **TABLE FOR SUBMISSION OF ASSESSMENTS**

REMS assessment reports must be submitted to the FDA at 18 months, 3 years and in the 7<sup>th</sup> year from the date of the initial approval of the REMS.

## **IS ASSESSMENT PLAN**

The following information should be included in the REMS assessment reports.

1. The results of surveys of Omontys prescribers establishing the diagnoses, including dialysis status, of patients for whom the prescriber uses Omontys.

2. Use data establishing the site of prescribing and dispensing of Omontys; that is, how much (and percent) Omontys is used within dialysis centers, how much (and percent) Omontys is used outside of dialysis centers, how much (and percent) is administered to/by patients receiving dialysis, how much (and percent) is administered to/by patients who do not receive dialysis, and the diagnoses for use.

The source of each data point should be described.

3. Data establishing 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.

## **ERAL COMMENTS**

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Omontys 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.

<< File: NDA202799 draft PI 3-9-2012.doc >> << File: NDA 202799 Med guide 3-9-2012.doc >> << File: NDA 202799 REMS Document 3-9-12.doc >> << File: NDA 202799 FDA Revision DHCP letter 3-9-2012.doc >>

Please accept the changes acceptable to you and leave your edits in tracked changes.

Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

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/s/  
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EBLA ALI IBRAHIM  
03/13/2012

## Ali Ibrahim, Ebla

---

**From:** Ali Ibrahim, Ebla  
**Sent:** Tuesday, March 13, 2012 9:08 AM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine; Rogers, Zane  
**Subject:** Web Instructions

Hello,

Here is the web page instructions from DRISK:

The REMS Communication materials will be maintained on a dedicated stand alone REMS website. Include a prominent link on the product website's homepage for REMS materials. Any component of a REMS proposal must be reviewed and approved by the FDA, including any post-approval modifications. Because of this requirement, we recommend creating a single-click, prominent direct link off the main website that includes REMS-specific materials. This link will direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. The REMS-related webpage(s) should not be a means to promote this drug or any other product. Only the separate webpage(s) and /or link will be considered a component of the Communication Plan.

- The landing page of the separate REMS link should contain brief background information on the REMS along with the REMS communication materials.
- This page should include a prominent header to communicate the risks addressed through the REMS.
- We recommend the following language as background information on the REMS landing page:

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks. [sponsor name] has worked with the FDA to develop materials to communicate the risks of [list risks] to healthcare providers.

Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
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/s/  
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EBLA ALI IBRAHIM  
03/13/2012

## Ali Ibrahim, Ebla

---

**From:** Ali Ibrahim, Ebla  
**Sent:** Friday, March 09, 2012 3:06 PM  
**To:** Ali Ibrahim, Ebla; 'Ingolia, Diane'  
**Cc:** 'Conroy, Christine'  
**Subject:** RE: NDA 202799 - Revised IFU

**Attachments:** NDA 202799 FDA's Revision IFU (vial) 3-9-2012.doc

Hello,

Please find attached FDA's revised IFU document. Thank you.



NDA 202799 FDA's  
Revision IFU ...

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

---

**From:** Ali Ibrahim, Ebla  
**Sent:** Friday, March 09, 2012 1:00 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** NDA 202799 - Revised PI, Revised Med guide, REMS document, Revised DHCP Letter  
**Importance:** High

Hello,

Please find attached the following documents:

1. minor changes to the PI
2. FDA's revision to the Med guide
3. REMS document (not in track change because everything in your version has been changed)
4. and FDA's revision to the DHCP letter

The REMS document submitted was not in the correct format. The FDA has written a REMS document for Omontys in the correct format that incorporates the FDA's comments below. The REMS Supporting Document should be amended to incorporate the changes in the REMS document. The REMS and REMS Supporting Document should be submitted to the FDA within 7 days.

### GOALS

Revise the goals for the Omontys REMS as follows:

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- To inform healthcare professionals of the serious risk associated with the use of OMONTYS Injection including potentially fatal cardiovascular and/or thromboembolic adverse events, and the increased risk of these events in non-dialysis patients.

## **MEDICATION GUIDE**

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## **COMMUNICATION PLAN**

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Please accept the changes acceptable to you and leave your edits in tracked changes.

Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

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/s/  
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EBLA ALI IBRAHIM  
03/13/2012

## Ali Ibrahim, Ebla

---

**From:** Ali Ibrahim, Ebla  
**Sent:** Friday, March 09, 2012 1:00 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** NDA 202799 - Revised PI, Revised Med guide, REMS document, Revised DHCP Letter

**Importance:** High

**Follow Up Flag:** Follow up  
**Flag Status:** Red

**Attachments:** NDA202799 draft PI 3-9-2012.doc; NDA 202799 Med guide 3-9-2012.doc; NDA 202799  
REMS Document 3-9-12.doc; NDA 202799 FDA Revision DHCP letter 3-9-2012.doc

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NDA202799 draft  
PI 3-9-2012.do...



NDA 202799 Med  
guide 3-9-2012....



NDA 202799 REMS  
Document 3-9-1...



NDA 202799 FDA  
Revision DHCP I...

Please accept the changes acceptable to you and leave your edits in tracked changes.

Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
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/s/  
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EBLA ALI IBRAHIM  
03/13/2012

**Ali Ibrahim, Ebla**

---

**From:** Ali Ibrahim, Ebla  
**Sent:** Monday, February 27, 2012 12:35 PM  
**To:** 'Rogers, Zane'  
**Cc:** Conroy, Christine; Ingolia, Diane  
**Subject:** FDA's Recommendations and Comments (Observational Study Protocol)- NDA 202799 OMONTYS (peginesatide)  
**Attachments:** NDA 202799 FDA Recommendations and Comments-Observational Study Protocol.doc

Hello,

Please find attached the FDA's recommendations and comments on the observational study protocol as discussed during the Friday, February 24, 2012 tecon. I will forward you the names of the FDA attendees shortly.

Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

---

**From:** Rogers, Zane [mailto:Zane\_Rogers@Affymax.com]  
**Sent:** Friday, February 24, 2012 6:03 PM  
**To:** Ali Ibrahim, Ebla  
**Cc:** Conroy, Christine; Ingolia, Diane  
**Subject:** RE: Vial and Carton Labels Comments - NDA 202799 OMONTYS (peginesatide)

Dear Ebla,

We have received the proposed changes to the packaging artwork and labels. We will review the changes and get back to you.

We were also expecting to receive additional FDA comments on the proposed observational study today. Can you let us know when we might receive these?

Regards,

Zane Rogers  
Director, Regulatory Affairs  
Affymax  
650-521-4429

---

**From:** Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]  
**Sent:** Friday, February 24, 2012 1:28 PM  
**To:** Ingolia, Diane; Rogers, Zane  
**Cc:** Conroy, Christine  
**Subject:** Vial and Carton Labels Comments - NDA 202799 OMONTYS (peginesatide)  
**Importance:** High

Hello,

Please find attached comments for the vial and carton labels. Please make changes to the vial and carton labels as stated in the attachment. Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

---

**From:** Ingolia, Diane [mailto:Diane\_Ingolia@Affymax.com]  
**Sent:** Thursday, February 16, 2012 12:53 PM  
**To:** Ali Ibrahim, Ebla  
**Cc:** Conroy, Christine  
**Subject:** RE: FDA's Draft - PI - NDA 202799 OMONTYS (peginesatide)

Dear Ebla,

In the FDA's draft PI changes were made to the names of the dosage forms, specifically (b) (4) vials and (b) (4) vials were changed to single use vials and multiple use vials. We will make these changes. Since this will require changes to the draft packaging (unit labels and carton labels) submitted with the NDA we would appreciate if you could let us know whether additional changes to the draft packaging will be requested and when we might receive any additional requests. We would like to make all changes to the packaging at once if that is possible.

Kind regards,

Diane

Diane Ingolia, Ph.D.  
Executive Director, Regulatory Affairs  
Affymax, Inc.  
4001 Miranda Avenue  
Palo Alto, CA 94304  
Phone: 650-812-8746

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---

**From:** Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]  
**Sent:** Wednesday, February 15, 2012 1:59 PM  
**To:** Ingolia, Diane  
**Cc:** Conroy, Christine  
**Subject:** FDA's Draft - PI - NDA 202799 OMONTYS (peginesatide)  
**Importance:** High

Hello,

Please find attached the PI with the agency's revision in track change. Please accept the changes acceptable to you and leave your edits in track change. Please respond by next Wednesday, February 22, 2012 or sooner. Please note that there might be more revisions to sections under discussion.

I will plan a tecon for PMR/PMC discussions soon. Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
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/s/  
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EBLA ALI IBRAHIM  
02/27/2012

**Ali Ibrahim, Ebla**

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**From:** Ali Ibrahim, Ebla  
**Sent:** Friday, February 24, 2012 4:28 PM  
**To:** 'Ingolia, Diane'; 'Rogers, Zane'  
**Cc:** Conroy, Christine  
**Subject:** Vial and Carton Labels Comments - NDA 202799 OMONTYS (peginesatide)  
**Importance:** High  
**Attachments:** NDA 202799 - Vial and Carton Labels Comments.doc

Hello,

Please find attached comments for the vial and carton labels. Please make changes to the vial and carton labels as stated in the attachment. Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

*Tel: 301-796-3691  
Fax: 301-796-9849*

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**From:** Ingolia, Diane [mailto:Diane\_Ingolia@Affymax.com]  
**Sent:** Thursday, February 16, 2012 12:53 PM  
**To:** Ali Ibrahim, Ebla  
**Cc:** Conroy, Christine  
**Subject:** RE: FDA's Draft - PI - NDA 202799 OMONTYS (peginesatide)

Dear Ebla,

In the FDA's draft PI changes were made to the names of the dosage forms, specifically (b) (4) vials and (b) (4) vials were changed to single use vials and multiple use vials. We will make these changes. Since this will require changes to the draft packaging (unit labels and carton labels) submitted with the NDA we would appreciate if you could let us know whether additional changes to the draft packaging will be requested and when we might receive any additional requests. We would like to make all changes to the packaging at once if that is possible.

Kind regards,

Diane

Diane Ingolia, Ph.D.

Executive Director, Regulatory Affairs  
Affymax, Inc.  
4001 Miranda Avenue  
Palo Alto, CA 94304  
Phone: 650-812-8746

*The preceding e-mail message (including any attachments) contains information that may be confidential, be protected by applicable legal privileges, or constitute non-public information. It is intended to be conveyed only to the designated recipient(s). If you are not an intended recipient of this message, please notify the sender by replying to this message and then delete it from your system. Use, dissemination, distribution, or reproduction of this message by unintended recipients is not authorized and may be unlawful.*

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**From:** Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]  
**Sent:** Wednesday, February 15, 2012 1:59 PM  
**To:** Ingolia, Diane  
**Cc:** Conroy, Christine  
**Subject:** FDA's Draft - PI - NDA 202799 OMONTYS (peginesatide)  
**Importance:** High

Hello,

Please find attached the PI with the agency's revision in track change. Please accept the changes acceptable to you and leave your edits in track change. Please respond by next Wednesday, February 22, 2012 or sooner. Please note that there might be more revisions to sections under discussion.

I will plan a tecon for PMR/PMC discussions soon. Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
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Vial and Carton Labels Comments

A. (b) (4) Vial Labels (10 mg/mL and 20 mg/2 mL)

1. (b) (4)  
In this case the 10 mg vial may be read as 20 mg vial and vice versa; thus, leading to overdoses and underdoses. Revise accordingly.
2. (b) (4)  
This information is included in the total drug content statement.
3. Relocate or also include the strength with the background colored block to the principle display panel. If placed on the shelf with the principle display panel facing forward, the side panel with the strength and different background colored blocks will not be seen because this information can only be seen from a side.
4. Add the route of administration “For Intravenous or Subcutaneous Use Only” to the principle display panel to help prevent wrong route of administration errors. DMEPA identified multiple wrong route of administration error cases involving similar products in the same class. Patients and healthcare practitioners administered the products intramuscularly instead of intravenously or subcutaneously.
5. Relocate the manufacturer’s information to the side panel, so that the most important information is prominent on the principle display panel (e.g., proprietary and established names, dosage form, product strength, and route of administration).

B. Single-Use Vials Labels (2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5mL, 6 mg/mL)

1. See comments A.3 through A.5 and revise single-use vials labels accordingly.
2. (b) (4) located on the principle display panel as this statement is confusing and occupies space.
3. Revise the statement (b) (4) to state “Single Use Vial Only. Discard Unused Portion”. We recommend this revision to emphasize that this vial is for single use only because the statement “single dose” implies that the entire vial is administered every time. However, since package insert labeling expresses the

dose in mg/kg (i.e., 0.04 mg/kg to 0.08 mg/kg), the dose may not be rounded up or down to equal the contents of the entire vial.

**C. <sup>(b) (4)</sup> Vial Carton Labeling (10 mg/mL and 20 mg/2 mL)**

1. See comments A.1 and A.2 above and revise multi-use vial carton labeling accordingly.
2. Different strengths of the product appear similar due to insufficient difference in the background color. Prominent red-brown color blocks appear on each carton making all the cartons look similar to each other. The upper, differently-colored, triangle blocks containing the products' strength are smaller than the red-brown color blocks. This decreases the differentiation between the strengths. Thus, use only the differently-colored upper blocks for the entire background color block.
3. Delete, move, or minimize the three colored line graphic above the proprietary name "Omontys" as this graphic reduce the readability of the proprietary name.
4. Revise the statement "For IV or SC Use Only" to read for "For Intravenous or Subcutaneous Use Only". Additionally, increase the prominence of this statement by increasing font size. Abbreviations 'IV' and 'SC' appear on ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because abbreviation 'IV' has been confused with the abbreviations 'IM' (intramuscular), 'IU' (international units), and 'IN' (intranasal) and abbreviation 'SC' has been confused with the abbreviation 'SL' (sublingual). Additionally, we identified medication error cases involving Epogen and Aranesp that reported administration of these products intramuscularly instead of intravenously or subcutaneously.
5. Revise medication guide statement to be consistent with other medication guide statements for other product. For example, you medication guide statement can read as follows "ATTENTION PHARMACIST: Dispense enclosed Medication Guide to each patient".

**D. Single-Use Vial Carton Labeling (2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5mL, 6 mg/0.5mL)**

1. See comments B.2 and B.3 and revise single-use vial carton labeling accordingly.
2. See comments C.2 through C.5 and revise single-use vial carton labeling accordingly.

**E. Single-Use Prefilled Syringe (1 mg/0.5 mL, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, 6 mg/0.5 mL)**

1. Relocate the colored blocked to appear around the horizontally placed strength. Additionally, delete the vertically placed strength. We recommend this revision to help differentiate among the different strengths and to increase the readability of the strength.
2. [REDACTED] <sup>(b) (4)</sup> from the principle display panel as this statement is confusing and occupies space.
3. Revise the statement [REDACTED] <sup>(b) (4)</sup> to read “Single Use Prefilled Syringe. Discard After One Use” to emphasize that the syringe should not be re-used.
4. Add the route of administration “For Intravenous or Subcutaneous Use Only” if space permits.

**F. Single-Use Prefilled Syringe Tray Labeling and Carton Labeling (1 mg/0.5 mL, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5mg/0.5 mL, 6 mg/0.5 mL)**

1. See comments C.3 through C.5 and revise single-use prefilled syringe tray labeling and carton labeling accordingly.
2. See comment E.3 and revise single-use prefilled syringe tray labeling and carton labeling accordingly.
3. Although different product strengths appear sufficiently differentiated, we ask you use only the differently-colored upper blocks for the entire background color block to be consistent with carton labeling for single dose and multi dose vials.

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/s/  
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EBLA ALI IBRAHIM  
02/24/2012

## Ali Ibrahim, Ebla

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**From:** Ali Ibrahim, Ebla  
**Sent:** Wednesday, February 15, 2012 4:59 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** FDA's Draft - PI - NDA 202799 OMONTYS (peginesatide)

**Importance:** High

**Attachments:** NDA 202799 - Omontys FDA draft label 2-15-2012.doc

Hello,

Please find attached the PI with the agency's revision in track change. Please accept the changes acceptable to you and leave your edits in track change. Please respond by next Wednesday, February 22, 2012 or sooner. Please note that there might be more revisions to sections under discussion.

I will plan a tecon for PMR/PMC discussions soon. Thank you.



NDA 202799 -  
Omontys FDA draft..

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
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EBLA ALI IBRAHIM  
02/15/2012

**Ali Ibrahim, Ebla**

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**From:** Ali Ibrahim, Ebla  
**Sent:** Monday, February 13, 2012 9:16 AM  
**To:** 'Ingolia, Diane'  
**Subject:** NDA 202799

Good Morning,

This is to acknowledge your voice mail from Friday, February 10, 2012. The review team is still working on the labeling and the PMR/PMCs. I plan to email you the draft labeling by mid week.

Here is a comment from the Quality Microbiology Reviewer:

At the Takada manufacturing site, the bioburden sample is taken after the [REDACTED] (b) (4) This sample point does not assess the quality control on the formulation of the bulk drug product. A bioburden sample point prior to the [REDACTED] (b) (4) should be considered.

Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
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EBLA ALI IBRAHIM  
02/13/2012

## Ali Ibrahim, Ebla

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**From:** Ali Ibrahim, Ebla  
**Sent:** Wednesday, February 08, 2012 10:37 AM  
**To:** 'Ingolia, Diane'  
**Subject:** Information Request - NDA 202799

**Importance:** High

Good Morning,

Please respond as soon as possible to the question below:

Regarding your reply of Jan 23 to the FDA tecon held on 1/19,  
Please see the first bullet on your page 3 of your reply of Jan 23, where you state that ..." 74% of these incident patients were naïve to ESA treatment."

