CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761028Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111960

MEETING MINUTES

Amgen Incorporated
Attention: Diana Landa, M.S.
Director, Global Biosimilar Regulatory Affairs
One Amgen Center Drive
Mail Stop 28-3-A
Thousand Oaks, CA 91320

Dear Ms. Landa:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABP 215.

We also refer to the meeting between representatives of your firm and the FDA on February 5, 2016. The purpose of the meeting was to discuss the format and content of the planned application for ABP 215 as a proposed biosimilar to US licensed Avastin under Section 351(k) of the Public Health Service Act (PHS Act).

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

If you have any questions, please call me at (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Biosimilar
Meeting Category:	Biosimilar Biological Product Development (BPD) Type 4
Meeting Date and Time:	Friday, February 5, 2016 / 9:00 – 10:30 AM (EST)
Meeting Location:	White Oak Building 22 / Room 1309
Application Number:	111960
Product Name:	ABP 215
Indication:	The same indications as approved for US-licensed Avastin
Sponsor/Applicant Name:	Amgen Inc.
Meeting Chair:	Sandra Casak
Meeting Recorder:	Leah Her

FDA ATTENDEES

Steven Lemery	Associate Director (Acting), DOP2
Sandra Casak	Clinical Team Lead (Acting), DOP2
Damiette Smit	Clinical Reviewer, DOP2
Melanie Pierce	Chief, Project Management Staff
Leah Her	Regulatory Project Manager, DOP2
Whitney Helms	Nonclinical Supervisor, DHOT
Janet Jiang	Statistical Reviewer, OTS/OB/DBV
Hong Zhao	Clinical Pharmacology Team Lead, OTS/OCP/DCPV
Jun Yang	Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Michelle Dougherty	Acting Review Chief, OBP/DBRRIV
Joslyn Brunelle	Product Quality Team Lead, OBP/ DBRRIV
Bazarragchaa Damdinsuren	Product Quality Reviewer, OBP/ DBRRIV
Xiaoyu Dong	Product Quality Statistical Reviewer, OTS/OB/DBVI
Sungwoo Choi	Product Quality Statistical Reviewer, OTS/OB/DBVI
Sue Lim	Senior Staff Fellow, OND/TBBS
Stacey Ricci	Senior Toxicologist, OND/TBBS
Neel Patel	Director, Project Management Staff, OND/TBBS
Daniel Orr	Regulatory Counsel, ORP/DRPI
Donna Synder	Clinical Team Lead, DPMH
Erica Radden	Clinical Reviewer, DPMH
Sabine Haubenreisser	EMA Liaison Official (observer)

SPONSOR ATTENDEES

Vladimir Hanes	Medical Director, Biosimilar Development
Samuel Higbie	Senior Manager, Global Biosimilars Regulatory Affairs, Chemistry, Manufacturing, and Controls (CMC)
Simon Hotchin	Executive Director, Global Biosimilars Regulatory Affairs
Margaret Karow	Executive Director, Biosimilars Process Development
Diana Landa	Director, Global Biosimilars Regulatory Affairs
Jennifer Liu	Director, Biosimilars Analytical Services
Richard Markus	Vice President, Global Development, Biosimilars Development
Jean Pan	Senior Manager, Biostatistics, Biosimilars Development
Barbara Rellahan	Director, Product Quality
Suresh Vunnum	Director, Biosimilars Operations

BACKGROUND

Amgen Inc. (Amgen) is developing ABP 215 as a proposed biosimilar to US-licensed Avastin, seeking the same indications approved for US-licensed Avastin. In the briefing package, however, Amgen stated that they would not request the ovarian, primary peritoneal, and fallopian tube cancer indication in the BLA as this indication has an orphan drug designation with the exclusivity end date of November 14, 2021.

On December 7, 2015, Amgen requested a Type 4 meeting to obtain FDA guidance on the format and content of the proposed biosimilar biological product application for ABP 215. Amgen anticipates submitting the application in the fourth quarter of 2016.

Product Information
ABP 215 is a humanized recombinant IgG1 monoclonal antibody against vascular endothelial growth factor (VEGF). ABP 215 drug product (DP) is supplied as a sterile, single use, preservative-free solution for intravenous (IV) infusion in a vial containing 100 mg/4 mL or 400 mg/16 mL of ABP 215 (25 mg/mL).