Please confirm this to be a true statement. Other evidence that we have indicates that the majority of patients with CKD going onto dialysis are not ESA naïve."

Thank you.

*Ebla Ali Ibrahim, MS  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

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Fax: 301-796-9849*

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EBLA ALI IBRAHIM  
02/08/2012



NDA 202799

**MEETING REQUEST WITHDRAWN**

Affymax, Inc  
Attention: Diane Ingolia, Ph.D  
Executive Director, Regulatory Affairs  
4001 Miranda Avenue  
Palo Alto, CA 94304

Dear Dr. Ingolia:

Please refer to your Pending New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Peginesatide Injection.

We also refer to your January 27, 2012 communication requesting withdrawal of your December 15, 2011 meeting request because Affymax had a tecon with the Division on January 19, 2012. Your meeting request is hereby withdrawn.

If you have any questions, call me at (301) 796-3691.

Sincerely,

*{See appended electronic signature page}*

Ebla Ali Ibrahim, M.S.  
Lead Regulatory Health Project Manager, Acting  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/

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EBLA ALI IBRAHIM  
02/03/2012

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# **FDA**

## **DIVISION HEMATOLOGY DRUG PRODUCTS (DHP)**

### **TELECONFERENCE (TCON) MEETING MINUTES**

**NDA: 202799**

**DRUG NAME: Omontys® (Peginesatide)**

**SPONSOR: Affymax, Inc.**

**TCON DATE: Wednesday, January 25, 2012; 2:30PM – 3:30PM (EST)**

**TCON DIAL-IN: (866) 630-5224**

#### **SPONSOR PARTICIPANTS**

Kathryn Woodburn, Ph.D., Executive Director Nonclinical, Affymax

(b) (4)

Martha Mayo, Pharm.D., Executive Director, Clinical Development, Affymax

Krishna Polu, M.D., VP, Clinical Development, Affymax

Anne-Marie Duliege, M.D., M.S., Chief Medical Officer, Affymax

Christine Conroy, Pharm.D., VP, Regulatory Affairs, Affymax

Diane Ingolia, Ph.D., Executive Director, Regulatory Affairs, Affymax

Binita Kwankin, Sr. Director, Regulatory Strategy, Takeda

Dan Cooper, M.D., Sr. Director Pharmacovigilance and Drug Safety

Zane Rogers, Director, Regulatory Affairs

Lydie Yang, Sr. Program Manager, Regulatory Affairs

#### **FDA PARTICIPANTS**

John Leighton, Ph.D., Acting Director, Division of Hematology Oncology Toxicology Products

Haleh Saber, Ph.D., Supervisory Pharmacologist

Brenda Gerhke, Ph.D, Pharmacologist/Toxicologist

Janice Brown, Ph.D., CMC Lead

Li Shan Hsieh, Ph.D., Review Chemist

Ebla Ali Ibrahim, M.S., Regulatory Project Manager

Trinh Scott, M.S., Regulatory Project Manager

**AGENDA: To discuss the Pregnancy Category of C versus D for the labeling, and to request justification for the proposed specification of (b) (4) for the residual solvent (b) (4)**

Prior to the teleconference, FDA emailed to Affymax:

1. A PDF copy of the Federal Registry, Vol. 44, No. 124, June 26, 1979, with specific reference to #67. [Attached]
2. The proposed specification for the residual solvent (b) (4) (b) (4). According to your batch analyses, the batches of drug substance used in nonclinical studies and clinical trials contained much lower levels (b) (4) of (b) (4). Lower the acceptance criterion appropriately, or alternatively, provide justification for the proposed specification of (b) (4) for the residual solvent (b) (4).

After introductions, FDA reiterated the request for justification for the proposed specification of (b) (4) for the residual solvent (b) (4). FDA requested the written justification by Friday, January 27, 2012.

After inconclusive discussion regarding the Pregnancy Category C versus D for the labeling, FDA and Affymax agreed that Affymax should submit written rationale to support their position for Pregnancy Category C on the labeling. FDA requested that this rationale should also be submitted by Friday, January 27, 2012.

**ACTION ITEMS**

Affymax to submit by Friday, January 27, 2012:

1. Justification for the proposed specification of (b) (4) for the residual solvent (b) (4).
2. Rationale for the classification of Pregnancy Category C in the labeling.

**TCON Minutes Recorded by:** Trinh Scott, DHP

and effectiveness, the Commissioner concludes that there is no legitimate basis for limiting the labeling to hazards arising from the approved use of the drug, particularly when dangerous unapproved use of the drug has been found. Thus, this requirement has been retained in the final regulation.

67. One comment contended that the warning section should contain information based on animal data, because that may be the only information available on serious hazards, particularly long-term hazards (e.g., cancer, birth defects). Another comment suggested that the sentence describing data to be included in boxed warnings be rewritten to require that boxed warnings be based on clinical data.

The Commissioner concludes that animal data, in certain circumstances, are an appropriate ground upon which to base warning statements, including boxed warnings, and the labeling format so provides in § 201.56(a)(3). In addition, § 201.57(e) has been revised to state clearly that serious animal toxicity data may require warnings in drug labeling.

68. A comment asked whether a manufacturer may include a boxed warning without prior FDA approval and whether FDA would consider the labeler's desires when specifying the location of boxed warnings in labeling.

The Commissioner advises that, to ensure the significance of boxed warnings in drug labeling, they are permitted in labeling only when specifically required by FDA. The labeler's desires about location and wording of boxed warnings, however, will be considered.

69. A comment asked what sources of information would be permitted to provide the frequency of serious adverse reactions and the approximate mortality and morbidity rates of patients sustaining such reactions. A comment contended that, because pertinency is a subjective standard, the words "if pertinent," relating to mortality and morbidity rates, should be changed to "if known."

The Commissioner advises that, in general, information concerning the frequency and the approximate mortality and morbidity rates of serious adverse reactions will be obtained in the same manner as that for frequency of adverse reactions in § 201.57(g)(4) discussed in paragraph 117 of this preamble. The data may be obtained, in certain cases, from the same source as the information upon which the warning is based, e.g., the study or studies demonstrating an association of the hazard with the drug. In addition, the

Commissioner has revised the requirement to clarify that approximate mortality and morbidity rates for patients sustaining the reaction shall be listed if they are known and if they are important to the safe and effective use of the drug. Although the rates are known, if they are not important to the safe and effective use of the drug, they are not required to appear in drug labeling.

70. A comment suggested that the regulation provide for referencing substantial differences of opinion among experts or for discussing other serious medical controversies relating to the "Warnings" section of the labeling format.

The Commissioner rejects this comment. This comment was discussed fully in the preamble to the final regulation revising § 1.21 (formerly § 1.3) published in the Federal Register of July 7, 1975 (40 FR 28582). The statutory scheme for drug labeling requires that potential hazards, as well as known hazards, be included in labeling. Including conflicting opinions about such warnings would result in uncertainty and confusion and, accordingly, decrease the usefulness of the warnings in protecting the public.

#### Precautions

71. A comment contended that because certain labeling requirements for habit-forming drugs are stated in § 329.10 (21 CFR 329.10), repetition of that information should not be required in the "Precautions" section of the labeling format.

The Commissioner agrees that information should not be unnecessarily duplicated in drug labeling. It was not intended that information required under § 329.10 be repeated in this part of the labeling format. Therefore, the Commissioner has revised § 201.57(f)(1) to require that general precautions include only that information not required to appear under any other specific section or subsection of the labeling format.

72. Several comments objected to § 201.57(f)(2) requiring that complete patient information on a drug be included in physician labeling, on the ground that patient labeling is a controversial matter that should be the subject of a separate proposal, rather than being included in the proposal concerning prescription drug labeling format directed at professionals. One comment contended that issuing regulations requiring printed patient information before thoroughly investigating the best language and modalities for informing the patient is

irresponsibly premature. Several comments alleged that printed patient labeling on prescription drugs would interfere with the practice of medicine and the physician-patient relationship, in violation of section 503(b)(2) of the act (21 U.S.C. 353(b)(2)).

Several comments requested that the Commissioner clarify whether § 201.57(f)(2) permits giving professional labeling to patients upon request, whether a request can be refused, whether this part covers all "patient aids" relating to a drug or only to printed instructions containing information specifically directed to the use of the drug by the patient, whether the professional labeling will be required to be updated with the preparation of each new printed patient information piece, whether the pharmacist, when dispensing a prescription, must provide the printed information to the patient, and whether a sufficient number of reprints of the patient information will be required for each package of a drug shipped to the pharmacist to accommodate the number of prescriptions that may be dispensed from it.

Two comments suggested that patient information should contain warnings concerning drug interactions, information about side effects, and special instructions concerning clinically significant information that the patient should report to the physician. Three comments objected to including information relating to possible adverse reactions, asserting that the risks from the use of drugs may induce unwarranted anxiety in patients, who will develop symptoms of the adverse reactions through suggestion. Therefore, the comments contended, patient information concerning the use of a drug should be disseminated under a physician's discretion. Another comment asked that the second sentence clearly refer to patient labeling.

The Commissioner concludes that these comments misunderstand the intent of § 201.57(f)(2). The Commissioner does not intend that patient labeling must be prepared for distribution to patients for all prescription drugs. The regulation requires only that information necessary for a patient's safe and effective use of the labeled drug be stated; e.g., if a drug may cause drowsiness and the patient taking it should therefore be cautioned against driving or operating machinery, a statement to that effect is required to be included in this subsection of the physician labeling for the drug.

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/s/  
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TRINH N SCOTT  
01/31/2012

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# **FDA**

## **DIVISION HEMATOLOGY DRUG PRODUCTS (DHP)**

### **TELECONFERENCE (TCON) MEETING MINUTES**

**NDA: 202799**

**DRUG NAME: Omontys<sup>®</sup> (Peginesatide)**

**SPONSOR: Affymax, Inc.**

**TCON DATE: Thursday, January 19, 2012; 11:39AM –12:17PM (EST)**

**TCON DIAL-IN: (866) 630-5224**

#### **SPONSOR PARTICIPANTS**

Anne-Marie Duliege, M.D., M.S., Chief Medical Officer, Affymax  
Krishna Polu, M.D., VP, Clinical Development, Affymax  
Martha Mayo, Pharm.D., Executive Director, Clinical Development, Affymax  
Sandra Tong, M.D., Senior Director, Clinical Development, Affymax  
Whedy Wang, Ph.D., Executive Director, Biostatistics, Affymax  
Christine Conroy, Pharm.D., VP, Regulatory Affairs, Affymax  
Diane Ingolia, Ph.D., Executive Director, Regulatory Affairs, Affymax  
Zane Rogers, Director, Regulatory Affairs, Affymax  
Rachel Melman, MBS, Program Manager, Regulatory Affairs, Affymax  
Binita Kwankin, Sr. Director, Regulatory Strategy, Takeda  
Ping Qiu, M.D., Senior Medical Director

#### **FDA PARTICIPANTS**

Robert Kane, M.D., Deputy Director Safety (Acting)  
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader  
Andrew Dmytrijuk, M.D., Medical Officer  
Diane Leaman, B.S., Safety Regulatory Project Manager  
Trinh Scott, M.S., Regulatory Project Manager

**AGENDA: To discuss and exchange possible post-marketing requirements (PMR) with the Applicant.**

Prior to the teleconference, on January 17, 2012, FDA emailed to Affymax the following draft PMR:



Background:

The sponsor has conducted two trials in patients with CKD not on dialysis (NOD) in which the safety (by MACE criteria) of peginesatide appears numerically worse than that of the active control comparator, Darbepoetin. While two trials of a total of approximately 1000 patients with CKD on dialysis show similar safety to that of an Epoetin comparator regimen, there remains some residual uncertainty of the true safety of peginesatide, and the safety outcomes are not likely to be able to be assessed further in the indicated population (CKD on dialysis), should the drug be approved for that indication. Thus, the need to study the safety of the drug in the CKD NOD population which is expected to be less confounded for assessing the contribution of peginesatide to the safety of the product in all uses. Even if the drug is limited to marketing to dialysis centers, patients with CKD NOD may be treated with the product at some time point, and the overall size of the entire population treated with Peginesatide is modest, considering the size of trials showing uncertainty of safety of the approved comparator products, Epoetin and Darbepoetin, in patients with CKD.

Affymax also submitted Background Information on January 17, 2012 for the teleconference discussion (attached). Affymax proposed meeting discussion included:

- Affymax's proposal for the use of the (b) (4) to conduct an observational study to further evaluate safety of peginesatide injection in a real world setting
- Address any FDA questions regarding the proposed plans for pediatric studies to meet the requirements of the Pediatric Research Equity Act (PREA)
- Understand FDA's thoughts with regard to post-marketing commitments and requirements for peginesatide injection

After introductions, FDA stated that we would like to start dialogue of post-marketing expectations. FDA acknowledged that Affymax's proposal (b) (4) may be useful; however, there is a question as to how soon (b) (4) will be able to produce a (b) (4). FDA requests that Affymax submit information on how they plan to accomplish this observational study, assuring that all possible biases are eliminated.

FDA acknowledged Affymax REMS proposal (b) (4) but stated that it could also be accomplished (b) (4) which could be an alternative to a REMS. FDA requested that Affymax submit a description of the plan (b) (4).

FDA also requested Affymax sketch a randomize control trial for patients not yet on dialysis, but just starting dialysis or ESA. List in bullets the limitations and prospective controls of the investigation. Propose the minimum number of patients that will be followed and the accrual time. FDA invited interest in the Not-on-Dialysis trial in the CKD population to gain further understanding of overall safety, and suggested a double-blind control against once-a-month Aranesp. Furthermore, use the more contemporary Hbg recommendations in the Aranesp label. This will address a gap of uncertainty in the overall concept of safety in peginesatide.

Affymax responded that given the uncertainty and the safety data for the non-dialysis population, from a practical viewpoint, enrolling and conducting the trial would be difficult. They propose that the observational study may (b) (4). Affymax will provide additional information on the proposed study.

### **ACTION ITEMS**

Affymax to submit responses to FDA's questions by Monday, January 23, 2012:

1. Information on when a (b) (4) use would be available.
2. Proposal for a minimum number of ESA naïve patients that would be accrued. Propose patient accrual time for these patients.
3. How to ensure comparability between the two treatment groups (peginesatide compared with epoetin alfa) to eliminate variability.

4. Describe limitations of the proposed observational study versus an RCT.
5. Provide practical considerations and timing with respect to conduct of a randomized controlled trial in patients not on dialysis.
6. Submit a description of the plan [REDACTED]<sup>(b) (4)</sup>, and reporting to FDA [REDACTED]<sup>(b) (4)</sup>.

**TCON Minutes Recorded by:** Trinh Scott, DHP

**Peginesatide Injection**  
**Background Information for**  
**Discussion of Post-Marketing Studies on 19 January 2012**  
**NDA 202,799**

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/s/  
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TRINH N SCOTT  
01/31/2012

## Scott, Trinh

---

**From:** Scott, Trinh  
**Sent:** Monday, January 09, 2012 6:01 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** NDA 202799 - PI label sections 8.1 and 13.1

Dear Diane,

Regarding the Package Insert labeling for NDA 202799, we propose the following text for sections 8.1 and 13.1, and have comments we would like you to address. Please respond by 12:00 p.m. EST on Thursday January 12, 2012.

(b) (4)



### **Comments and Questions for section 8.1**

**We used a dose of 0.35 mg/kg in patients or the corresponding AUC for animal: human dose or AUC calculations. This dose was chosen based on the communication dated Nov 3, 2011 for the carcinogenicity study. Please confirm that the dose of 0.35 mg/kg is relevant. Was this dose given to patients on dialysis? Was this dose given IV?**

(b) (4)



### Comments for section 13.1

**See our comments regarding animal: human extrapolation under section 8.1 for the first paragraph (carcinogenicity).**

**Use the same concept for animal: human dose or AUC extrapolations for the last paragraph (fertility). Note that the dose extrapolation is used only when the systemic exposure data are not available or are deemed inappropriate.**

Thank you,  
Trinh

---

CDR Trinh Scott, USPHS | Regulatory Project Manager | Division of Hematology Products, CDER, FDA  
10903 New Hampshire Avenue, WO22, Room 2173 | Silver Spring, MD 20993  
☎ 301.796.3311 (phone) • 301.796.9845 (fax) | ✉ [trinh.scott@fda.hhs.gov](mailto:trinh.scott@fda.hhs.gov)

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/s/  
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TRINH N SCOTT  
01/09/2012



John Orwin, CEO  
Affymax, Inc.  
4001 Miranda Ave.  
Palo Alto, CA 94304

Dear Mr. Orwin:

Between October 7 and 14, 2011, Mr. Timothy C. Grome, representing the Food and Drug Administration (FDA), conducted an investigation and met with your staff to review your conduct as sponsor of the following clinical investigations of the investigational drug peginesatide, performed for Affymax, Inc:

Protocol #AFX01-12, entitled "A Phase 3, Randomized, Active-controlled, Open-label, Multicenter Study of the Safety and Efficacy of AF37702 Injection for the Maintenance Treatment of Anemia in Hemodialysis Patients Previously Treated with Epoetin Alfa,"

Protocol #AFX01-14, entitled "A Phase 3, Randomized, Active-controlled, Open-label, Multicenter Study of the Safety and Efficacy of AF37702 Injection for the Maintenance Treatment of Anemia in Hemodialysis Patients Previously Treated with Epoetin," and

Protocol #AFX01-15, entitled "A Phase 2, Randomized, Active-controlled, Open-label, Multi-center Study of the Safety and Efficacy of AF37702 Injection for the Correction of Anemia in Patients with Chronic Renal Failure (CRF) Undergoing Hemodialysis and Not on Erythropoiesis Stimulating Agent (ESA) Treatment."

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Grome during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Bldg. 51, Rm. 5366  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

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/s/

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SUSAN LEIBENHAUT  
12/15/2011

## Scott, Trinh

---

**From:** Scott, Trinh  
**Sent:** Thursday, November 17, 2011 1:39 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** NDA 202799 - Information Request (SAS macro code)

Dear Diane,

Please provide the SAS code for the function/macro 'm\_chart3d'. This function/macro is called under your SAS code f-hgbr-pe2.sas.

Please submit this file by November 21, 2011. Please let me know if you have any questions.

Thank you,  
Trinh

---

Trinh Scott, M.S. | Regulatory Project Manager | Division of Hematology Products, CDER, FDA  
10903 New Hampshire Avenue, WO22, Room 2173 | Silver Spring, MD 20993  
 301.796.3311 (phone) • 301.796.9845 (fax) |  [trinh.scott@fda.hhs.gov](mailto:trinh.scott@fda.hhs.gov)

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/s/  
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TRINH N SCOTT  
11/17/2011

## Scott, Trinh

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**From:** Scott, Trinh  
**Sent:** Wednesday, November 02, 2011 2:10 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** NDA 202799 - Nonclinical Information Request

Dear Diane,

For NDA 202799, please respond to this nonclinical information request by Friday, November 4, 2011:

Please provide the mean human AUC at the highest recommended dose of the drug. This information is needed for animal-to-human exposure extrapolation.

Please let me know if you have any questions.

Sincerely,  
Trinh

---

Trinh Scott, M.S. | Regulatory Project Manager | Division of Hematology Products, CDER, FDA  
10903 New Hampshire Avenue, WO22, Room 2173 | Silver Spring, MD 20993  
 301.796.3311 (phone) • 301.796.9845 (fax) |  [trinh.scott@fda.hhs.gov](mailto:trinh.scott@fda.hhs.gov)

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/s/  
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TRINH N SCOTT  
11/02/2011



NDA 202799

**METHODS VALIDATION  
MATERIALS RECEIVED**

Affymax, Inc.  
Attention: Diane Ingolia, Ph.D.  
Senior Director, Regulatory Affairs  
4001 Miranda Ave.  
Palo Alto, CA 94304

Dear Ms. Diane Ingolia:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Peginesatide Injection, Prefilled Syringe, (b) (4) (b) (4) Vial (2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5mg/0.5mL, 6 mg/0.5) mL and (b) (4) Vials (10 mg/1 mL, 20 mg/2 mL (b) (4) and to our October 3, 2011, letter requesting sample materials for methods validation testing.

We acknowledge receipt on October 27, 2011, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire  
Team Leader  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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JAMES F ALLGIRE  
10/28/2011

**Scott, Trinh**

---

**From:** Scott, Trinh  
**Sent:** Friday, October 14, 2011 5:10 PM  
**To:** 'Ingolia, Diane'  
**Cc:** 'Conroy, Christine'  
**Subject:** NDA 202799 - CMC information request

Dear Diane,

I have the following CMC information request for NDA 202799:

It is noted that the (b) (4) in peptide mapping chromatograms in Figure 3 and Figure 70 appear to elute at a similar retention time (b) (4) for AF37702 (the drug substance) and (b) (4), respectively. Can the analytical method for total (b) (4) distinguish the (b) (4)

Please provide analytical results and a comparison chromatogram from the analysis of (b) (4) for AF37702 (drug substance), (b) (4) (b) (4) (b) (4) (b) (4) and (b) (4) and for SDV and MDV drug product.

Please respond by October 20, 2011. If that date is not possible, please let me know.

Thank you,  
Trinh

---

Trinh Scott, M.S. | [Regulatory Project Manager](#) | [Division of Hematology Products, CDER, FDA](#)  
10903 New Hampshire Avenue, WO22, Room 2173 | [Silver Spring, MD 20993](#)  
[301.796.3311](#) (phone) ● [301.796.9845](#) (fax) | [✉\\_trinh.scott@fda.hhs.gov](mailto:trinh.scott@fda.hhs.gov)

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/s/  
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TRINH N SCOTT  
10/14/2011



NDA 202799

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Affymax, Inc.  
Attention: Diane Ingolia  
Senior Director, Regulatory Affairs  
4001 Miranda Ave.  
Palo Alto, CA 94304

Dear Ms. Diane Ingolia:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Peginesatide Injection, Prefilled Syringe, (b) (4) Vial (2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5mg/0.5mL, 6 mg/0.5) mL and (b) (4) Vials (10 mg/1 mL, 20 mg/2 mL (b) (4))

We will be performing methods validation studies on Peginesatide Injection, (b) (4) Vial (2 mg/0.5 mL) mL and (b) (4) Vials (20 mg/2 mL), as described in NDA 202799.

In order to perform the necessary testing, we request the following sample materials and equipments:

**Current methods for (b) (4) Vials and (b) (4) Vials:**

AF37702-TS.ID Identification: RP HPLC Retention Time

AF37702-TS.CT Assay

**Current Methods for Drug Substance**

100137 Total Sulfoxidation

100133 Biopotency (ELISA)

**Samples**

30 vials- Peginesatide Injection 2 mg/0.5 mL (b) (4) Vials

30 vials- Peginesatide Injection 20 mg/2 mL (b) (4) Vials

100 mg - AF37702 Drug substance

**Reference Standards**

200 mg - AF37702 Reference Standard

100 mg - (b) (4) Reference Standard

200 mg - (b) (4) Reference Material

200 mg - (b) (4)

5 vials - AF37702 (b) (4)

50 mg - (b) (4) AF37702 API Lot # 12AD1

50 mg - (b) (4)

**Equipment and Reagents**



Send the MSDSs and Certificates of Analysis for the chemicals, reference standards and products.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: James F. Allgire  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email ([James.Allgire@fda.hhs.gov](mailto:James.Allgire@fda.hhs.gov)).

Sincerely,

*{See appended electronic signature page}*

James F. Allgire  
Team Leader  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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JAMES F ALLGIRE  
10/03/2011

**Akinsanya, Lara**

---

**From:** Akinsanya, Lara  
**Sent:** Tuesday, September 27, 2011 3:37 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Akinsanya, Lara; Scott, Trinh  
**Subject:** Information Request: Clinical Pharmacology/ NDA 202799 peginesatide

Dear Dr. Ingolia,

Please respond to the information request below by **noon on Friday, September 30, 2011** :

- **For Study AFX01\_104 and AFX01\_105, submit all the raw PK parameters in SAS file and resubmit Table 11 of both studies with Cmax, AUC(0-tlqc), AUC(0-inf) instead of dose normalized parameters.**

Thank You  
Lara

Lara Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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/s/  
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LARA M AKINSANYA  
09/27/2011



NDA 202799

**INFORMATION REQUEST**

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Affymax, Inc.  
Attention: Diane Ingolia, Ph.D.  
Senior Director, Regulatory Affairs  
4001 Miranda Ave  
Palo Alto, CA 94304

Dear Dr. Ingolia:

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

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)<sup>(w)</sup> 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.

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.

(b) (4)

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 your NDA. 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, call Janet Jamison, Regulatory Project Manager, at (301) 796-2313

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, M.D.  
Division Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Research and Evaluation

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/s/  
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ANN T FARRELL  
09/16/2011

## Scott, Trinh

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**From:** Scott, Trinh  
**Sent:** Wednesday, September 14, 2011 5:56 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** NDA 202799 - Stats Information Request

Dear Diane,

Regarding NDA 202799, we have the following information request. Please respond by Monday, September 19, 2011.

Please submit the time-to-event data sets and programs for the transfusion for study AFX01-12, AFX01-14, AFX01-11, AFX01-13 and AFX01-15 separately following the requests below:

1) Time-to-first event for the transfusion with indicator of different period: Titration period, Titration +Evaluation period and Evaluation Period only. Please also send your results for time to first transfusion using Cox PH model by different study period for review.

2) Time-to-multiple events for the transfusion using counting process for Titration + Evaluation period. The data sets should include the column of starting event time (tstart) and the column of event ending time (tstop) with the censor variable (Yes/No). Please also send your results using Andersen-Gill model of multiple transfusion for review.

All the data sets should include: demographics, baseline status and baseline disease characteristics, especially baseline Hgb value. Please also include mean of Hgb during Titration period, Titration +Evaluation period, and Evaluation period.

Please let me know if you have any questions or need additional time to respond.

Thank you,  
Trinh

---

Trinh Scott, M.S. | Regulatory Project Manager | Division of Hematology Products, CDER, FDA  
10903 New Hampshire Avenue, WO22, Room 2173 | Silver Spring, MD 20993  
☎ 301.796.3311 (phone) • 301.796.9845 (fax) | ✉ [trinh.scott@fda.hhs.gov](mailto:trinh.scott@fda.hhs.gov)

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/s/  
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TRINH N SCOTT  
09/14/2011



IND 063257  
NDA 202799

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Affymax, Inc.  
4001 Miranda Ave.  
Palo Alto, California 94304

ATTENTION: Anne-Marie Duliege, M.D., M.S.  
Chief Medical Officer

Dear Dr. Duliege:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act; and to your New Drug Application (NDA) dated May 23, 2011, received May 27, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Peginesatide (b) (4) Injection, (b) (4) vials (2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL); Prefilled syringes (1 mg/ 0.5 mL, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL); and (b) (4) vials (10 mg per 1 mL solution and 20 mg per 2 mL).

We also refer to your March 1, 2011, IND correspondence, received March 2, 2011; and to your June 22, 2011, NDA correspondence, received June 23, 2011, requesting review of your proposed proprietary name, Omontys.

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

The proposed proprietary name, Omontys, 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 June 22, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions, call Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology (OSE), at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Trinh Scott at (301) 796-3311.

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  
08/29/2011

**Scott, Trinh**

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**From:** Scott, Trinh  
**Sent:** Friday, August 19, 2011 6:26 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** RE: Draft patient narrative (NDA 202799)

Dear Diane,

The team believes that your example narrative is understandable and should be very helpful. Therefore, we would not need a teleconference to discuss the example.

I understand that you may not be able to submit the Excel spreadsheet electronically, but you should submit the complete patient narratives electronically to the NDA as a response to the Information Request.

As a reminder, I will be away between August 22 and September 2. I won't have access to phone or email, so if there is anything that cannot wait until my return on September 6, please contact these project managers who will be covering me for on these dates:

August 22-23: Amy Baird (301-796-3338)  
August 24-26: Marcus Cato (301-796-3909)  
August 29-Sept 2: Diane Leaman (301-796-1424)

Thank you, and I hope you have a great weekend.

Sincerely,  
Trinh

---

Trinh Scott, M.S. | Regulatory Project Manager | Division of Hematology Products, CDER, FDA  
10903 New Hampshire Avenue, WO22, Room 2173 | Silver Spring, MD 20993  
☎ 301.796.3311 (phone) • 301.796.9845 (fax) | ✉ [trinh.scott@fda.hhs.gov](mailto:trinh.scott@fda.hhs.gov)

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**From:** Ingolia, Diane [[mailto:Diane\\_Ingolia@Affymax.com](mailto:Diane_Ingolia@Affymax.com)]  
**Sent:** Friday, August 19, 2011 4:31 PM  
**To:** Scott, Trinh  
**Cc:** Conroy, Christine  
**Subject:** Draft patient narrative

Dear Trinh,

Attached please find an example patient narrative provided as a pdf containing hyperlinks to related documents for this example patient. The hyperlinks are provided to illustrate the linking we propose for the patient narratives for Studies AFX01-12 and AFX01-14. We have also included an Excel spreadsheet which may be a helpful tool to allow reviewers to sort on potential CSE events. Please keep in mind that these documents are sample drafts and will be finalized and fully quality checked once we know that this will meet the needs of the reviewers.

Explanatory text is provided on the page preceding the patient narrative and on the first tab on the Excel spreadsheet. We welcome the opportunity to discuss these samples with the review team. Please let us know if Drs. Dmytrijuk, Kane, and Robie Suh would like to have a teleconference to discuss our examples. Alternatively, if they do not believe a teleconference is necessary and that the attached spreadsheet is a useful tool and that the narrative example presented is acceptable, please let us know and we will proceed to complete the work related to this request.

I hope you have a great vacation. Please keep in mind that I will be out of the office on Monday and Tuesday of next week (August 22 and 23), so any response to this message on these days should be send directly to Christine Conroy (christine\_conroy@affymax.com; cell phone: 650-387-6706).

Kind regards,

Diane

Diane Ingolia, Ph.D.  
Senior Director, Regulatory Affairs  
Affymax, Inc.  
4001 Miranda Avenue  
Palo Alto, CA 94304  
Phone: 650-812-8746

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/s/  
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TRINH N SCOTT  
08/19/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information	
NDA # 202799	
Proprietary Name: Omontys (pending) Established/Proper Name: Peginesatide Dosage Form: Solution (for injection) Strengths: 2 mg, 3 mg, 4 mg, 5 mg, and 6 mg in (b)(4) vials; 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, and 6 mg in pre-filled syringes; 10 mg and 20 mg in (b)(4) vials	
Applicant: Affymax, Inc. Agent for Applicant (if applicable):	
Date of Application: May 27, 2011 Date of Receipt: May 27, 2011	
PDUFA Goal Date: March 27, 2012	Action Goal Date (if different):
Filing Date: July 26, 2011	Date of Filing Meeting: July 12, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) : 1	
Proposed indication(s)/Proposed change(s): Treatment of anemia in adult patients for chronic renal failure on dialysis	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>            and refer to Appendix A for further information.</i>	
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>  - ONDQA sent consult to CDRH and OC Combination Products on 6/24/11	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): 63257, 102846				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			Emailed Document Room 7/19/11 to change review type from Priority to Standard.
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			Emailed Document Room 7/19/11 to change review type from Priority to Standard.
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at:  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>				
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>				
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	Not required for this drug.

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			PeRC is scheduled for January 25, 2012.
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>		X		

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>	X			
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>	X			
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>	X			Per DepDir for Safety's advice, DRISK consult will be requested after Mid-Cycle.
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	X			QT/IRT (7/11/11); CDRH (6/24/11)
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s) <b>Date(s):</b> 2/1/2007 – CMC; 2/23/2007 - Nonclinical  <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 10/21/2010  <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> SPA-Carcinogenicity: Agreement (1/30/2008) SPA-Stability: No Agreement (5/2/2008)  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** July 12, 2011

**BLA/NDA/Supp #:** NDA 202799

**PROPRIETARY NAME:** Omontys

**ESTABLISHED/PROPER NAME:** Peginesatide

**DOSAGE FORM/STRENGTH:** Solution for Injection;  
Strengths: 2 mg, 3 mg, 4 mg, 5 mg, and 6 mg in (b) (4) vials;  
1 mg, 2 mg, 3 mg, 4 mg, 5 mg, and 6 mg in pre-filled syringes;  
10 mg and 20 mg in (b) (4) vials.

**APPLICANT:** Affymax, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Treatment of anemia for chronic renal failure for adult patients on dialysis.

**BACKGROUND:** Peginesatide (AF37702) is a synthetic, PEGylated dimeric peptide that binds specifically to and activates the erythropoietin receptor. It is an erythropoiesis-stimulating agent (ESA). The PK/PD characteristics allow doses to be administered monthly with similar intravenous or subcutaneous doses. It is **not** indicated for the treatment of anemia in CRF patients not on dialysis or for the treatment of anemia due to cancer chemotherapy.

Referenced IND 63257 has been Active since May 2005; IND 102846 has been Active since July 2008.

End-of-Phase 2 meeting: February 1, 2007 (CMC); February 23, 2007 (Nonclinical)

Pre-NDA meeting: October 21, 2010

SPA-Carcinogenicity: Agreement (January 30, 2008)

SPA-Stability: No Agreement (May 2, 2008)

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Trinh Scott	Y
	CPMS/TL:	Janet Jamison	Y
Cross-Discipline Team Leader (CDTL)	Kathy Robie Suh		Y
Clinical	Reviewer:	Andrew Dmytrijuk	Y

	TL:	Kathy Robie Suh	Y
Biopharmaceutics	Reviewer:	Kareen Riviere	Y
	TL:	Angelica Dorantes	Y
Biopharmaceutics	Reviewer:	Justin Earp	Y
	TL:	Christine Garnett	N
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Young-Jin Moon	Y
	TL:	Julie Bullock	Y
Biostatistics	Reviewer:	Qing Xu	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kimberly Ringgold	Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Li Shan Hsieh	Y
	TL:	Sarah Pope	N
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Steven Fong	Y
	TL:	Jim McVey	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Anthony Orenca	Y
	TL:	Lauren Iacono-Connor	Y
OSE/DMEPA (proprietary name)	Reviewer:	Yelena Maslov	Y
	TL:	Zachary Oleszczuk	N
OSE/DRISK (REMS)	Reviewer:		
	TL:	Mary Dempsey	N
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	CDRH: Mary Brooks/James Chapman DDMAC: James Dvorsky		N

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b> Will be going to ODAC. Two available dates (TBD): December 7-8, 2011 or February 8-9, 2012.</p> <p><b>If no, for an original NME or BLA application, include the reason. For example:</b></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> Information request to provide supporting data for animal-to-human exposure ratios for pregnancy and carcinogenicity, as listed in the labeling.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b> CMC will follow-up</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b> IR for details of preservative effectiveness validation of the (b) (4) phenol added to the multi-dose drug product formulation.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b> CMC will follow-up</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Richard Pazdur, M.D., OODP Office Director</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p>STAMP DATE: May 27, 2011  DAY 74: August 9, 2011  MID-CYCLE: October 27, 2011  LABELING: Start soon after Mid-Cycle meeting; 5-7 meetings  ODAC: December 7-8, 2011 <u>or</u> February 8-9, 2012 (pending)  PRIMARY REVIEWS DUE: January 31, 2012 (8 weeks before Action)  SECONDARY REVIEWS DUE: February 7, 2012  WRAP-UP: approx. January 31, 2012  PDUFA GOAL DATE: March 27, 2012 (Standard review)</p> <p>Comments:</p>	
<p><b>REGULATORY CONCLUSIONS/DEFICIENCIES</b></p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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/s/  
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TRINH N SCOTT  
08/10/2011



NDA 202799

**FILING COMMUNICATION**

Affymax, Inc.  
Attention: Ann-Marie Duliege, M.D., M.S.  
Chief Medical Officer  
4001 Miranda Avenue  
Palo Alto, CA 94304

Dear Dr. Duliege:

Please refer to your New Drug Application (NDA) dated May 27, 2011, received May 27, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Peginesatide Injection.