Nonclinical
Amgen states the similarity between ABP 215 and bevacizumab was assessed using in vitro functional assays that consider the mechanism of action and both the fragment antigen binding and Fc mediated activities. Additional in vitro pharmacology studies included an assessment of binding to VEGF and VEGF isoforms and induction of VEGF receptor tyrosine kinase autophosphorylation. In vivo pharmacology studies consisted of inhibition of tumor growth and tumor-associated vascularization in two xenograft tumor models and inhibition of VEGF-mediated vascular permeability. Additional nonclinical studies to compare the pharmacokinetics (PK) and toxicity of ABP 215 to bevacizumab were conducted in rats and cynomolgus monkeys, respectively.

Clinical
The results of two clinical studies for ABP 215 will be submitted in the BLA.

Study 20110216 is a PK similarity study that enrolled 202 healthy volunteers and was reviewed as part of the December 17, 2013, BPD Type 3 meeting. FDA preliminarily agreed that PK similarity appeared to have been established between ABP 215 and US-licensed Avastin, between ABP 215 and EU-approved bevacizumab, and between EU-approved bevacizumab and US-licensed Avastin. However, final determination of the PK similarity would be made during review of the BLA submission.

Study 20120265 is a randomized (1:1), double-blind comparative clinical study that compared ABP 215 to EU-approved bevacizumab. Patients with metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC) received either ABP 215 or EU-approved bevacizumab in addition to carboplatin and paclitaxel. Randomization was stratified by geographic region (Eastern Europe vs. Western Europe vs. Asia Pacific/Other vs. North America), performance status (ECOG 0 vs. 1), and sex (male vs. female). A total of 642 patients were enrolled across 101 centers in 17 countries. Patients received ABP 215 or EU-approved bevacizumab at a dose of 15 mg/kg IV every 3 weeks for 6 cycles. Carboplatin and paclitaxel were administered for 4-6 cycles. The primary efficacy variable was risk ratio (RR) of the objective response rate (ORR). Response was assessed using RECIST 1.1 and assessed by central, independent, blinded radiologists.

According to Amgen, in the comparative clinical study, ORR was 39% in the ABP 215 arm (Arm 1) versus 41.7% in the EU-approved bevacizumab arm (Arm 2). ORR risk ratio was 0.93. The 90% confidence interval of (0.8, 1.09) fell within the pre-specified equivalence margin of (0.67, 1.5). Although FDA recommended that the selected margin in the comparative clinical study should maintain a fraction of at least 50% of the bevacizumab treatment effect determined by the bound of a confidence interval of at least 70% around the risk-ratio calculated from the meta-analysis consisting of the four published comparative studies cited in Botrel et al., Lung Cancer, 2011, this recommendation was discussed after the study completed enrollment, making changes in the sample size of the study not possible (January 21, 2015, BPD Type 1 meeting). Amgen reported results for other efficacy variables including, duration of response (median 5.8 months in Arm 1 vs. 5.6 months in Arm 2), progression free survival (median 6.6 months in Arm 1 vs. 7.9 months in Arm 2) and overall survival (medians not reached). The percentage of patients with any grade and with Grade 3 or higher treatment emergent adverse events (TEAEs) were similar in both arms (95.1% vs. 93.5% for any TEAE and 42.9% vs. 44.3% for Grade 3 or higher). Amgen stated that overall a comparable safety profile was seen between ABP 215 and bevacizumab. The numbers of subjects developing binding antibodies during the study were 4 (1.4%) in Arm 1 versus 7 (2.5%) in Arm 2. Among these subjects, no subject in either treatment group tested positive for neutralizing antibodies.

FDA sent Preliminary Comments to Amgen on February 3, 2016.

DISCUSSION

FDA may provide further clarifications of, or refinements and/or changes to these responses and the advice provided at the meeting based on further information provided by Amgen and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

NOTE to Amgen: Some questions below were broken out and renumbered to facilitate a more efficient review and response process.