We also refer to your amendments dated June 8, July 13, 18, 27, and 28, 2011.

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 27, 2012.

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, midcycle, 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 January 27, 2012.

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

**Clinical:**

1. Results of studies AFX01-11 and AFX01-13 in non-dialysis CRF patients suggest that safety of peginesatide relative to darbepoetin may be worse. Any implication these findings might have for the hemodialysis population will be a review issue.

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 respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We also request that you submit the following information:

**Pharmacology/Toxicology:**

- Please provide animal-to-human exposure ratios for pregnancy (section 8.1) and carcinogenicity (section 13.1) studies included in the label. Provide supporting data (i.e. the animal and human AUC values and the study numbers) for proposed ratios.

**Clinical:**

- Supply a narrative summary for each patient that had a composite safety endpoint event for studies AFX01-12, AFX01-14.

**LABELING**

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Highlights:

- Highlights limitation statement should be bolded and be placed on the line immediately beneath the heading.
- The drug name should be followed by dosage form and route of administration on one line. [See 21 CFR 201.57(a)(2)].
- Drug name, dosage form and route of administration statement under the Highlights limitation statement should be bolded.
- In the Warnings and Precautions section, list the warnings and precautions in decreasing order of importance (i.e. reflecting the relative public health significance).

Full Prescribing Information: Contents:

- The Table of Contents subsection headings must be indented.

We request that you resubmit labeling that addresses these issues by August 26, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

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

If you have any questions, contact Trinh Scott, Regulatory Project Manager, at (301) 796-3311 or [Trinh.Scott@fda.hhs.gov](mailto:Trinh.Scott@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, M.D.  
Acting Director  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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ANN T FARRELL  
08/09/2011

**Scott, Trinh**

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**From:** Scott, Trinh  
**Sent:** Tuesday, July 26, 2011 4:34 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** RE: NDA 202,799 - Day 60 communication

Dear Diane,

Yes, we are filing the NDA. We do have a couple of comments that will be listed in the Day 74 letter (August 9).

Best regards,  
Trinh

---

Trinh Scott, M.S. | Regulatory Project Manager | Division of Hematology Products, CDER, FDA  
10903 New Hampshire Avenue, WO22, Room 2173 | Silver Spring, MD 20993  
☎ 301.796.3311 (phone) • 301.796.9845 (fax) | ✉ [trinh.scott@fda.hhs.gov](mailto:trinh.scott@fda.hhs.gov)

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**From:** Ingolia, Diane [mailto:[Diane\\_Ingolia@Affymax.com](mailto:Diane_Ingolia@Affymax.com)]  
**Sent:** Tuesday, July 26, 2011 2:39 PM  
**To:** Scott, Trinh  
**Cc:** Conroy, Christine  
**Subject:** NDA 202,799 - Day 60 communication

Dear Trinh,

I wanted to follow-up on a voicemail message I left for you earlier today. At the Applicant Orientation Meeting last week you indicated that you would let us know by email whether the NDA has been accepted for filing on Day 60 (26 July). We'd appreciate hearing from you today.

Kind regards,

Diane

Diane Ingolia, Ph.D.  
Senior Director, Regulatory Affairs  
Affymax, Inc.  
4001 Miranda Avenue  
Palo Alto, CA 94304  
Phone: 650-812-8746

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/s/  
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TRINH N SCOTT  
07/27/2011

## Scott, Trinh

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**From:** Scott, Trinh  
**Sent:** Monday, July 25, 2011 3:08 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** NDA 202799 - IRT/QT information request 7/25/11

Dear Diane,

For NDA 202799 (Peginesatide), please provide information for the below request by July 29, 2011 (both email to me and a formal submission to the NDA):

- ECG analysis dataset. The ECG analysis dataset is the average of triplicate ecgs from EG.XPT and should include values for all parameters (QTCl, QTcB, QTcF, QT, PR, HR, QRS, RR), single delta for all parameters (change from baseline) and information of period, nominal day, nominal time point. Please be sure to have QTcI calculated and provide us QTcI coefficient bi for each subject.
- A mapping file between USUBJID (in EG.XPT dataset) and ECG warehouse subject ID or update EG.XPT with ECGID information (the 7 digit found in ECG filename like 2714315, 2918948 )

The primary end point is QTcI but there is no QTcI in the datasets. In your response, please reference the date of this information request.

Thank you,  
Trinh

---

Trinh Scott, M.S. | Regulatory Project Manager | Division of Hematology Products, CDER, FDA  
10903 New Hampshire Avenue, WO22, Room 2173 | Silver Spring, MD 20993  
☎ 301.796.3311 (phone) • 301.796.9845 (fax) | ✉ [trinh.scott@fda.hhs.gov](mailto:trinh.scott@fda.hhs.gov)

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/s/

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TRINH N SCOTT  
07/25/2011

**Scott, Trinh**

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**From:** Scott, Trinh  
**Sent:** Friday, July 22, 2011 2:03 PM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** RE: NDA 202799 - information request 7/22/11

Hi Diane,

Sorry I didn't clarify. Please both email to me and send a copy to the NDA.

Thank you,  
Trinh

---

Trinh Scott, M.S. | Regulatory Project Manager | Division of Hematology Products, CDER, FDA  
10903 New Hampshire Avenue, WO22, Room 2173 | Silver Spring, MD 20993  
☎ 301.796.3311 (phone) • 301.796.9845 (fax) | ✉ [trinh.scott@fda.hhs.gov](mailto:trinh.scott@fda.hhs.gov)

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**From:** Ingolia, Diane [mailto:[Diane\\_Ingolia@Affymax.com](mailto:Diane_Ingolia@Affymax.com)]  
**Sent:** Friday, July 22, 2011 2:01 PM  
**To:** Scott, Trinh  
**Cc:** Conroy, Christine  
**Subject:** RE: NDA 202799 - information request 7/22/11

Dear Trinh,

Thanks for your email. Can I clarify if you want the response only by email to you or both by email to you and a copy to the NDA?

Have a good weekend,

Diane

Diane Ingolia, Ph.D.  
Senior Director, Regulatory Affairs  
Affymax, Inc.  
4001 Miranda Avenue  
Palo Alto, CA 94304  
Phone: 650-812-8746

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**From:** Scott, Trinh [mailto:Trinh.Scott@fda.hhs.gov]  
**Sent:** Friday, July 22, 2011 10:59 AM  
**To:** Ingolia, Diane  
**Cc:** Conroy, Christine  
**Subject:** NDA 202799 - information request 7/22/11  
**Importance:** High

Dear Diane,

For NDA 202799 (Peginesatide), please complete the attached Highlights of Clinical Pharmacology form and email back to me as soon as possible.

Thank you, and have a nice weekend.

Best regards,  
Trinh

---

Trinh Scott, M.S. | Regulatory Project Manager | Division of Hematology Products, CDER, FDA  
10903 New Hampshire Avenue, WO22, Room 2173 | Silver Spring, MD 20993  
 301.796.3311 (phone) • 301.796.9845 (fax) |  [trinh.scott@fda.hhs.gov](mailto:trinh.scott@fda.hhs.gov)



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## Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C <sub>max</sub> and AUC
	Multiple Dose	Mean (%CV) C <sub>max</sub> and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	T <sub>max</sub>	<ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul>
Distribution	V <sub>d</sub> /F or V <sub>d</sub>	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C <sub>max</sub> and AUC
	Sex	Specify mean changes in C <sub>max</sub> and AUC
	Race	Specify mean changes in C <sub>max</sub> and AUC
	Hepatic & Renal Impairment	Specify mean changes in C <sub>max</sub> and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C <sub>max</sub> and AUC
	Food Effects	Specify mean changes in C <sub>max</sub> and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical	Describe worst case scenario and expected fold-change in C <sub>max</sub> and	

Exposure Scenario	AUC. The increase in exposure should be covered by the supra-therapeutic dose.
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/s/  
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TRINH N SCOTT  
07/22/2011

## Scott, Trinh

---

**From:** Scott, Trinh  
**Sent:** Thursday, July 14, 2011 11:05 AM  
**To:** 'Ingolia, Diane'  
**Cc:** Conroy, Christine  
**Subject:** NDA 202799 - Information Request

**Follow Up Flag:** Follow up  
**Due By:** Tuesday, July 19, 2011 9:00 AM  
**Flag Status:** Flagged

Dear Diane,

Please refer to your New Drug Application (NDA) submitted on May 27, 2011 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Peginesatide (AF37702) Injection.

Regarding the filing of your submission, we request the following information or reference to its location in the Application:

1. Validation procedures, acceptance criteria and data demonstrating preservative effectiveness of the (b) (4) phenol added to the (b) (4) drug product formulation. Submission Section 3.2.P.2.1 states the rationale for selection of phenol (b) (4) and notes that its inclusion in the formulation satisfied the requirements of USP <51>. However, details of (b) (4) validation were not presented.
2. Validation procedures, acceptance criteria and data supporting container closure integrity of the pre-filled syringe (PFS). Container closure validation was presented in Submission Section 3.2.P.2.4 for the s (b) (4) (b) (4) vial, but not for the PFS.
3. For Study Protocol AFX01-15:
  - a. Provide the most current contact information (principal investigator name, clinical investigational site number, number of patients enrolled at that site, complete mailing address, phone number, fax and e-mail, and sub-investigators under each principal investigator).
  - b. Provide patient data listings by principal clinical investigator and site, to include at least the following information:
    - i) randomization code/scheme,
    - ii) subject discontinuation status,
    - iii) prior concomitant and prohibited medications,
    - iv) adverse events including deaths or serious adverse events as applicable,
    - v) primary efficacy endpoint,
    - vi) secondary endpoints,
    - vii) protocol deviations.
4. Provide the most current information (full address, contact person, most responsible person, phone number, fax and e-mail) of the Contract Research Organization/clinical site monitor, (b) (4)
5. Provide full address and contact person where Sponsor's data reside for a FDA audit of NDA 202799.

Please send your response by 10:00 AM (EST), July 19, 2011. In addition to submitting a formal response to the NDA, please email a courtesy copy to me.

Thank you, and if you have any questions, feel free to call or email me.

Sincerely,  
Trinh

10903 New Hampshire Avenue, WO22, Room 2173 | Silver Spring, MD 20993

 301.796.3311 (phone) • 301.796.9845 (fax) |  [trinh.scott@fda.hhs.gov](mailto:trinh.scott@fda.hhs.gov)

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TRINH N SCOTT  
07/14/2011



NDA 202799

**APPLICANT ORIENTATION PRESENTATION**

Affymax, Inc.  
Attention: Ann-Marie Duliege, M.D., M.S.  
Chief Medical Officer  
4001 Miranda Avenue  
Palo Alto, CA 94304

Dear Dr. Duliege:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act dated December 1, 2010 for AF37702 (Peginesatide) Injection.

This is an application orientation meeting for you to present your development status of AF37702. Please provide an electronic copy of the slides by July 14, 2011 and submit it as a formal submission to the NDA. Also, please structure your presentation for approximately 45 minutes, leaving 15 minutes for questions and answers. Your presentation should summarize the data that you are relying on to support market approval.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting. The meeting is scheduled as follows:

**Date:** July 18, 2011  
**Time:** 10:30 AM – 12:00 PM (Eastern Standard Time)  
**Location:** FDA/CDER  
White Oak Building 22, Room 2205  
10903 New Hampshire Avenue  
Silver Spring, MD 20903

**CDER participants:** Richard Pazdur, M.D., Office Director  
Ann Farrell, M.D., Acting Director  
Robert Kane, M.D., Acting Associate Director for Safety  
Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader  
Andrew Dmytrijuk, M.D., Clinical Reviewer  
Haleh Saber, Ph.D., Pharmacology/Toxicology Team Leader  
Kimberly Ringgold, Ph.D., Pharmacology/Toxicology Reviewer  
Julie Bullock, Pharm.D., Clinical Pharmacology Team Leader  
Young Jin Moon, Ph.D., Clinical Pharmacology Reviewer  
Sarah Pope, Ph.D., Chemistry Team Leader  
Li-Shan Hsie, Ph.D., Chemistry Reviewer

James McVey, Ph.D., Microbiology Team Leader  
Stephen Fong, Ph.D., Microbiology Reviewer  
Angela Dorantes, Ph.D., Biopharmaceutics Team Leader  
Kareen Riviere, Ph.D., Biopharmaceutics Reviewer  
Mark Rothmann, Ph.D., Biostatistics Team Leader  
Qing Xu, Ph.D., Biostatistics Reviewer  
Tamy Kim, Pharm.D., Associate Director for Regulatory Affairs  
Janet Jamison, R.N., CCRP, Chief, Project Management Staff  
Diane Leaman, Safety Regulatory Project Manager  
Trinh Scott, MS, Regulatory Project Manager

Please email me any updates to your attendees at [Trinh.Scott@fda.hhs.gov](mailto:Trinh.Scott@fda.hhs.gov), at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Trinh Scott, 796-3311; Brent Adkins, 796-1366.

If you are submitting background information for the presentation, send three paper copies or one electronic copy to the application and 30 desk copies to me) at least three days prior to the meeting.

Submit the 30 desk copies to the following address:

If sending via USPS, please send to:

Trinh Scott  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 2173  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20993

If sending via any carrier other than USPS  
(e.g., UPS, DHL), please send to:

Trinh Scott  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 2173  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20903

If you have any questions, please contact me at [Trinh.Scott@fda.hhs.gov](mailto:Trinh.Scott@fda.hhs.gov) or (301) 796-3311.

Sincerely,

*{See appended electronic signature page}*

Trinh Scott, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

ENCLOSURE: Foreign Visitor Data Request Form

## FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	July 18, 2011; 10:30 AM (EST)
MEETING ENDING DATE AND TIME	July 18, 2011; 12:00 PM (EST)
PURPOSE OF MEETING	Applicant Orientation Presentation
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	White Oak Building 22, Conference Room: 2205
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Trinh Scott Regulatory Project Manager CDER/OODP/DHP WO 22, Room 2173 (301) 796-3311
ESCORT INFORMATION (If different from Hosting Official)	

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/s/  
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TRINH N SCOTT  
07/06/2011



NDA 202799

**NDA ACKNOWLEDGMENT**

Affymax, Inc.  
Attention: Ann-Marie Duliege, M.D., M.S.  
Chief Medical Officer  
4001 Miranda Avenue  
Palo Alto, CA 94304

Dear Dr. Duliege:

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: Peginesatide (AF37702) Injection

Date of Application: May 23, 2011

Date of Receipt: May 27, 2011

Our Reference Number: NDA 202799

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 26, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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 Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, please contact me at (301) 796-3311 or [Trinh.Scott@fda.hhs.gov](mailto:Trinh.Scott@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Trinh Scott, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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TRINH N SCOTT  
06/10/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 63,257

MEETING MINUTES

Affymax, Inc.  
Attention: Diane Ingolia, Ph.D.  
Senior Director, Regulatory Affairs  
4001 Miranda Avenue  
Palo Alto, CA 94304

Dear Dr. Ingolia:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AF37702 Injection (Hematide™).

We also refer to the meeting between representatives of your firm and the FDA on October 21, 2010. The purpose of the meeting was to review the results of the AF37702 Injection clinical development program, and to obtain FDA feedback on a number of issues related to the planned NDA submission.

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, please contact me at [Trinh.Scott@fda.hhs.gov](mailto:Trinh.Scott@fda.hhs.gov) or (301) 796-3311.

Sincerely,

*{See appended electronic signature page}*

Trinh Scott, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

Enclosure



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** October 21, 2010, 12:30 PM – 2:00 PM (EST)  
**Meeting Location:** WO, Building 22, Conference room 1309

**Application Number:** IND 63,257  
**Product Name:** AF37702 Injection  
**Indication:** For the treatment of anemia in patients with chronic renal failure (CRF), including patients on dialysis [REDACTED] (b) (4)

**Sponsor/Applicant Name:** Affymax, Inc.

**Meeting Chair:** Edvardas Kaminskas, M.D.  
**Meeting Recorder:** Trinh Scott, M.S.

**FDA ATTENDEES**

Division of Hematology Products

Julie Bullock, Pharm.D., Clinical Pharmacology Team Leader  
Edvardas Kaminskas, M.D., Deputy Director (Acting)  
Robert Kane, M.D., Deputy Director for Safety (Acting)  
Timothy Kropp, Ph.D., Pharmacologist/Toxicologist  
Diane Leaman, Safety Regulatory Project Manager  
Young Jin Moon, Ph.D., Clinical Pharmacology Reviewer  
Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader  
Mark Rothmann, Ph.D., Biostatistics Team Leader  
Haleh Saber, Ph.D., Pharmacology/Toxicology Team Leader  
Suzanne Robottom, Pharm.D., Team Leader, Division of Risk Management  
Trinh Scott, M.S., Regulatory Project Manager

**SPONSOR ATTENDEES**

Affymax, Inc.

Christine Conroy, Pharm.D., VP, Regulatory Affairs and Clinical QA, Affymax  
Anne-Marie Duliege, M.D., M.S., Chief Medical Officer, Affymax  
Carol Francisco, Ph.D., VP, Biostatistics and Data Management  
Diane Ingolia, Ph.D., Senior Director, Regulatory Affairs  
Martha Mayo, Pharm.D., Executive Director, Clinical Development  
Krishna Polu, M.D., Executive Director, Clinical Development

Kathryn Woodburn, Ph.D., Executive Director, Preclinical Development

Takeda

Richard Czerniak, Ph.D., Associate Director, Clinical Pharmacology

Binita Kwankin, Senior Director, Regulatory Strategy

Ping Qiu, M.D., Senior Medical Director

Other

(b) (4)



## 1. BACKGROUND

In a letter dated May 26, 2010, and received May 27, 2010, Affymax, Inc. requested a Pre-NDA meeting to review the results of the AF37702 Injection clinical development program, and to obtain FDA feedback on a number of issues related to the planned NDA submission. A meeting was scheduled for August 31, 2010; however, on July 22, 2010, Affymax requested, in an email, to reschedule the meeting to the week of October 18, 2010. FDA rescheduled the meeting to October 21, 2010.

On September 17, 2010, FDA received Affymax's meeting background package. On October 19, 2010, FDA sent Affymax, Inc., via e-mail, preliminary responses to the questions raised in the September 17, 2010 background materials (see questions and responses below). Affymax responded on October 20, 2010 with the order of preference for questions/responses/comments that they would like to discuss at the meeting. The order of preference for discussion was: 1a, 1c, 3, OODP's End of Phase 2 document, 9, 10, 11. Affymax also provided sponsor responses to FDA's preliminary response.

## 2. DISCUSSIONS

### **QUESTION 1**

*The pivotal clinical development program for AF37702 Injection was designed to evaluate AF37702 Injection for use in the treatment of anemia due to chronic renal failure (CRF), including treatment of patients on dialysis and patients not on dialysis. The program included two similarly designed Phase 3 studies in the treatment of anemia in CRF patients on dialysis who were switched from Epoetin therapy (AFX01-12 and AFX01-14) and two similarly designed Phase 3 studies in the treatment of anemia in CRF patients not on dialysis and not on ESA therapy (AFX01-11 and AFX01-13). A controlled Phase 2 study that had several of the same design features of the four Phase 3 studies evaluated the treatment of anemia in CRF patients on dialysis not on ESA treatment (AFX01-15). The program also included an evaluation of a cardiovascular composite safety endpoint (CSE) based on data pooled from all four Phase 3 studies, with pre-specified plans to then analyze the CSE by CRF sub-population (i.e., dialysis patients and non-dialysis patients).*

*The Sponsor's evaluation of data from these studies suggest a safety and efficacy profile for AF37702 Injection that will support registration for the treatment of anemia of CRF in the dialysis patient population. The safety and efficacy profile, and thus the risk-benefit profile, in anemia of CRF in the non-dialysis patient population are less clear. As a result, we have revised the registration plan for AF37702 Injection in CRF to focus the initial NDA submission on the treatment of anemia in the dialysis patient population.*

- a. *Based on efficacy and safety data in the dialysis studies (AFX01-12 and AFX01-14), as well as supportive efficacy and safety data from study AFX01-15, the Sponsor plans to submit an NDA for AF37702 Injection for the target indication "treatment of anemia in CRF patients on dialysis." Does FDA agree that the data and information from these studies in the dialysis patient population, as*

*summarized in the pre-meeting information package, appears to be sufficient in size and scope to support filing an NDA for the target indication?*

**FDA Response:**

The information outlined in the background package may be acceptable for submission of an NDA for use of AF37702 in CRF patients on hemodialysis. However, we are concerned that the studies conducted may not provide sufficient information to conclude that the studied dosing regimen is the most appropriate one for maximizing safe use of AF37702 in these patients. For instance, in spite of tiered dosing in Studies AFX01-12 and AFX01-14 and use of a 1-week washout period between prior ESA and study drug, 19%-26% of dialysis patients in the AF37702 arm experienced Hgb excursions above 13 g/dL and more than 80% experienced excursions above 12 g/dL. The fact that similar excursions were seen for the comparator does not provide comfort, considering the safety issues raised by results of recent studies (Normal Hematocrit, CHOIR and TREAT) of ESAs where target hemoglobins were above 12 g/dL. The FDA discussions of the planned AF37702 studies with the sponsor from February 2007 onward have emphasized the importance of demonstration of acceptable safety and recommended that where a placebo control is not possible, demonstration of superior safety to the comparator is recommended.

**Sponsor Response (10/20/10):**

This will be discussed with FDA in the meeting on October 21, 2010.

**Discussion (10/21/10):**

FDA reiterated concerns of review issues such as hemoglobin excursions above 13, amounts of missing data, and clear identification of the appropriate dose. Sponsor will provide additional analyses and other information in the NDA to address the concerns. The sponsor emphasized that they had prespecified cardiovascular events and analyses in the protocol for the studies. The sponsor understands that the decision to file is made after the application has been submitted. However, FDA comments that based on the information in the background package, there does not appear to be "on the face of it" any issues that would preclude filing at this time.

- b. *Does FDA have comments regarding potential or anticipated review issues with an NDA for AF37702 Injection targeting an indication for the treatment of anemia in CRF patients on dialysis?*

**FDA Response:**

Clear understanding of the dose and dosing regimen is a major consideration for approval of erythropoiesis stimulating agents in order to maximize safety. See response to 1.a.

There are some potential review issues that we may need to consider:

- 1). For the AFX01-12 study, 15% of subjects randomized to the experimental arm and 7% of subjects randomized to the control arm were excluded from the evaluation period. This missing data may undermine the confidence in the results of the trial.
- 2). Provide a justification of the non-inferiority margin for the mean change in hemoglobin.

**Sponsor Response (10/20/10):**

The Sponsor does not anticipate discussion in the meeting is needed. The following responses are provided for clarification.

- 1) We understand that this is a review issue. Sensitivity analyses will be submitted in the NDA to assess the robustness of the primary analysis result using different methods of imputing missing values.
- 2) Justification for margin of non-inferiority for the mean change in hemoglobin was based on both clinical and statistical rationales and was provided in S-059 (dated May 10, 2007) Section 14.11 Margin of Non-Inferiority for Efficacy Parameters in Information Package for Type A Meeting held June 14, 2007. Follow-up information was provided in S-061 (dated May 22, 2007) Additional Statistical Justification for Margin of Non-Inferiority. These rationales also will be provided in the NDA.

**Discussion (10/21/10):**

**No further discussion.**

- c. *Exploratory analyses the Sponsor has conducted or will conduct to better understand the data in the Phase 3 program are summarized in the pre-meeting information package. Are there additional analyses FDA suggests the sponsor include in the NDA in support of the target indication in dialysis patients?*

**FDA Response:**

The types of exploratory analyses of the data described in your background package appear appropriate and may be useful in evaluating the performance and safety of AF37702. Include analyses of safety and response based on maximum dose of the drug as well as rate of rise in hemoglobin levels.

Based on other ESA review experience, we suggest you perform some additional sensitivity or exploratory analyses which include:

**Primary and secondary efficacy endpoints**

- 1). Subgroup analysis of mean change in Hgb between Baseline and Evaluation period between 2 groups by baseline of eGFR<30 (Y/N).
- 2). Subgroup analysis of transfusion between 2 groups by eGFR<30 (Y/N).
- 3). Time to event analysis of transfusion using Cox model.

- 4). Subgroup analysis of mean change in Hgb between Baseline and Evaluation period between 2 groups by region
- 5). Subgroup analysis of transfusion between 2 groups by region

**Sponsor Response (10/20/10):**

No discussion during the meeting is needed. The requested analyses for the primary and secondary efficacy endpoints noted above will be provided in the NDA.

**Safety endpoints**

- 1). Descriptive analysis to compare “exposure length” between two arms.
- 2). Subgroup analysis of time to stroke by history of stroke.

**Sponsor Response (10/20/10):**

The Sponsor would like to clarify Safety request #1 in the meeting. In response to Safety request #2, we confirm that the requested analysis as described below will be included in the NDA.

**Safety request #1:** (Request for descriptive analysis to compare “exposure length” between two arms.). Table 5 on p. 33 of the pre-meeting briefing document summarizes total patient exposure (PEY) and average PEY/patient. In addition, total patient follow-up (PFY) and average PFY/patient are also provided in Table 5. Are there additional exposure summaries that FDA would like to see in the NDA?

**Discussion (10/21/10):**

**FDA requests the same exposure information broken down by IV and subcutaneous administration, as well as by region.**

**Safety request #2:** (Request for subgroup analysis of time to stroke by history of stroke). History of stroke (any type) was collected as a “yes/no” question on the eCRF. A subgroup of time to stroke (CSE component) by history of stroke analysis will be performed.

**Discussion (10/21/10):**

**We anticipate that we will have additional questions for you as we perform our review.**

d.

(b) (4)

**FDA Response:**



**Sponsor Response (10/20/10):**

Thank you, we will discuss this at another time.

**MEDICAL AND SAFETY - REMS**

***QUESTION 2***

*An overview of the Sponsor's planning for an anticipated REMS program for the use of AF37702 Injection in the treatment of anemia in dialysis patients with CRF is described in the pre-meeting information package. Does FDA have comments on the Sponsor's proposal for REMS as described in the pre-meeting information package, including the possibility of having an early planning meeting that includes representatives from the Office of New Drugs and the Office of Drug Safety that would be held during the NDA review process?*

**FDA Response:**

**Your proposed risk evaluation and mitigation strategy (REMS) does not provide sufficient detail for OND and OSE to determine that it will be adequate to meet FDAAA criteria and goals, and we have insufficient information to determine whether a REMS will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be.**

**A complete review of the proposed REMS, in conjunction with the full clinical review of the NDA will be necessary to determine whether the proposed REMS is acceptable, since additional information regarding benefits, risks and safe product use may emerge during the review of your NDA.**

**If you plan to submit a REMS with the original NDA submission, please submit all planned materials (e.g., proposed communication and education materials) identified within the plan that will be necessary to implement your proposal.**

In addition, we have the following high-level comments on the proposed REMS submitted as part of this meeting package. These comments should be considered as general advice only and cannot be considered final until a complete REMS review has been performed.

- Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.
- Product marketing materials generally are not appropriate to educate about product risks.
- At a minimum; we anticipate that the proposed REMS will require the same elements that are required for the ESAs indicated for the anemia secondary to CRF (i.e., a Medication Guide and communication plan).

We remind you that a proposed REMS will not be approved as a REMS unless and until the FDA determines that it is required to ensure that the benefits of the drug outweigh the risks and that it meets the FDAAA criteria.

We would be agreeable to a request for a meeting early in the review cycle after filing to discuss possible REMS. An appropriately timed meeting request should be submitted.

**Sponsor Response (10/20/10):**

Thank you for your comments. No discussion during meeting is needed. We will take your comments into consideration as we prepare and submit the NDA and look forward to further discussion during review. We appreciate your willingness to meet with us at an appropriate time during review to facilitate these discussions.

**Discussion (10/21/10):**

**No further discussion.**

**MEDICAL AND BIOSTATISTICS – INTEGRATED SUMMARIES**

***QUESTION 3***

*The strategy regarding the Integrated Summary of Safety (ISS), the Integrated Summary of Efficacy (ISE), and the Cardiovascular Composite Safety Endpoint (CSE) Technical Report are described in the pre-meeting information package. Does FDA have comments on these plans?*

**FDA Response:**

**In pooled analysis, variations among studies, such as different patient populations, should be addressed.**

**The sponsor should be aware that the overall usefulness of the ISS and ISE, however, is dependent on adequate and well-controlled individual trials with high**

**data quality as well as the balance between risk and benefit in an each of the individual trials.**

**Utility of the ISS will depend upon multiple factors including, the duration and thoroughness of patients' follow-up and data collection (especially for dose, hemoglobin levels, and adverse events), consistency of findings across the database, and potential impact of missing data.**

**Sponsor Response (10/20/10):**

Thank you for your comments. One point we would like to discuss and clarify during the meeting is the strategy for pooling patient populations in the ISS. The strategy was provided in the ISS SAP that was submitted in S-209 (dated 18 December 2009) for meeting that was scheduled for March 4, 2010. FDA provided pre-meeting comments that did not require further discussion and the meeting was cancelled. Following this feedback, the ISS SAP was revised to incorporate FDA comments (S-239 dated 28 May 2010). The Sponsor believes that the pooling strategy is still appropriate but because the FDA's review and feedback was prior to knowledge of the Phase 3 data and a decision to revise the registration strategy to include patients with CRF on dialysis only, we would like to reconfirm the acceptability of the pooling strategy. A slide depicting the pooling strategy is provided for discussion.

**Discussion (10/21/10):**

**The sponsor's ISS slide appears generally acceptable.**

***QUESTION 4***

*The Sponsor's plans for submission of Event Review Committee materials supporting blinded adjudication of CSE events are described in the pre-meeting information package. Does FDA have comments on these plans?*

**FDA Response:**

**Please include in the index a listing of patients with potential CSE events with a link to the individual CRFs.**

**Sponsor Response (10/20/2010):**

No discussion during the meeting is needed. The requested information will be provided in the NDA.

**Discussion (10/21/10):**

**No further discussion.**

**CLINICAL PHARMACOLOGY – DRUG-DRUG INTERACTIONS**

***QUESTION 5***

*Based on information provided in the pre-meeting information package, the Sponsor believes that the in vitro studies conducted following the recommendation of FDA at an End of Phase 2 meeting have adequately characterized the potential for a lack of expected drug interactions based on lack of interactions between cytochrome P450 enzymes (CYPs) and fragmented portions of AF37702, and that formal drug-drug interaction studies are not required. Does FDA agree?*

**FDA Response:**

**Yes, we agree based on the information provided in the meeting package.**

**Sponsor Response (10/20/2010):**

No discussion or further comment is needed.

**Discussion (10/21/10):**

**No further discussion.**

## **NONCLINICAL PHARMACOLOGY AND TOXICOLOGY**

### ***QUESTION 6***

*A summary of the nonclinical pharmacology and toxicology studies planned for inclusion in the NDA is provided in the pre-meeting information package. The nonclinical program meets the requirements for nonclinical testing set forth in ICH Guidance documents, including M3 (Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals). The Sponsor believes that the nonclinical package is adequate to support NDA filing for the proposed indication, and that no additional nonclinical studies are warranted at this time. Does FDA have any comments with regard to requirements for NDA filing or potential review issues?*

**FDA Response:**

**The nonclinical studies listed appear appropriate for filing of the NDA, but the adequacy of the studies will be a review issue. If you have study data tabulations in electronic format for your nonclinical studies, we encourage you to submit these files along with the full study reports in the NDA application.**

**Sponsor Response (10/20/2010):**

No discussion or further comment is needed.

**Discussion (10/21/10):**

**No further discussion.**

## **PEDIATRIC STUDIES**

### ***QUESTION 7***

*The pediatric development plan designed to meet the requirements of the Pediatric*

*Research Equity Act proposed for inclusion in the NDA is described in the pre-meeting information package. Does FDA have comments on the proposed pediatric development plan?*

**FDA Response:**

**It is premature to comment upon requirements and design for pediatric investigations of AF37702. You should include in your NDA submission a description of planned studies and requests for waiver and/or deferrals, as desired.**

**Sponsor Response (10/20/10):**

No discussion during meeting is needed. A description of planned studies and requests for waiver and/or deferrals will be included in the NDA. We also note that a protocol for the first study described in the deferral document in the pre-meeting information package will be submitted to the Takeda IND 102,846 and will start before submission of the NDA, because the study will also fulfill requirements of a European Pediatric Development Program.

**Discussion (10/21/10):**

**No further discussion.**

**FINANCIAL DISCLOSURE INFORMATION**

**QUESTION 8**

*The Sponsor's plan for inclusion of Financial Disclosure information is provided in the pre-meeting information package. Does FDA have comments on these plans?*

**FDA Response:**

**The plans appear acceptable.**

**Sponsor Response (10/20/10):**

No discussion or further comment needed.

**Discussion (10/21/10):**

**No further discussion.**

**ELECTRONIC DATASETS AND DATA LISTINGS**

**QUESTION 9**

*Plans for submission of SDTM datasets, ADaM datasets, and individual patient data listings for Phase 2 and Phase 3 clinical study reports are described in the pre-meeting information package. Does the FDA have comments on these plans?*

**FDA Response:**

**Datasets should have one and only one unique subject ID for each patient among all trials. One record should contain all data for one patient.**

**Variables used in the define datasets should be the same for all datasets so that sets can be combined or sorted as needed for cross study evaluations (i.e., one definition, well-annotated, per one variable).**

**All SAS programs that were used to create all of the efficacy and safety tables and figures should be included in the main test portion of the CSR. Please also provide all necessary macros and SAS utility programs. All programs should be thoroughly commented and have passed Sponsor's validation procedures.**

**Ensure the SAS dataset file name are consistent with those in the SAS programs that call them, so that the Agency can run the programs smoothly to verify the results/figures/tables reported in the submission.**

**Annotations for all efficacy and safety tables and figures should be included in the main test portion of the CSR. The annotations should indicate which analysis dataset variables were used to produce the table or figure.**

**Sponsor Response (10/20/10):**

The following are proposed for discussion in the meeting or in a follow-up teleconference:

9(a) We plan to submit with the NDA SDTM datasets for all Phase 2 and Phase 3 studies and ADaM datasets for the Phase 3 studies AFX01-11 through AFX01-14 and the later Phase 2 studies AFX01-15 (comparative initiation of treatment in hemodialysis), AFX01\_201 (peritoneal dialysis), and AFX01\_202 (switch from darbepoetin alfa). In addition, ADaM datasets will be submitted to support analyses conducted for the CSE, ISS and the ISE. Is this acceptable?