Administrative

1. *Background: See Company Position in Section 3.1 [Labeling] and Appendix 2 [Draft United States Prescribing Information for ABP 215] of the Briefing Document.*

Does the Agency agree with Amgen's proposal [redacted (b) (4)] **in the ABP 215 USPI? Does the Agency have any comments on the proposed ABP 215 USPI?**

FDA Response: No, FDA does not agree. FDA recommends that Amgen use the FDA-approved prescribing information (PI) for US-licensed Avastin as a starting point for developing the PI for ABP 215. FDA requests that Amgen's annotated labeling identify, with adequate specificity, the source of all data and information presented. FDA will provide additional comments on draft proposed labeling during review of the 351(k) BLA.

Amgen's Email Response of 2/4/16: Amgen acknowledges that the reference product USPI will serve as a starting point for the ABP 215 PI. Amgen wishes to clarify that, in addition to the Avastin data, our proposal is to also include key ABP 215 clinical data in the USPI to inform the prescribing physician.

Examples:

- Section 6.1. Clinical Trial Experience will reflect ABP 215 safety data (Table 1)
- Section 14 Clinical Studies will reflect ABP 215 efficacy data in the NSCLC indication (Table 9)

Discussion During Meeting of 2/5/16: Amgen stated that ABP 215 clinical data should be included in product labeling. FDA acknowledged Amgen's position. FDA stated that the Agency cannot comment further as the draft guidance on labeling has not been made available to the public. As such, FDA will provide comments on the proposed labeling during review of the BLA.

2. *Background: See Company Position in Section 3.1 [Labeling] and Appendix 2 [Draft United States Prescribing Information for ABP 215] of the Briefing Document.*

[redacted (b) (4)]

FDA Response: Amgen's reference [redacted (b) (4)] is unclear.

(b) (4)

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

3. *Background: See Company Position in Section 3.2 [REMS] of the Briefing Document.*

Does the Agency agree that a REMS is not required in the original BLA submission?

FDA Response: At this time, FDA agrees a REMS will not be required in Amgen's planned 351(k) BLA submission; however, final determination will be made upon review of the application.

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

(b) (4)

5. *Background: See Company Position in Section 4.1 [Summary of Clinical Pharmacology Studies] of the Briefing Document.*

Does the Agency agree with Amgen's plan to locate the summary of PK and immunogenicity results from Study 20110216 (pivotal PK study) in Module 2.7.2, recognizing that the full CSR will be included in Module 5.3.3.1?

FDA Response: Yes, FDA agrees with the above proposal. Include the summary of PK results and an assessment of the effects of immunogenicity on the pharmacokinetics, pharmacodynamics, efficacy and safety of the products in Module 2.7.2 of the BLA. Also, include the summary of bioanalytical assay validation in Module 2.7.2.

Amgen's Email Response of 2/4/16: Amgen intends to follow the ICH M4E: The CTD – Efficacy guidance and provide the summary of bioanalytical assay validation data in Module 2.7.1. Is this proposal acceptable to the Agency?

Discussion During Meeting of 2/5/16: FDA agreed to Amgen's proposal. No further discussion occurred.

Chemistry, Manufacturing and Controls

6. *Background: See Company Position in Section 5.2 [Proposed Structure and Content of the Drug Substance Section] of the Briefing Document.*

Does the Agency agree that the proposed content, structure, and format of the Drug Substance section (3.2.S) will facilitate review of the BLA?

FDA Response: Amgen's proposed content, structure, and format of the Drug Substance section (3.2.S) appear reasonable. However, the adequacy of the information, such as Amgen's proposed in-process controls and release testing, will be a determined based on the review of the data package in the BLA. Note that strong scientific justification should be included in the BLA to support the ABP 215 control strategy. In the BLA, provide Amgen's manufacturing production schedule for ABP 215 at the Amgen Thousand Oaks (ATO) facility to facilitate pre-approval inspection. Include a comprehensive Post-Approval Stability Protocol and Stability Commitment in section 3.2.S.7.2.

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

7. *Background: See Company Position in Section 5.3 [Proposed Structure and Content of the Drug Product Section] of the Briefing Document.*

Does the Agency agree that the proposed content, structure, and format of the Drug Product section (3.2.P) will facilitate review of the BLA?

FDA Response: Amgen's proposed content, structure, and format of the Drug Product section (3.2.P) appear reasonable. However, the adequacy of the information, such as Amgen's proposed in-process controls and release testing, will be a determined based on the review of the data package in the BLA. Include a comprehensive Post-Approval Stability Protocol and Stability Commitment in section 3.2.P.8.2.

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

8. *Background: See Company Position in Section 5.4 [Proposed Structure and Content of the Appendices] of the Briefing Document.*

Does the Agency agree that the proposed content, structure, and format of the Appendices section (3.2.A) will facilitate review of the BLA?

FDA Response: Amgen's proposed content, structure, and format of the Appendices section (3.2.A) appear reasonable.

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

9. *Background: See Company Position in Section 5.5 [Proposed Structure and Content of the Regional Section] of the Briefing Document.*

Does the Agency agree that the proposed content, structure, and format of the Regional Information section (3.2.R) will facilitate review of the BLA?

FDA Response: Amgen's proposed content, structure, and format of the Regional Information section (3.2.R) appear reasonable.

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

10. *Background: See Company Position in Section 5.5.2 [Analytical Similarity Assessment] of the Briefing Document.*

Does the Agency agree that, subject to review of the data to be presented in the BLA, the proposed content and presentation of the comprehensive analytical similarity assessment in 3.2.R Regional Information section will be sufficient to support a conclusion that:

a. ABP 215 is analytically similar to the reference product?

FDA Response: Regarding the structure and content of 3.2.R Regional Information section, please see FDA response to Question 9.

Regarding Amgen's statement on page 37 of the background information package, which states "the analytical similarity assessment will be provided in the Regional Information section and includes comparative physiochemical and functional characterization studies to demonstrate ABP 215 and the reference product are similar," please note that Section 351(i) of the PHS Act defines biosimilarity to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

FDA currently recommends that Amgen use a statistical approach to evaluate quality attributes of ABP 215 that is consistent with the risk assessment principles set forth in the International Conference on Harmonisation Quality Guidelines Q8, Q9, Q10, and Q11. Consistent with the principles, Amgen's program should implement an analytical similarity assessment that is based on a tiered system in which approaches of varying statistical rigor are used. One approach to determining the tier to which a particular quality attribute would be assigned would depend upon a criticality risk ranking of quality attributes with regard to their potential impact on activity, PK/PD, safety, and

immunogenicity with quality attributes being assigned to tiers commensurate with their risk.

For Amgen's program, equivalence testing would be recommended for quality attributes with the highest risk ranking (Tier 1) and generally would include assay(s) that evaluate clinically relevant mechanism(s) of action of the product for each indication for which approval is sought. FDA recommends that Amgen considers the use of quality ranges (mean +/- Xσ, where X should be appropriately justified) for assessing quality attributes with lower risk ranking (Tier 2), and an approach that uses raw data/graphical comparisons for quality attributes with the lowest risk ranking (Tier 3).

In addition to criticality, other factors should be considered in assigning quality attributes and assays to a particular tier using this approach. This approach includes, but it is not limited to, the levels of the attribute in both the reference product and proposed biosimilar product, the sensitivity of an assay to detect differences between products, if any, and an understanding of the limitations in the type of statistical analysis that can be performed due to the nature of a quality attribute.

FDA also recommends that Amgen carefully assess the analytical similarity plan to identify and address any other factors that could potentially impact the ability to demonstrate that ABP 215 is highly similar to the reference product. This could include, for example, considering the ages of ABP 215 and reference product lots tested, optimizing assays and pre-specifying the criteria under which wider similarity acceptance criteria for a particular assay would be considered appropriate.

FDA thinks it would be appropriate for Amgen to consider a statistical approach, such as the one set forth below based on FDA's current thinking on the topic, to evaluate certain quality attributes of the proposed biosimilar and the reference product. Amgen may propose alternative statistical approach to evaluate quality attributes and support a demonstration that ABP 215 is highly similar to the reference product.

Further, FDA notes that while a statistical approach to evaluate quality attributes of a proposed biosimilar product may be considered in support of a demonstration that the proposed biosimilar product is highly similar to the reference product, FDA's determination that a proposed biosimilar product is highly similar to the reference product will be based upon the totality of the evidence relevant to the assessment.