**Discussion (10/21/10):**

**Yes.**

9(b) We are following ADaM dataset guidance (Version 2.0). Following this guidance, some datasets include one record per subject (eg, subject-level ADaM dataset ADSL), while other time-dependent datasets have one record per time point (eg, ADaM laboratory dataset ADLB and ADaM dosing dataset ADEX). In all cases we have followed the principle of "one proc away" for analyses. As such, the data required to conduct the statistical analyses provided in the NDA are based on ADaM data sets and do not require merging of data files. Is the above described ADaM dataset format acceptable?

**Discussion (10/21/10):**

**Yes.**

9(c) We plan to submit SAS programs, including macros, that were used to create all of the primary and secondary efficacy results tables and figures included in the main text

portion of the following seven CSRs: Phase 3 studies AFX01-11 through AFX01-14, Phase 2 studies AFX01-15, AFX01\_201, and AFX01\_202. In addition, we plan to submit SAS programs, including macros, that were used to create the composite safety endpoint (CSE), ISS, and ISE tables and figures included in the main text portion of the these reports. Is this plan acceptable?

**Discussion (10/21/10):**

**Yes. The sponsor will also submit any programs that support numbers proposed for inclusion in the label.**

9(d) Dataset file names will be consistent with those in the SAS programs. Note: the libname statement in the programs will need to be modified by FDA to be consistent with where the FDA stores the datasets in their computing environment. Is this acceptable?

**Discussion (10/21/10):**

**Yes.**

9(e) SAS analysis programs were developed on a Sun Unix system and most likely would require minor modification by FDA to run on the computing system used by the FDA. Is this acceptable?

**Discussion (10/21/10):**

**Yes.**

9(f) Output from SAS programs used for analyses undergoes further processing to format the output as a Word table. For example, for the ISS and ISE, we obtain table titles and footnotes from an Excel spreadsheet that is converted to a CSV file by a SAS macro that calls a StarOffice macro on our Sun Unix server. Another SAS macro then merges the summary analysis output data with the title/footnote data to create an RTF file in Word. If the FDA does not have a similarly configured Unix server, they will be able to replicate results of analysis but not produce the formatted table. The Affymax analysis programs, that are proposed for inclusion in the NDA when run in the FDA computing environment, would be able to reproduce the content of the Affymax NDA tables, but may not reproduce formatting aspects of the tables. Is this acceptable?

**Discussion (10/21/10):**

**Yes. Sponsor will provide contact information of a person to provide technical guidance.**

Note: Affymax will provide technical support if run-time difficulties are introduced by running the SAS analysis programs on a different computer system.

9(g) We plan to provide ADaM dataset and variable documentation for the tables and figures described in item 9(c). The documentation will follow ADaM guidance for documentation of analysis results as described in Section 6 of the ADaM guidance

document (CDISC, Analysis Data Model: Version 2.0). Included in the documentation will be the following information for the tables and figures described in item 9(c):

**DESCRIPTION** – Table/Figure number and title

**REASON** – The high-level reason for performing the analysis.

**DATASET** – The name of the dataset(s) used in the analysis and the variables included in the analysis dataset(s) that were used in the analysis. This column may also include specific selection criteria so that the appropriate records from the analysis dataset(s) can be identified easily.

**DOCUMENTATION** – This column contains the information about how the analysis in the table or figure was performed.

Is the metadata file approach to documentation of analysis results presented in the tables and figures listed in item 9(c) acceptable?

**Discussion (10/21/10):**

**Sponsor will provide annotations for each table in the application.**

9(h) Would it be acceptable to submit ADaM datasets, analysis programs, and analysis results metafile documentation for a sample study prior to submission of the NDA?

**Discussion (10/21/10):**

**Sponsor will supply hyperlinks to data listings that support in-text tables in the CSRs.**

9(i) Data listings in individual study CSRs.

Individual patient data listings are included in all clinical study reports (CSRs). Data listings for AFX01-11 through AFX01-15 are based on the SDTM datasets and list the individual patient data that are important for analysis. The data listings exclude certain types of variables that are present in the raw data but not in the SDTM datasets, and in some cases exclude variables that are present in the SDTM datasets. Data excluded from the CSR listings fall into two categories:

- a. Data fields from the electronic case report form that are not included in SDTM datasets: These include variables that are data management/ data cleaning aids (e.g., for central laboratory specimen: “Was a specimen drawn?” <Yes/No>).
- b. Data fields included in SDTM datasets but analytically unimportant: Example data fields excluded from listings include:
  - i. The response to the electronic case report form question that relates to the first dose of study medication: “Is the dose administered the same as the IVRS calculated dose?” is not included in a patient data listing, as the determination of whether the first dose was administered per protocol (i.e., as computed by the IVRS) is a calculated variable.
  - ii. Dates are included, but not clock times for a number of variables (e.g., laboratory specimen draw times, phlebotomy time).

Are the data listings provided with the CSRs for studies AFX01-11 through AFX01-15 acceptable, given that SDTM and ADaM datasets for the Phase 3 studies are being submitted?

**Discussion (10/21/10):**

**It seems reasonable; if more information is needed about these items during the review, it will be requested.**

***QUESTION 10***

*As discussed in the pre-meeting information package, a sample display of analysis data model (ADaM) datasets that support the analyses presented in the ISS and CSE technical report were requested by FDA previously and are provided in the pre-meeting information package. Does FDA have comments on the display?*

**FDA Response:**

**Refer to the answer to question 9.**

**Sponsor Response (10/20/2010):**

For discussion during the meeting: We assume that the FDA is requesting the following for the tables and figures included in the main text portion of the CSE Technical Report and the ISS:

- (a) SAS analysis programs
- (b) ADaM metadataa
- (c) ADaM datasets used by the analysis programs

Is this understanding correct?

**Discussion (10/21/10):**

**Time did not permit further discussion of this question.**

***QUESTION 11***

*As discussed in the pre-meeting information package, the Sponsor plans to submit ADaM datasets in support of the ISE. No data listings for the ISE are planned. The ADaM datasets will be derived from the individual study SDTM and/or ADaM datasets. Does FDA have any comments on these plans?*

**FDA Response:**

**There are no further comments.**

**Sponsor Response (10/20/2010):**

For discussion during the meeting: We assume that the FDA is requesting the following for the tables and figures included in the main text portion of the ISE:

- (d) SAS analysis programs
- (e) ADaM metadataa
- (f) ADaM datasets used by the analysis programs

Is this understanding correct?

**Discussion (10/21/10):**

Time did not permit further discussion of this question.

**QUESTION 12**

*The Sponsor's plan to provide FDA with ECG data from Study AFX01\_101 (QTc study) is described in the pre-meeting information package. Does FDA have comments on this plan?*

**FDA Response:**

The Sponsor's plan to provide FDA with ECG data from the Study AFX01-101 (QTc study) is acceptable. Please also refer to the answer to question 10.

Furthermore, the following items should be submitted with your study report:

- Electronic copy of the study report
- Electronic or hard copy of the clinical protocol
- Electronic or hard copy of the Investigator's Brochure
- Annotated CRF
- Copies of the study reports for any other clinical QT study for this product that has been performed
- A Define file which describes the contents of the electronic data sets
- Electronic data sets as SAS transport files
- Please make sure that the ECG raw data set includes at least the followings: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, intervals (QT, RR, PR, QRS), HR, QTc [all corrected QT as end points, e.g. QTcB, QTcF, QTcI (including individual correction factor), or QTcN (including the correction factor)], Lead, ECG ID (link to waveform files if applicable).
- SAS code for the primary statistical analysis
- Data set whose QT/QTc values are the average of the replicates
- Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis
- Narrative summaries and case report forms for any of the following that occur in this thorough QT study:
  - 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.
- Submission of the related ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))
- A completed "HIGHLIGHTS OF CLINICAL PHARMACOLOGY" table (a template of this form is attached on the next page)

**Sponsor Response (10/20/2010):**

No discussion or further comment is needed.

**Discussion (10/21/10):**

No further discussion.

***ADDITIONAL COMMENTS***

Attached to the preliminary response is "*OODP's End-of-Phase 2 General Advice for Planned Marketing Applications*". You may refer to this document for additional advice to prepare the new drug application.

**Additional Clinical Pharmacology Comments**

In the appropriate clinical pharmacology sections of the eCTD include the following:

- **Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.**

**Sponsor Response (10/20/10):** No discussion during the meeting needed; the requested datasets will be provided.

**Discussion (10/21/10):**

No further discussion.

- **Provide a table listing of patients with renal or hepatic impairment who have received AF37702, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.**

**Sponsor Response (10/20/10):** The Sponsor does not anticipate that discussion during the meeting will be needed. The Sponsor plans to provide the requested information as part of the Population PK-PD dataset. The population PK-PD plan was reviewed by the Agency as part of the information package for a Type C meeting that was scheduled for 4 March 2010. The meeting was canceled due to the sufficiency of the pre-meeting responses dated 26 February 2010.

**Discussion (10/21/10):**

**No further discussion.**

**Sponsor Response (10/20/10):**

Reference is made to the OODP's "General Advice for Planned Marketing Applications" that was provided with the pre-meeting comments for the pre-NDA meeting scheduled on October 21, 2010. The Sponsor requests clarification on several points to ensure the Agency receives appropriate information in the NDA.

**Discussion (10/21/10):**

**No further discussion.**

**NDA/BLA Content and Format, CLINICAL, Studies, Data and Analyses #18 – Narratives**

As agreed upon at the 3 August 2009 meeting, the Sponsor is planning to provide CIOMS forms for deaths and other SAEs in AF37702 clinical study reports in lieu of text narratives. Text narratives will be provided for patients who discontinued due to AEs and for other clinically significant events that are not SAEs.

The Sponsor would like to confirm that this prior agreement remains acceptable with respect to provision of patient narratives in the NDA.

**Discussion (10/21/10):**

**Sponsor proposal is acceptable at this time. If additional clarification is required, it will be asked during the review.**

**NDA/BLA Content and Format, CLINICAL #11 – Standard MedRA Queries (SMQs)**

The Sponsor would like to note that the following SMQs will be used to identify adverse events of special interest for events other than death in the ISS are:

- Cerebrovascular disorders (identified using the Cerebrovascular Disorders SMQ)
  - Central nervous system haemorrhages and cerebrovascular accidents (identified using the Central Nervous System Haemorrhages and Cerebrovascular Accidents SMQ)
    - Haemorrhagic cerebrovascular conditions (identified using the Haemorrhagic Cerebrovascular Conditions SMQ)
    - Ischaemic cerebrovascular conditions (identified using the Ischaemic Cerebrovascular Conditions SMQ)
    - Other Central nervous system haemorrhages and cerebrovascular accidents (identified using the Central Nervous System Haemorrhages and

Cerebrovascular Accidents SMQ for terms not classified as Haemorrhagic or Ischaemic Cerebrovascular conditions)

- Other cerebrovascular disorders (identified using the Cerebrovascular Disorders SMQ for preferred terms not classified as Central Nervous System Haemorrhages and Cerebrovascular Accidents)
- Cardiac Failure (identified using the Cardiac Failure SMQ)
- Cardiac Arrhythmias (identified using the Cardiac Arrhythmias SMQ)
- Torsade de pointes/QT prolongation (identified using the Torsade de Pointes/QT Prolongation SMQ)
- Ischaemic Heart Disease (identified using the Ischaemic Heart Disease SMQ)
  - Myocardial infarction (identified using the Myocardial Infarction SMQ within the ischaemic Heart Disease SMQ)
  - Other ischemic heart disease including unstable angina (identified using the Ischemic Heart Disease SMQ for preferred terms not grouped in the Myocardial Infarction SMQ )
- Hypertension events of interest (identified using the preferred terms listed in Appendix 2 in the ISS SAP)
- All thromboembolic events (identified using the Embolic and Thrombotic Events SMQ)
  - Venous thromboembolic events (identified using the Embolic and Thrombotic Events, Venous SMQ)
  - Arterial thromboembolic events (identified using the Embolic and Thrombotic Events, Arterial SMQ)
  - Other thromboembolic events including vascular access thrombosis (identified using the Embolic and Thrombotic Events, Vessel Type Unspecified and Mixed Arterial and Venous SMQ)
- Convulsions (identified using the Convulsions SMQ)
- Infusion/injection related reactions (e.g. Infusion related reaction; Hypersensitivity; Drug hypersensitivity; Infusion site hypersensitivity; Injection site hypersensitivity; Infusion site urticaria; Injection site urticaria; Anaphylactic reaction; Anaphylactic shock)
- Malignancy-related adverse events (identified using the Malignant or Unspecified Tumours SMQ)

Do AE and SAE summaries based on these SMQs meet the Agency's request for information?

**Discussion (10/21/10):**

**They appear reasonable at this time. FDA will look more closely after the meeting and let the sponsor know promptly if changes are necessary.**

**NDA/BLA Content and Format, CLINICAL #9 – Quantitative Safety Analysis Plan (QSAP)**

The quantitative safety analysis plans (QSAPs) for the ISS and the composite safety endpoint (CSE) were submitted to the FDA on 18 December 2009 (IND 63,257/S-209) and feedback from the FDA was received in a letter dated 26 February 2010. The ISS and CSE QSAPs were modified in response to this feedback and resubmitted to FDA (S-239 dated 28 May 2010). In keeping with item 9 instructions, the ISS QSAP will be hyperlinked to the Data Monitoring Committee Charter and the Event Review Committee (ERC) charter that will be provided in Module 5 of the NDA. In addition, the CSE QSAP will be hyperlinked to the ISS QSAP. Is the hyperlinking strategy acceptable?

**Discussion (10/21/10):**

**They appear reasonable at this time.**

**NDA/BLA Content and Format, CLINICAL #5 – Datasets Used to Track Adjudications**

The Sponsor would like to note that CSE SDTM and ADaM datasets will be provided (see Question 9 above) in the NDA. These datasets contain the results of ERC adjudication of CSE events. Does this meet the Agency's request for information?

**Discussion (10/21/10):**

**The ERC Adjudication of CSE events which are carried out in a blinded fashion will be submitted separately and will be hyperlinked to individual case reports.**

**3. ISSUES REQUIRING FURTHER DISCUSSION**

None

**4. ACTION ITEMS**

None

**5. ATTACHMENTS AND HANDOUTS**

ISS\_Populations\_CAF\_HT final.ppt  
S0178\_Appendix\_9\_CIOMS\_for\_Narratives.pdf

# Populations Summarized in the ISS

## Population 1: All CRF Single-dose/Multiple-dose Studies

### Dialysis and Non-Dialysis

(AFX01-02, AFX01-03, AFX01-04, AFX01-06, AFX01-07, AFX01-09, AFX01-10, AFX01-15, AFX01\_201, AFX01\_202, AFX01-11, AFX01-12, AFX01-13, AFX01-14)

- AF37702 Injection (N=2,383)
- Reference (N=911)

## Population 2: All Phase 3 Studies

### Dialysis and Non-Dialysis

(AFX01-11, AFX01-12, AFX01-13, AFX01-14)

- AF37702 Injection (N=1,722)
- Reference (N=869)

## Population 3: All Phase 3 CRF patients not on dialysis

(AFX01-11, AFX01-13)

- AF37702 Injection Q4W (N=656)
  - AF37702 Injection 0.025 mg/kg Q4W starting dose (N=328)
  - AF37702 Injection 0.04 mg/kg Q4W starting dose (N=328)
- Darbepoetin alfa 0.75 mcg/kg Q2W starting dose (N=327)

## Population 4: All Phase 3 CRF patients on dialysis

(AFX01-12, AFX01-14)

- AF37702 Injection Q4W (N=1,066)
- Epoetin alfa/beta 1-3 times per week (N=542)

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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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TRINH N SCOTT  
11/19/2010

EDVARDAS KAMINSKAS  
11/20/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 63,257

Affymax, Inc.  
Attention: Christine Conroy, Pharm.D.  
Executive Director, Regulatory Affairs  
4001 Miranda Avenue  
Palo Alto, CA 94304

Dear Dr. Conroy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Hematide (AF37702) Injection.

We also refer to the teleconference between representatives of your firm and the FDA on February 23, 2007.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-2050.