A potential approach for the different statistical tiers is described below:

(i) Tier 1 (Equivalence Test): One needs to test against the following null hypothesis. H_0: $\mu_B - \mu_R \leq -\delta$ or $\mu_B - \mu_R \geq \delta$, where μ_B and μ_R are the mean responses of the proposed biosimilar and reference product lots, respectively, and $\delta > 0$ is the equivalence margin.

Acceptance Criterion: Analytical similarity would be accepted for the quality attribute if the (1-2α) 100% two-sided confidence interval of the mean

difference is within (–δ, δ). In this context, the equivalence margin, δ, would be a function of the variability of the reference product as identified in studies by the biosimilar applicant (σ_R).

(ii) Tier 2 (Quality Range Approach): The quality range of the reference product for a specific quality attribute is defined as $(\hat{\mu}_R - X\hat{\sigma}_R, \hat{\mu}_R + X\hat{\sigma}_R)$, where the standard deviation multiplier (X) should be appropriately justified.

Acceptance Criterion: Analytical similarity would be accepted for the quality attribute if a sufficient percentage of test lot values (e.g. 90 percent) fall within the quality range.

(iii) Please note that each lot contributes one value for each attribute being assessed. Thus, σ_R refers to the standard deviation of those lot values of the reference product.

(iv) Ideally, the reference variability, σ_R, should be estimated from testing different lots than those used in the statistical equivalence test. This may be a challenge when there are a limited number of lots. Amgen should provide a plan for how the reference variability, σ_R, will be estimated with a justification for the approach and identify the lots that will be used.

(v) FDA would also recommend that the same number of replicates be performed within each proposed biosimilar lot as within each reference product lot, and that the same lots be used for equivalence testing, quality range testing, and visual assessment of graphical displays.

(vi) Please note that high assay variability would not be a justification for a large σ_R. In such a situation, the assay would need to be optimized and/or the number of replicates increased to reduce variability.

(vii) In cases where the equivalence margins or quality ranges are too wide, it may be scientifically justified and appropriate to narrow the margins or range.

One potential statistical approach to evaluate quality attributes is based on a standard statistical test of equivalence with the margin defined as a function of the reference product variability (e.g., $c * \sigma_R$). The constant c would be selected as the value that provides adequate power to show equivalence if there is only a small difference in the true mean between the biosimilar and the reference product, when a moderate number of reference product and biosimilar lots are available for testing. If, for example, one selected $\delta = 1.5\sigma_R$ for all sample sizes used in equivalence testing to illustrate this potential statistical approach, the test would yield a positive result if the 90% confidence interval about the difference in sample means lies within ($-1.5\ \sigma_R$, $1.5\ \sigma_R$). If 10 biosimilar and 10 reference product lots, this test would have approximately 87% power when the true underlying mean difference between the proposed biosimilar and reference product lots was equal to $\sigma_R/8$, assuming a test with $\alpha = 0.05$.

Note that with this potential approach, the margin would be a function of the reference product variability as demonstrated in testing by the biosimilar applicant; therefore, a larger margin would be used for attributes with larger variability. In addition, the confidence level would depend on the number of lots available for testing. For a more limited number of lots, as described in the sponsor's briefing package, Amgen may consider calculating the confidence interval with a lower confidence level to ensure adequate power. In this situation, the lower confidence level would be expected to be appropriately addressed by the final manufacturing control strategy. In contrast, when a moderate or greater number of lots are available for testing, the equivalence test would be based on a 90% confidence interval.

Amgen has not specified the number of lots of ABP 215, US-licensed Avastin, and EU-approved Avastin for Tier 1 and Tier 2 statistical assessments. A sufficient number of lots for ABP 215, US-licensed Avastin, and EU-approved Avastin should be included. Also, in regards to the use of [(b) (4)] for each attribute assigned to Tier 2 testing, FDA does not agree [(b) (4)] to all attributes tested using Tier 2 testing. The multiplier X for the standard deviation should be scientifically justified, taking into account the variability of the assay and the clinical impact of each individual attribute.

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

b. An acceptable analytical bridge has been established between bevacizumab (US) and bevacizumab (EU)?

FDA Response: To support the analytical bridge, all 3 comparisons (ABP 215 to US-licensed Avastin, ABP 215 to EU-approved bevacizumab, and EU- approved bevacizumab to US-licensed Avastin) should meet the pre-specified acceptance criteria for analytical similarity. Please see FDA's response to Question 10a for advice regarding the statistical approach to support a demonstration that the products are highly similar.

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

11. *Background: See Company Position in Section 5.5.2.2 [Tiering of Analytical Similarity Attributes] of the Briefing Document.*

With respect to the similarity assessment of biological activity assays, does the Agency agree to Amgen's proposal that:

a. [(b) (4)] assay for ABP 215 that will be evaluated using a Tier 1 equivalence test?

FDA Response: No, FDA does not agree. Evaluate both potency and binding to VEGF-A using Tier 1 equivalence testing. If Amgen is able to provide data to demonstrate that inhibition of proliferation in the HUVEC (potency) assay is at least as sensitive as the binding assay to discriminate differences between the products and justify that the

HUVEC results provide similar information on bevacizumab function and activity that would be provided by the binding assay, then FDA would consider a proposal to evaluate binding to VEGF-A in a lower testing tier.

Amgen's Email Response of 2/4/16: Amgen will develop a VEGF-binding assay and include results in the similarity assessment.

Discussion During Meeting of 2/5/16: FDA acknowledged the response.

b. Binding assays for FcRn and FcγRIIIa are included in Module 3.2.R to support analytical similarity and evaluated using a Tier 2 quality range assessment?

FDA Response: The proposal to evaluate binding assays for FcRn and FcγRIIIa using the Tier 2 quality range assessments in Module 3.2.R appears reasonable. Appropriate justification for the approach should be included in the BLA.

FDA notes that Amgen did not provide additional information on the tier placement of the other assays listed in Table 7, or additional non-biological assays that will be included in the final analytical similarity assessment. For example, FDA recommends that Amgen include an evaluation of protein content in the analytical similarity assessment, taking into consideration how the product is dosed (e.g., dosed to saturation or on the linear portion of the dose-response curve) when assigning a criticality score. FDA strongly recommends that Amgen submit to the IND the criticality risk ranking assignment of all quality attributes (both physicochemical and functional) and their placement into appropriate statistical tiers, and obtain FDA agreement on this information as part of the proposed analytical similarity plan prior to submission of a BLA.

Amgen's Email Response of 2/4/16: See the proposed tiering and location outlined on the next slide.

Proposed Tiering and Location for Biological Assays (Updated Table 7)

Discussion During Meeting of 2/5/16: FDA reiterated the recommendation to include the FcγRIIIa binding in Tier 2. FDA clarified that the binding to FcγR can impact the safety of the molecule due to the role of FcγR binding in ADCC and CDC. Amgen indicated that they agreed with the recommendation to maintain the FcγRIIIa assessment as a Tier 2 assessment. FDA also stated that the advice provided regarding criticality ranking and tier placement of attributes having a minimal impact on activity, PK/PD, safety and immunogenicity was intended to be broadly applied to all quality attributes and was not intended to be applied solely to functional assays.

FDA reiterated the recommendation to submit the additional proposed criticality ranking and statistical tier placement for functional assays and physicochemical assays to the IND and gain agreement before submitting the BLA. FDA commented that alignment prior to the BLA submission would facilitate efficient review of the submission and prevent a situation where Amgen would need to reanalyze existing data or generate additional data to support the similarity assessment. Amgen acknowledged the recommendation and asked about timeline for review of such amendment. FDA stated that the Agency acknowledged the importance of receiving timely advice and would, to the extent possible, work to maintain Amgen's projected submission timelines.

c. All other qualitative assays listed in Table 7 will be included in Module 4 pharmacology section without statistical assessment?

FDA Response: No. In vivo assays should be reported in Module 4 and do not need to be included in the analytical similarity assessment. Data generated from in vivo assays would be considered supportive of a demonstration of biosimilarity. Other assays listed in Table 7 should be reported in 3.2.R as part of the analytical similarity assessment. Assays demonstrating lack of ADCC, lack of CDC, and assays for quality attributes having minimal impact on activity, PK/PD, safety, and/or immunogenicity should be evaluated using Tier 3 assessments. Refer to FDA's response to 10a regarding factors to be considered in assigning quality attributes and assays to a particular tier in addition to criticality.