Sincerely,

*{See appended electronic signature page}*

Hyon-Zu Lee, Pharm.D.  
Regulatory Health Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF TELECONFERENCE

**MEETING DATE:** February 23, 2007  
**TIME:** 11 AM – 12:30 PM  
**LOCATION:** Conference Room 1415 (White Oak)  
**APPLICATION:** IND 63,257  
**DRUG NAME:** Hematide (AF37702) Injection  
**TYPE OF MEETING:** End of Phase 2 meeting

**MEETING CHAIR:** Kathy Robie-Suh, M.D., Ph.D.

**MEETING RECORDER:** Hyon-Zu Lee, Pharm.D.

### **FDA ATTENDEES:**

#### Division of Medical Imaging and Hematology Products (DMIHP)

Rafel Rieves, M.D., Acting Division Director  
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader  
David Bailey, Ph.D., Pharmacology/Toxicology Reviewer  
Ravi Harapanhalli, Ph.D., Chemistry Team Leader  
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader  
Hao Zhu, Ph.D., Clinical Pharmacology Reviewer  
Jyoti Zalkikar, Ph.D., Statistics Team Leader  
Satish Misra, Ph.D., Statistics Reviewer  
Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager

### **EXTERNAL CONSTITUENT ATTENDEES:**

#### Affymax

Robert Naso, Ph.D., Executive V.P., Research & Development  
Anne-Marie, Duliege, M.D., M.S., V.P., Clinical, Medical, and Regulatory Affairs  
William Lang, M.D., Sr. Director, Clinical Research  
Julie Iwashita, B.S., Sr. Director, Clinical Operations  
Stephen Chang, Ph.D., Sr. Director, Biostatistics  
Kathryn Woodburn, Ph.D., Sr. Director, Preclinical Development  
Peter Schatz, Ph.D., Sr. Director, Biology,  
Christine Conroy, Pharm.D., Executive Director, Regulatory Affairs  
Zane Rogers, M.A., Manager, Regulatory Affairs

#### Consultants and others

(b) (4)

Ben Stockholm, Associate Director, Regulatory Affairs, Takeda (corporate partner)  
Mark Weinberg, M.D., Sr. Medical Director, Development, Takeda

## **BACKGROUND AND PURPOSE OF THE TELECONFERENCE:**

Affymax submitted an End of Phase 2 meeting request on December 21, 2006 to discuss plans for proceeding to Phase 3, the proposed Phase 3 registration plan, and to identify any additional information needed to support a marketing application for Hematide Injection in Chronic Kidney Disease (CKD).

## **SUMMARY OF THE TELECONFERENCE:**

Affymax started the discussion with their proposal based on the Agency's recommendations (faxed to Affymax on February 21, 2007) as follows:

### “Proposal to Incorporate a Primary Safety Evaluation in the Hematide Program

To address the FDA concerns expressed in the pre-meeting minutes that Hematide is not importantly inferior to currently available erythropoiesis stimulating agents (ESA), that safety be included as a major outcome assessment, and that hypothesis testing for safety be included in the program, Affymax proposes the following:

- To conduct a pooled analysis of the safety data from the four main controlled Phase 3 trials described in the briefing document (AFX01-11, 12, 13, and 14) by analyzing the incidence of a composite cardiovascular endpoint between the Hematide and comparators across these studies.
- The primary endpoint of the pooled safety analysis will be a composite cardiovascular endpoint (similar to the one in the CHOIR study) with events classified by a blinded, independent Event Review Committee (ERC).
- Although this assessment would not be a co-primary endpoint of any individual study, Affymax would consider this pooled safety analysis pivotal to approval.
- If the FDA is agreeable to this concept (composite cardiovascular endpoint, data generated by a blinded, independent ERC, pooled data from four Phase 3 controlled studies), Affymax would like to submit a detailed statistical analysis plan for this primary safety analysis as soon as possible. This plan will include hypotheses on incidence rates, anticipated power of the primary analysis, sensitivity analyses, subset analyses as appropriate (e.g., pre-dialysis and hemo-dialysis) with the intent of reaching concurrence with FDA on the acceptability of this plan to support an NDA.”

The Agency responded the following:

- Your proposal appears reasonable but it would depend on the adequacy of the statistical analysis plan. Also, we need sufficient experience and data for definitive demonstration for safety.
- We are particularly interested in the pre-dialysis patients for drug treatment effect and adverse reactions.

- The four studies have to be carefully designed and conducted, and sufficiently similar to ensure appropriateness of combining for pooled analysis. We will examine the differences between the patient populations across studies closely to determine the validity of the safety analysis based on pooled data.
- Our understanding is that you will propose decision making criteria for superiority hypothesis for safety.

Affymax responded as follows:

- We are planning to enroll 1100 patients to Hematide (600 patients on hemo-dialysis and 500 patients on pre-dialysis) and have 500 patients in the control patient pool (300 patients on hemo-dialysis and Epogen and 200 patients on pre-dialysis and Aranesp).
- We will submit a more detailed proposal with plan for hypothesis testing as well as justification of the power.

FDA responded as follows:

- You should submit your revised proposal with a detailed statistical analysis plan to the Agency for review.

In response to the questions in the January 18, 2007 background package, the following agreements were reached after the discussion. The format provides the firm's questions in italics followed by DMIHP in bolded font and the sponsor's response to FDA's response in regular font.

#### ***I. Medical/Clinical/Statistical***

- 1. As described in Section 4.1 of the briefing document, the proposed registration program for AF37702 Injection consists of three studies to evaluate correction of anemia and three studies to evaluate maintenance treatment of anemia. Together, these six studies are designed to support an indication for "treatment of anemia in patients with CKD, including patients on dialysis (b) (4)" Does FDA agree that the overall structure of the proposed registration program is adequate to support the proposed indication?*

#### **FDA Response:**

**We request that you revise the program to thoroughly evaluate the safety of your product, particularly in light of recent concerns of erythropoietin therapies with regard to cardiovascular risks in connection with target Hgb levels (CHOIR study). You need to demonstrate that your product is not importantly inferior in safety or efficacy to available products. Hence, it is essential that both safety and efficacy are the major outcomes from your clinical studies, including hypothesis testing for both safety and efficacy. For example, you may wish to consider the CHOIR study design as a template for one of your clinical studies. We do not regard the proposed registration program, as outlined in the briefing package, as acceptable to sufficiently evaluate the safety and efficacy of your product.**

**We note that the efficacy trials for both correction and maintenance are non-inferiority studies. Statistical aspects of the studies with regard to non-inferiority margins and other requirements of non-inferiority studies are critical. Results across studies must show consistency with regard to safety and efficacy in order to support the proposed indication.**

2. *Affymax is seeking comments from FDA on the design of Study AFX01-11. This study is as summarized in Section 4.3.1 of the briefing document and a draft study protocol provided in Appendix 6. In particular, does FDA agree with the design of AFX01-11 as a pivotal safety and efficacy study and have comments on the patient population, inclusion/exclusion criteria, endpoints, choice of darbepoetin alfa as the control treatment, dosing regimens of the test and control treatments, Hgb target and dosage adjustment criteria, definition of clinically meaningful response rate for correction of anemia, margin of non-inferiority, study duration, and the proposed statistical analysis plan as described in the protocol?*

**FDA Response:**

**See response to question 1. However, specific concerns with regard to the proposed study in the background package are as follows:**

- Your target Hgb for response/success should incorporate achievement of Hgb within an appropriate specified range (i.e., upper and lower boundaries specified). Excessive Hgb rise may confer additional safety risk. Provide discussion and justification for your proposed target Hgb range. Determination of response/success should also incorporate a measure of durability of response to demonstrate sustained beneficial effect of your drug during the study.**

The sponsor responded that the target Hgb would be 12 g/dL, and boundary of (b) (4), and asked for recommendation of the dose reduction point.

**FDA responded that Hgb should not exceed 12 g/dL, that excursions above 12 g/dL would be concerning. The major demonstrated treatment benefit of ESA is blood transfusion avoidance and benefit/risk needs to be considered in the study design.**

The sponsor responded that practically it would be very difficult to enroll and maintain patients in a narrow Hgb range of (b) (4)

**The Agency responded that we can consider and agree on the target Hgb. A lower Hgb boundary (b) (4) would be acceptable to the Agency**

Affymax inquired if frequency of dosing of every other week would be acceptable.

**The Agency responded that Aranesp has every other week dosing, and at the current time there is no objection to the proposed dosing schedule, but stated that the comparator should be consistent with the comparator product's label.**

Affymax proposed a starting dose of 0.04 mg/kg (b) (4)

FDA responded that the sponsor should submit a proposal and justification to the Agency for review.

- **Please clarify the rationale for your selection and definitions of your co-primary endpoints. Determination of efficacy should be based on statistical comparison of treatment effect between concurrent treatment groups. Success in both primary outcomes is needed in order to consider the trial a success.**

The sponsor agreed to propose statistical comparison of treatment effect between concurrent treatment groups for both co-primary endpoints.

- **Please note that analysis populations that preserve randomization (e.g., Intent To Treat (ITT)) offer highest level of evidence for treatment comparisons. We will treat ITT as the primary analysis population for both co-primary endpoints and look for consistency of results for the Per Protocol (PP) population. Particularly because this is a non-inferiority study, it will need to be conducted with a high level of excellence. Any discrepancies between the results for ITT and PP populations will need to be addressed.**

Sponsor agreed.

- **Please describe clearly the methods used to handle missing data in the protocol. Please propose several sensitivity analyses to assess the impact of missing data on the results.**

The sponsor agreed and stated that they will provide clarifications.

- **The stated 30% drop-out rate is too high. Please outline measures you plan to implement to minimize the amount of missing data due to drop-outs.**

The sponsor stated that lost to follow ups were high in the hemo-dialysis patients.

- **Please provide data to justify the selected non-inferiority margin. We strongly recommend utilizing a superiority design for at least one endpoint (either safety or efficacy) in the study to provide an assessment of “added value” of your product over the existing already approved products in this class.**

The sponsor stated that they will provide published data to justify the proposed non-inferiority margin. The sponsor stated that other than pure red cell aplasia (PRCA), there are no other superiority endpoints for safety.

- **The number of patients achieving a hemoglobin  $\geq$  13g/dL and the duration of time that these patients had hemoglobin levels  $\geq$  13g/dL should be analyzed as an exploratory endpoint. This applies to all studies in the clinical development program.**

Sponsor agreed.

- **Female patients should also have monthly negative serum HCG tests not only during the time of enrollment but also throughout the study. Female patients who become pregnant should be withdrawn from study treatment but followed for pregnancy outcome. This should also apply to all proposed studies.**

The sponsor stated that they did not expect occurrence in pregnant patients.

**Patients may become pregnant while taking Hematide and we need follow up safety data on these patients. Confirmatory studies should mirror the patient population that will receive the drug if approved.**

- **Patients receiving iron supplementation should be on stable doses throughout the study. The number of patients who require iron supplementation before and during the study should be analyzed separately as exploratory endpoints. This should also apply to all proposed studies.**

Sponsor agreed.

- **Clarify what role you anticipate measurement of C-reactive protein will play in clinical prescribing of your drug. Unless solidly justified, we request that you delete C-reactive protein aspects of your eligibility criteria.**

The sponsor responded that few patients have high C-reactive protein. Patients will not be excluded from participation in any pivotal study on the basis of C-reactive protein levels.

- **Lack of blinding may compromise the minimization of bias in the trial and complicate the interpretation of the study results. The impact of this on the utility of the study is a review issue.**

The sponsor stated that in practicality, it would be hard to remain blinded.

- **You should submit a final protocol for review.**

Sponsor agreed.

3. *Affymax is seeking comments from FDA on the design of Study AFX01-12. This study is summarized in Section 4.3.2 of the briefing document and a draft study protocol is provided in Appendix 7. In particular, does FDA agree with the design of AFX01-12 as a pivotal study safety and efficacy study and have comments on the patient population, inclusion/exclusion criteria, endpoints, dosing regimens of the test and control treatments, Hgb target and dosage adjustment criteria, choice of control, margin of non-inferiority, study duration, and the proposed statistical analysis plan as described in the draft protocol?*

**FDA Response:**

See response to question 1 and bullets 3 through 12 of the response to question 2 above.

- **Also, because we are concerned to limit excessive Hgb excursions as well as Hgb levels higher than needed to avoid blood transfusions, you should consider revising**

**your primary efficacy endpoint to include mean maximum Hgb excursion and incidence of out-of-target range Hgb values during the study.**

- **You should submit a final protocol for review.**

4. *In addition to Study AFX01-11 and Study AFX01-12, Affymax plans to conduct four additional registration studies that are intended to contribute patient data to the safety database, as well as to provide supportive evidence of efficacy (AFX01-13 and AFX01-14) and to provide additional information on which to make dosing recommendations in CKD sub-populations (AFX01-15 [REDACTED] (b) (4)). Based on information provided in Section 4.4 of the briefing document, and draft study synopses provided in Appendix 8, does FDA agree that these studies are sufficient to support their stated safety, efficacy, and dosing objectives?*

**FDA Response:**

- **While a persuasive demonstration of efficacy is essential, you must propose clinical studies that are powered to rule out the possibility that your product is importantly inferior in safety to available products. Your proposed studies do not sufficiently address this concern.**
- **For those studies where epoetin alfa and beta will be used as the comparator, you should ensure that there are generally equal numbers of patients who are using either drug.**

The sponsor stated that the majority of patients would be from U.S. and be on epoetin alfa.

- **For your studies AFX01-13 and AFX01-15, consider also bullets 3 through 12 of our response to question 2 above.**
- **Study AFX01-15 as currently designed cannot be used to evaluate efficacy as there is no control in the study. It may be considered exploratory.**

The sponsor stated that they would add a control group to study 15.

- **For your studies AFX01-14 and [REDACTED] (b) (4) consider also our response to question 3 above.**
- **You should submit final protocols for review.**

5. *Affymax plans to conduct open-label registration studies and proposes use of a blinded Event Review Committee (ERC) of cardiovascular and other clinically significant adverse events to provide an unbiased assessment of these events, as discussed in Section 4.2.6 of the briefing document. A draft charter for the Event Review Committee is provided in Appendix 9. Does FDA have comments on the Sponsor's plan to use an ERC, on the draft ERC charter, or on the implications of open-label studies on product labeling?*

**FDA Response:**

See response to question 1. Otherwise the use of an event review committee appears to be acceptable.

- As mentioned in the response to question 2, lack of blinding may compromise the minimization of bias in your trials and complicate the interpretation of your study results. The impact of this on the utility of the study is a review issue.

Sponsor agreed.

6. *The safety database that Affymax anticipates will be available at the completion of the proposed registration program for AF37702 Injection, including the number of patients exposed and the duration of the exposure, is provided in Section 4.5 of the briefing document. Does FDA have comments on the number of patients exposed and the duration of exposure anticipated in the CKD development program?*

**FDA Response:**

As noted above, you have not provided a sufficient program to assess the safety of your product. We suggest that you propose at least one major controlled, clinical study that uses a hypothesis-testing primary endpoint to assess safety. This endpoint may take the form of a co-primary endpoint, with an efficacy outcome as the other primary endpoint.

The sponsor agreed.

7. *Based on the information presented in Section 5.2 of the briefing document, Affymax believes that it is appropriate to defer the submission of pediatric use information until after approval of AF37702 Injection for any indication. Does FDA agree?*

**FDA Response:**

Your proposal for pediatric development of the drug and request for deferral of pediatric studies for any indication being sought should be included in your NDA submission. Lack of completed pediatric studies will not impact filing of an otherwise adequate NDA package or approval of the drug for use in adults if the NDA contains substantial evidence of efficacy and safety of the drug in adults.

## ***II. Clinical Pharmacology***

1. *The evaluation of the pharmacokinetics (PK) of AF37702 Injection has included PK data on normal healthy volunteers (IV), pre-dialysis patients (IV and SC), and dialysis patients (IV) as outlined in Appendix 3. Does FDA agree with the proposed PK data plan that Affymax anticipates in the CKD development program that is described in Appendix 3 (Section 1.6)?*

**FDA Response:**

The current PK plan is acceptable. However, we strongly suggest that you collect informative PK samples in the AFX01-11, AFX01-12, AFX01-15 and other clinical trials. Those PK sampling would allow further exploration of the exposure-response relationship following Hematide administration. This would provide more information for determining proper starting dose selection and dose adjustment during treatment.

The sponsor responded that they will submit an alternative proposal to the Agency for review.

2. *Based on the information presented in Section 5.3 of the briefing document, Affymax believes that drug interaction studies are not needed for AF37702 Injection. Does FDA agree?*

**FDA Response:**

**Your explanation of the metabolism of AF-37702 is reasonable.**

**However, based on the Agency's previous experience that some fragmented peptides inhibit metabolizing enzymes, inhibition/induction potential of fragmented portions of AF-37702 to CYP450 enzyme cannot be fully ruled out at present. It is recommended that you collect more information to support your request for waiver of drug interaction studies.**

The sponsor responded that they will provide more information to support for waiver of drug interaction studies, including results from in vitro CYP450 inhibition/induction studies and stability studies.

### **III. Nonclinical Pharmacology/Toxicology**

1. *Affymax has conducted a comprehensive non-clinical program, including primary and safety pharmacology studies, pharmacokinetic studies, genotoxicity studies, Segment I and II reproductive toxicology studies in rats and/or rabbits, and IV toxicology studies in rats and monkeys for up to 6 and 9 months, respectively. Subcutaneous bridging toxicology studies of 3 months in rats and 1 month in monkeys have also been conducted. A Segment III reproductive toxicology study is planned, a 2-year carcinogenicity study in rats is ongoing, and the specific type of carcinogenicity study to be conducted in mice is still to be agreed upon with FDA. An outline of the completed, ongoing, and planned non-clinical studies is provided in Section 6.0 and detailed information from these studies provided in Appendix 10. Does FDA agree that the non-clinical program is adequate to support a marketing application for AF37702 Injection by IV and SC administration for the proposed CKD indication?*

**FDA Response:**

**No.**

**That is a premature question. Upon evaluation of results of unreported and pending studies it may become necessary to conduct additional studies or collect additional data to resolve issues that may arise.**

**However, it appears that currently available information supports entry into Phase 3 clinical trials.**

The Sponsor confirmed that they were going to conduct a Segment III reproductive toxicology study, also that a 2-year carcinogenicity study in rats is ongoing. They indicated that they were planning to conduct a carcinogenicity study in transgenic mice and questioned whether that would be acceptable.

The Agency responded that the second carcinogenicity study could be conducted in transgenic mice and the protocol should be submitted under the SPA program.