Amgen's Email Response of 2/4/16: In line with Agency's recommendation, Amgen will move all in vitro assays from Module 4 to Module 3 (see next slide) and data will be subjected to qualitative comparison. Furthermore, consistent with the Agency's recommendation with regard to attributes having minimal impact on activity, Amgen proposes t (b) (4)

Does the Agency have any feedback on the proposed strategy?

Discussion During Meeting of 2/5/16: Refer to Discussion under 11b.

Amgen's Additional Email Response of 2/4/16 for 11a and 11c: Does the Agency's request represent a policy that:

(b) (4)

- All in vitro biological data should be placed in Module 3.2.R

Discussion During Meeting of 2/5/16: FDA noted that the recommendations regarding tier placement of bioassays and binding assays was provided in the context of Amgen's proposed biosimilar to Avastin and was not broadly applicable across product classes. FDA clarified that the HUVEC proliferation bioassay provides information on one biological outcome of VEGF signaling. Inclusion of the binding assay in the Tier 1 assessment provides an additional assessment of bevacizumab mechanism of action (MOA) to ensure that the same outcome would be observed for the other biological functions of VEGF signaling. Amgen acknowledged the recommendation.

FDA recommended that all data intended to support a conclusion related to analytical similarity should be placed in 3.2.R and data considered supportive could be placed in other appropriate modules in the submission. Amgen inquired as to whether this recommendation could be applied to other product classes. FDA indicated that the recommendation was specific to the ABP 215 application and that additional considerations might influence the placement of information for other products.

Post-meeting note: FDA's response above that the "recommendation was specific to the ABP 215 application" was intended to refer to the tier placement of the HUVEC and binding assay in Tier 1 for ABP 215. As noted, tier placement of quality attributes and assays depends on the product and should not be broadly applied across all proposed biosimilar products.

FDA agrees that analytical similarity data for all proposed biosimilar products should be placed in 3.2.R in the 351(k) BLA.

Nonclinical

12. *Background: See Company Position in Section 6.1 [Pharmacology] of the Briefing Document.*

Does the Agency agree with the proposed location of the in vitro pharmacology assessments in Module 4 of the BLA?

FDA Response: No, FDA does not agree. See FDA response to Question 11c.

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

13. *Background: See Company Position in Section 6.2 [Pharmacokinetics/Toxicology] of the Briefing Document.*

Does the Agency agree that the ABP 215 original BLA submission can include animal PK and toxicology reports (inclusive of individual animal data) in PDF format, without providing additional tabulations data in SAS (.xpt) format?

FDA Response: Yes, FDA agrees.

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

Clinical

14. *Background: See Company Position in Section 7.2 [Comparative Study of Efficacy, Safety, and Immunogenicity Study (Study 20120265)] of the Briefing Document.*

Does the Agency have any comments or questions regarding the Topline results from Study 20120265 in the NSCLC population?

FDA Response: No, FDA does not have any comments or questions at this time.

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

15. *Background: See Company Position in Section 7.3 [Extrapolation of Clinical Data Across Indications] of the Briefing Document.*

Does the Agency have a recommendation for any additional points to consider with respect to justifying extrapolation of clinical data across indications?

FDA Response: No, FDA does not have additional recommendations at this time.

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

ADDITIONAL COMMENTS

16. FDA acknowledges that the content and format of Module 5 of a 351(k) BLA submission was discussed in the Type 2 BPD meeting held on May 20, 2015. However, the meeting package submitted on December 7, 2015, does not include a table with the format and contents of the proposed BLA. As such, FDA cannot provide agreement regarding the contents of the BLA, which FDA expects be to be complete at the time of submission.

    Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

17. On January 29, 2016, Amgen submitted the following question via electronic (email) communication for FDA response:

"Amgen has conducted additional post-hoc analyses for PK Similarity Study 201110216 as well as the pivotal Ph3 study 20120265. Does the Agency have a preference for location of the post-hoc tables, i.e. Module 5.3.5.3 or within the study folders in Module 5.3.3.1 and Module 5.3.5.1, respectively?"