#### **IV. Medical/Immunogenicity**

1. *The AF37702 immunogenicity testing scheme is summarized in Appendix 5. This scheme consists of an initial evaluation of serum specimens for the presence of antibodies specific for AF37702 using a two part qualitative ELISA ("AF37702 antibody detection direct ELISA"). The AF37702 antibody detection direct ELISA consists of an initial evaluation of serum specimens by ELISA for the presence of antibodies that bind to AF37702, followed by a specificity retest based upon immunodepletion with AF37702. Specimens found to contain antibodies specific for AF37702 are designated as positive. Specimens that are positive in the AF37702 antibody detection direct ELISA are then evaluated for AF37702-neutralizing titer in a functional cell-based assay, and also tested for cross-reactivity with recombinant human EPO (rHuEPO) using a radioimmunoprecipitation assay.*
  - a. *Methods and validation data supporting the versions of these methods used to support clinical development have been submitted for review as a separate IND amendment (see IND 63,257/S-046, dated January 17, 2007). Notification of whether FDA agrees with Affymax that these methods are acceptable for use in testing clinical samples in Phase 3 is requested. Affymax would like to discuss the time-frame in which FDA expects to review and comment on these data and methods.*

#### **FDA Response:**

##### **Clinical:**

**Clinically the tests appear reasonable. However, the acceptability of the plan depends upon CMC review of the information. See also CMC comment.**

##### **CMC:**

**We will provide our review and comments by the 1<sup>st</sup> week of March.**

- b. *The AF37702 antibody sampling and testing plan proposed for use in the registration studies is described in Section 4.2.8 of the briefing document. Does FDA agree with our plans for antibody testing of clinical samples as described?*

#### **FDA Response:**

**From clinical and CMC perspectives, the proposed sampling and testing plan appear to be acceptable.**

The Agency asked for clarification whether the biopotency and ELISA assays proposed for clinical sample testing are the same as those proposed for product release and stability. The sponsor clarified that the methods are the same for both product release/stability and for the testing of biological samples. The Agency stated that some of the points discussed during CMC-specific meeting held on February 1, 2007 should be considered for the bioassay of biological samples.

**Clinical Pharmacology additional comments:**

**AFX01-15 starting dose selection is based on the modeling and simulation study to bridge the information from AFX01-03 and AFX01-04 trials. We applaud your using modeling and simulation approach to link information from different patient populations. Please provide the rationale for assuming E max value for the patients in the coming AFX01-15 study to be 20% lower than the patient population with no dialysis (AFX01-04).**

**ACTION ITEMS:**

Affymax will submit their revised protocol to the Agency for review.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 63,257

Affymax, Inc.  
Attention: Christine Conroy, Pharm.D.  
Executive Director, Regulatory Affairs  
4001 Miranda Avenue  
Palo Alto, CA 94304

Dear Dr. Conroy,

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AF37702, (Hematide).

We also refer to the meeting between representatives of your firm and the FDA on February 1, 2007. The purpose of the meeting was to discuss proposed starting materials, proposed drug substance and drug product specifications, identification and control of impurities, multiple manufacturing sites, and biopotency testing methods.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Karl Stiller, Regulatory Health Project Manager, at (301) 796-1993.

Sincerely,

*{See appended electronic signature page}*

Ravi Harapanhalli, PhD  
Branch Chief  
Division of Pre-Marketing Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** February 1, 2007  
**TIME:** 9:30 AM – 11:00 AM  
**LOCATION:** CDER WO 1415  
**APPLICATION:** IND 63,257  
**DRUG NAME:** AF37702, (Hematide)  
**TYPE OF MEETING:** Type B CMC

**MEETING CHAIR:** Ravi Harapanhalli, Ph.D.

**MEETING RECORDER:** Karl Stiller

**FDA ATTENDEES:** (Title and Office/Division)

Ravi Harapanhalli, Ph.D., Branch Chief, Division of Pre-Marketing Assessment III  
Ali Al Hakim, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment III  
William Adams, Review Chemist, Division of Pre-Marketing Assessment III  
Karl Stiller, Regulatory Health Project Manager

**EXTERNAL CONSTITUENT ATTENDEES:**

Robert Naso, Ph.D., Executive VP, Research & Development  
Douglas Cole, Ph.D., VP, Development  
Christopher Holmes, Ph.D., Senior Director, Chemistry  
Michael Holfinger, Ph.D., Director, Process Dev. & API Manufacturing  
Peter Schatz, Ph.D., Senior Director, Biology  
Robert Evans, Ph.D., Sr. Manager, CMC Biopharmaceutical Development, Takeda  
Christine Conroy, Pharm.D., Executive Director, Regulatory Affairs  
Diane Ingolia, Ph.D., Associate Director, Regulatory Affairs

**MEETING OBJECTIVES:**

The objectives of this meeting were to discuss proposed starting materials, proposed drug substance and drug product specifications, identification and control of impurities, multiple manufacturing sites, and biopotency testing methods.

**BACKGROUND:**

In reply to questions by the firm in their December 6, 2006 submission, FDA provided written responses to Affymax, Inc. via email on January 29, 2007. The following are the firm's questions in italics, and FDA's pre-meeting responses in plain lettering. Questions, responses, and additional meeting comments are indicated with headings.

**Question 1:**

The materials that the Sponsor designates as starting materials for synthesis of AF37702 are discussed in Section 5.1.2 of the briefing document. The proposed starting materials for the synthesis of AF37702 are:

[REDACTED] (b) (4)

Does FDA agree with the proposed starting material designations?

**FDA Response:**

[REDACTED] (b) (4)

(b) (4) The specifications for each of these materials should include analytical methods with sufficient selectivity for identity testing; and sufficient accuracy and precision for purity testing. The specification for [REDACTED] (b) (4) should include justified limits for identified impurities, unidentified impurities, total impurities and molecular weight. Data to address the selectivity, accuracy and precision of the [REDACTED] (b) (4) method used to determine [REDACTED] (b) (4) should be provided. You should also provide either a reference to a [REDACTED] DMF for this material or an adequate description of the synthesis and impurity profile [REDACTED] (b) (4). The currently proposed molecular weight range of [REDACTED] (b) (4) is wide relative to the batch analysis data provided in Table 2. This should be tightened to reflect the observed range qualified in the toxicology studies.

**Meeting Discussion:**

[REDACTED] (b) (4)

materials. FDA asked again that Affymax fully characterize [REDACTED] (b) (4)

[REDACTED] FDA also asked that extreme ranges [REDACTED] (b) (4) also be assessed, and that animal pharmacokinetic data be submitted confirming that at the extremes of the molecular weight ranges, the PK profiles are comparable. It was further clarified that in the event the PK profiles are different, this may trigger additional human studies or tighter weight range covered in the human studies. Affymax agreed. Affymax stated that [REDACTED] (b) (4) is likely to submit a DMF for [REDACTED] (b) (4), and that the specification has already been tightened to the recommended range. Affymax also stated that [REDACTED] (b) (4) is being used rather than [REDACTED] (b) (4) for ascertaining the [REDACTED] (b) (4). However, they were recommended to use [REDACTED] (b) (4)

**Question 2:**

The current specification for [REDACTED] (b) (4) in the manufacture of AF37702, is provided in Section 5.1.3.1. Affymax believes that the [REDACTED] (b) (4) specification is adequate to support Phase 3 clinical trials. Does FDA agree?

**FDA Response:**

Provide adequate justification for the specificity and selectivity of the [REDACTED] (b) (4)

**Meeting Discussion:**

Affymax provided an illustrated summary (b) (4) FDA requested that Affymax provide (b) (4) data for three reference batches and show the correlation between the (b) (4) methods at the time of NDA submission.

**Question 3:**

*The specification for AF37702 is provided in Section 5.1.6.1 of the briefing document. This specification is currently in use and is proposed for use in Phase 3 for AF37702 to be used to manufacture AF37702 Injection for use in Phase 3 clinical trials. Affymax believes that the AF37702 specification is adequate to support Phase 3 clinical trials. Does FDA agree?*

**FDA Response:**

Provide additional information regarding the selectivity of the (b) (4) methods and address their sensitivity to variations in the peptide and PEG arms of the molecule with respect to the effect of these variations on drug potency.

**Meeting Discussion:**

Affymax provided a summary of identification methods used for DS identification (see Handout 2). Affymax stated that they will study (b) (4), make authentic reference standards for validation of testing methods, and continue to explore orthogonal testing methods.

**Question 4:**

*Affymax believes that the testing (attributes) listed on the AF37702 specification for Phase 3 is adequate for NDA, with limits to be set on the basis of batch history at the time of NDA submission. Does FDA agree?*

**FDA Response:**

Given the complexity of the drug substance molecule, justification for the criterion should be risk-based and should consider safety and efficacy information as well as batch history data.

**Meeting Discussion:**

No further discussion.

**Question 5:**

*The specification for AF37702 Injection that is currently in use and proposed for Phase 3 clinical trials is provided in Section 5.2.1.4 of the briefing document. Affymax believes that the proposed AF37702 Injection specification is adequate to support Phase 3 clinical trials. Does FDA agree?*

**FDA Response:**

Based on the information submitted in the amendment, the proposed specification appears to be adequate to support the Phase 3 trials. Principles of ICH Q3B (R ) should be considered in proposing the acceptance criteria for impurities and adequate justification should be provided to support the proposed shelf life assay specification of (b) (4) However, detailed assessment of the acceptance criteria for each test will be carried out during the NDA review.

**Meeting Discussion:**

No further discussion

**Question 6:**

*Affymax believes that the testing (attributes) listed on the AF37702 Injection specification for Phase 3 is adequate for NDA, with limits to be set on the basis of batch history at the time of NDA submission. Does FDA agree?*

**FDA Response:**

Given the complexity of the drug substance molecule, justification for the criterion should be risk-based and should consider safety and efficacy information as well as batch history data.

**Meeting Discussion:**

No further discussion.

**Question 7:**

*The proposed reporting, identification, and qualification thresholds for peptide-related impurities in (b) (4) are discussed in Section 5.1.7.4 of the briefing document. Affymax believes that the reporting (b) (4), identification (b) (4) and qualification (b) (4) thresholds proposed for (b) (4) are appropriate. Does FDA agree?*

**FDA Response:**

Your proposed approach to control peptide-related impurities (b) (4) is acceptable provided the peptide related impurities resulting from the degradation of the drug substance are monitored and controlled separately in the drug substance. The proposed thresholds for peptide-related impurities (b) (4) are acceptable to support the phase 3 studies. Provide a discussion of toxicological qualification of impurities in the NDA.

**Meeting Discussion:**

Affymax stated that they will add the specification for the (b) (4) for Phase III and be able to have data for NDA submission. FDA asked that Affymax clearly show that all (b) (4), (b) (4). FDA also asked that Affymax continue investigating orthogonal methods to evaluate and identify (b) (4) products. Additionally, Affymax should review the degree of control that they have over vendors since changes in materials from these vendors may carry over into the API. They were asked to establish strong change controls and vendor qualification strategy including vendor obligations to report synthetic schemes for the starting materials and any changes made to the synthesis/purification following vendor qualification.

**Question 8:**

*The proposed reporting, identification, and qualification thresholds for impurities in drug substance are discussed in Section 5.1.7.5 of the briefing document. Affymax believes that the reporting (b) (4) identification (b) (4) and qualification (b) (4) thresholds proposed for AF37702. Does FDA agree?*

**FDA Response:**

As stated above, the (b) (4) products resulting from the drug substance should be controlled in the drug substance. The NDA review will evaluate the proposed thresholds and take into consideration the profiles of potential and observed impurities and their toxicities.

**Meeting Discussion:**

No further discussion.

**Question 9:**

The proposed reporting, identification, and qualification thresholds for impurities in drug product are discussed in Section 5.2.1.6 of the briefing document. Affymax believes that the reporting (b) (4) identification (b) (4) and qualification (b) (4) thresholds proposed for AF37702 Injection. Does FDA agree?

**FDA Response:**

The proposed thresholds are acceptable to support the phase 3 studies. The NDA review will evaluate the proposed thresholds and take into consideration the profiles of potential and observed impurities and their toxicities, and the maximum daily dose and the total daily intake of potential impurities and degradation products.

**Meeting Discussion:**

No further discussion.

**Question 10:**

As described in Section 5.1.5.5, the Sponsor proposes to consider (b) (4) (b) (4) based upon the in vivo and in vitro activity of the (b) (4) Does FDA agree with the designation of (b) (4) forms as product-related substances, rather than impurities/degradants in DS and DP, and with the proposed approach to establishing limits for the total level of (b) (4) in DS and DP?

**FDA Response:**

This proposal is subject to further evaluation of in vitro and in vivo effects of the (b) (4) and toxicological and toxico-kinetic assessments.

**Meeting Discussion:**

Affymax will request another meeting with PharmTox and CMC.

**Question 11:**

The Sponsor's plans to manufacture DS at multiple contract manufacturing sites during Phase 3 are described in Section 5.1.9. The elements of this plan include:

- 1) the addition of alternate suppliers and the information intended for submission to support each, including stability data; and
- 2) a plan to establish comparability of DS from the alternate suppliers.

Affymax believes that the plan for using DS made at a new supplier in DP to be used in Phase 3 clinical trials is appropriate. Does FDA agree?

**FDA Response:**

The comparability studies for (b) (4) and DS from the current vs. alternate suppliers should compare purity, potency, identity and physical attributes on a sufficient number of lots from each supplier to establish that the observed data is representative of the supplier. Lots from the alternate supplier should meet the same specification those from the current supplier. Note that our response to question 1 included a request to include qualified criteria for individual impurities.

The impurity profiles should be the qualitatively and quantitatively the same. The safety of quantitative differences in previously observed impurities should be addressed by comparing to the lots used in the pre-clinical studies. New impurities should be identified to the degree necessary to establish whether they affect potency or require additional toxicology studies. Given the complexity of the proposed material, an unqualified threshold for unidentified impurities is not appropriate. This information may be in a type II DMF or in the NDA.

**Meeting Discussion:**

Affymax stated that they intend to use (b) (4) DS from alternative suppliers during Phase III studies (see p. 66 of background package). FDA asked that the (b) (4) from all suppliers be fully characterized, and any new toxic impurities be qualified. FDA recommended that Affymax compare materials from existing and new vendors with respect to the firm's internal specifications. Typically, data from three batches each of the DS and DP are examined. Batches should reflect product from each of the different suppliers and should meet proposed specifications.

**Question 12:**

*As described in Section 5.1.10, in the event that at the time of NDA submission two DS suppliers are designated for the production of commercial lots of DS, and neither DS supplier is (b) (4) the Sponsor plans to provide at a minimum the following data from registration stability studies to support the use of DS from alternate suppliers:*

*Supplier A (primary supplier): stability data from three lots with 12 months of real time and six months of accelerated data for one of the three lots and with three months of both real time and accelerated data for the other two lots; and*

*Supplier B (secondary supplier): stability data from one lot with 3 months of both real time and accelerated data.*

*Does FDA agree that providing the above data is acceptable for DS registration stability studies?*

**FDA Response:**

A re-test period should be established for each alternate DS supplier using the NDA stability protocol and should include long term and accelerated condition studies with appropriate testing. The number of lots in these studies should be the same and be justified by the results from the comparability studies addressed in question 11 and supported by data from studies using the DS lots from the current supplier. Additionally, stability updates should be submitted to the NDA for a timely assessment. This may include 6 months of real time and accelerated stability data from an ongoing stability study.

**Meeting Discussion:**

FDA stated that at least one batch from each supplier at (b) (4) should be used for stability. All batches should meet proposed specifications. Sufficient data to support the retest period should be submitted. Typically, 12 months real-time and 6 months accelerated data is submitted. FDA also stated that Affymax may submit an SPA if they feel that it is necessary.

**Question 13:**

*On the basis of the argument presented in Section 5.4.3, Affymax believes that the receptor binding competition assay, an ELISA, is acceptable for assessing the biopotency of DS and DP at release and for stability testing of DS and DP during Phase 3. Does FDA agree?*

**FDA Response:**

Based on the submitted information, the proposed ELISA method is acceptable for assessing biopotency in DS and DP for the phase 3 studies. However, adequate data on the method validation should be submitted in the NDA. Also, it is recommended to establish the correlation between the data from this test with the clinical potency.

**Meeting Discussion:**

FDA stated that Affymax should submit data to show that there is a minimum potency that is relevant to clinical efficacy. FDA asked that Affymax consider making some batches with limited potency as part of the validation studies. Such information may be summarized in the Pharmaceutical Development Report and also critical quality attributes and critical process parameters be identified as described in ICH Q8. Affymax stated that they will look into validating potency assay using data from degraded FI's, and may submit an SPA for stability studies.

**Question 14:**

*Does FDA agree with the Sponsor's plan to select the biopotency method to be included in the NDA submission as described in Section 5.4.3.3?*

**FDA Response:**

Whichever biopotency method is selected for DS and DP release testing in the NDA, the method should be shown to correlate to clinical potency and should be validated as recommended in USP <1225> for an assay method. Based on the information in this submission, we recommend that the study address selectivity, accuracy, repeatability, intermediate precision, linearity, range, ruggedness, and stability -indication. Test data from the validation study should be sufficient to ensure that the method is reliable to correlate to clinical potency of the product.

**Meeting Discussion:**

See Meeting Discussion for Question 13.

**DECISIONS (AGREEMENTS) REACHED:**

See meeting discussion for individual questions.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

Affymax stated that increased [REDACTED] (b) (4)

[REDACTED] FDA stated that a discussion with PharmTox and CMC was needed to assess the pharmacokinetic, bioavailability, biopotency, and other relevant data for this [REDACTED] (b) (4) Affymax stated that they will submit a meeting request to discuss this issue.

**ATTACHMENTS/HANDOUTS:**

Two handouts from the meeting are attached below.

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