FDA Response: Include PK tables in Module 5.3.3.1 and 5.3.5.1, respectively. In addition, include the PK results in the summary of clinical pharmacology section (Module 2).

Amgen's Email Response of 2/4/16: Amgen did not request further discussion.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355c)], all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable

Section 505B(m) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred.

We refer to your amendment dated December 6, 2013, which contained your initial Pediatric Study Plan (iPSP) for non-small cell lung cancer (NSCLC), metastatic colorectal cancer, metastatic renal cell carcinoma and glioblastoma, and to your amendment dated April 11, 2014, which contained an Agreed Initial Pediatric Study Plan (iPSP) submitted in response to our letter of March 5, 2014. We confirmed our agreement to your April 11, 2014, Agreed iPSP in our May 14, 2014, letter.

We also refer to your amendment dated September 23, 2015, which contained your amended iPSP for ABP 215 to include two additional indications, cervical cancer and platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. We are currently reviewing this amendment.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the

Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all clinical studies used to support a demonstration of no clinically meaningful differences between the proposed biosimilar biological product and the reference product in the application. Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:

a. Site number
b. Principal investigator
c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the 351(k) BLA for each of the completed clinical studies:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

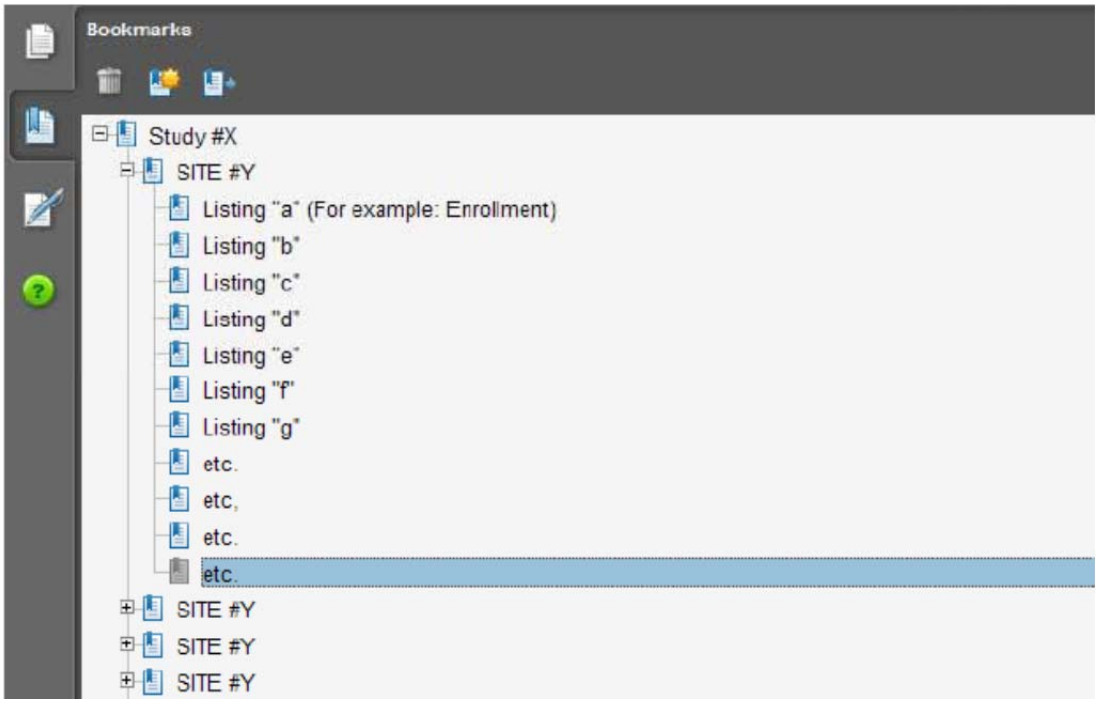
4. For each clinical study, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each clinical study provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each clinical study: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)

c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the 351(k) BLA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the clinical studies)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each clinical study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ATTACHMENTS AND HANDOUTS

- ABP 215 Type 4 FDA Meeting Presentation 5-Feb-16 received on February 4, 2016

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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.

/s/

LEAH S HER
02/29/2016