Overview of the Regulatory Framework and FDA's Guidance for the Development and Approval of Biosimilar Products in the US

Sue Lim, M.D.
Team Lead
OND Therapeutic Biologics and Biosimilars Staff/CDER/FDA

Overview of Presentation

- Overview
  - Background
  - Terminology
  - Approval Pathway for Biosimilars – General Requirements

- Development of Biosimilars
  - Approach to Development
  - Specific Development Concepts

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Overview of the BPCI Act

Background

- The **Biologics Price Competition and Innovation Act of 2009 (BPCI Act)** was signed into law on March 23, 2010.

- BPCI Act creates an ***abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with*** an FDA-licensed reference product.
  - A biological product that is demonstrated to be "***highly similar***" to an FDA-licensed biological product (the reference product) may rely for licensure on, among other things, publicly-available information regarding FDA's previous determination that the reference product is safe, pure and potent.
  - This licensure pathway permits a biosimilar biological product to be licensed under 351(k) of the Public Health Service Act (PHS Act) based on **less than a full complement of product-specific preclinical and clinical data** → **abbreviated licensure pathway.**

What is Meant by Abbreviated Licensure Pathway?

- The abbreviated licensure pathway does not mean that a lower approval standard is applied to biosimilar or interchangeable products than to originator biological products.
- The ability to rely on FDA's previous finding regarding the reference product to support approval of the biosimilar product allows for a potentially shorter and less costly drug development program. This is what is meant by an **abbreviated** licensure pathway.
- The **data package** required for approval of a biosimilar or interchangeable product is quite extensive; biosimilar applicants submit data from analytical, nonclinical, and clinical studies to support a demonstration of biosimilarity with the reference product.
- Once a biosimilar or interchangeable has been approved by FDA, patients and health care providers will be able to rely upon the safety and effectiveness of an FDA-approved biosimilar or interchangeable product just as they would for the reference product that the biosimilar was compared to.

Biosimilarity

Biosimilar or **Biosimilarity** means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and

- 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.

Reference Product

Reference Product:

- the **single biological product, licensed under section 351(a) of the PHS Act,** against which a biological product is evaluated in an application submitted under section 351(k) of the PHS Act.

– An application submitted under section 351(a) of the PHS Act is a "stand-alone" application that contains all information and data necessary to demonstrate that the proposed product is safe, pure and potent.

– In contrast, an application submitted under section 351(k) needs to demonstrate that the proposed product is biosimilar to the reference product. For licensure, a proposed biosimilar relies on (among other things) comparative data with the reference product, as well as publicly-available information regarding FDA's previous determination that the reference product is safe, pure and potent.

Interchangeability

Interchangeable or **Interchangeability:**

- the biological product is **biosimilar** to the reference product;
- it **can be expected** to produce the **same clinical result** as the reference product **in any given patient**; and
- for a product that is administered more than once to an individual, the risk in terms of **safety or diminished efficacy of alternating or switching** between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

An interchangeable product **may be substituted** for the reference product without the intervention of the health care provider who prescribed the reference product.

General Requirements

A 351(k) application must include information demonstrating that the biological product:

- Is **biosimilar** to a reference product;
- Utilizes the **same mechanism(s) of action** for the proposed condition(s) of use -- but only to the extent the mechanism(s) are known for the reference product;
- **Condition(s) of use** proposed in labeling **have been previously approved** for the reference product;
- Has the **same route of administration**, **dosage form**, and **strength** as the reference product; and
- Is manufactured, processed, packed, or held in a facility that **meets standards** designed to assure that the biological product continues to be safe, pure, and potent.

General Data Elements : 351(k) Application

The PHS Act requires that a 351(k) application include, among other things, **information demonstrating biosimilarity based upon data derived from**:

- **Analytical studies** demonstrating that the biological product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components;
- **Animal studies** (including the assessment of toxicity); and
- A **clinical study or studies** (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar product.

FDA may determine, in its discretion, that an element described above is unnecessary in a 351(k) application.

Use of Non-US-Licensed Comparator Products

- The PHS Act defines the “reference product” for a 351(k) application as the “single biological product licensed under section 351(a) against which a biological product is evaluated.”
- Data from animal studies and certain clinical studies comparing a proposed biosimilar product with a non-US-licensed product may be used to support a demonstration of biosimilarity to a US-licensed reference product.
- Sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product.

Support for Use of Non-US-Licensed Comparator

- Type of bridging data needed would include:
  - Direct physicochemical comparison of all 3 products (proposed biosimilar to US-licensed reference product; proposed biosimilar to non-US-licensed comparator product; US-licensed reference product to non-US-licensed comparator product)
  - Likely 3-way bridging clinical PK and/or PD study
  - All three pair-wise comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity.

- A sponsor should justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product.

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Overview of FDA's Approach to the Development of Biosimilars

FDA Guidance

1. **Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (final, 2015)**
2. **Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (final, 2015)**
3. **Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (final, 2015)**
4. **Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (final, 2015)**
5. **Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (final, 2016)**
6. **Nonproprietary Naming of Biological Products (final, 2017)**
7. Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (draft, 2014)
8. Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (draft, 2015)
9. Labeling for Biosimilar Products (draft, 2016)
10. Considerations in Demonstrating Interchangeability With a Reference Product (draft, 2017)

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm

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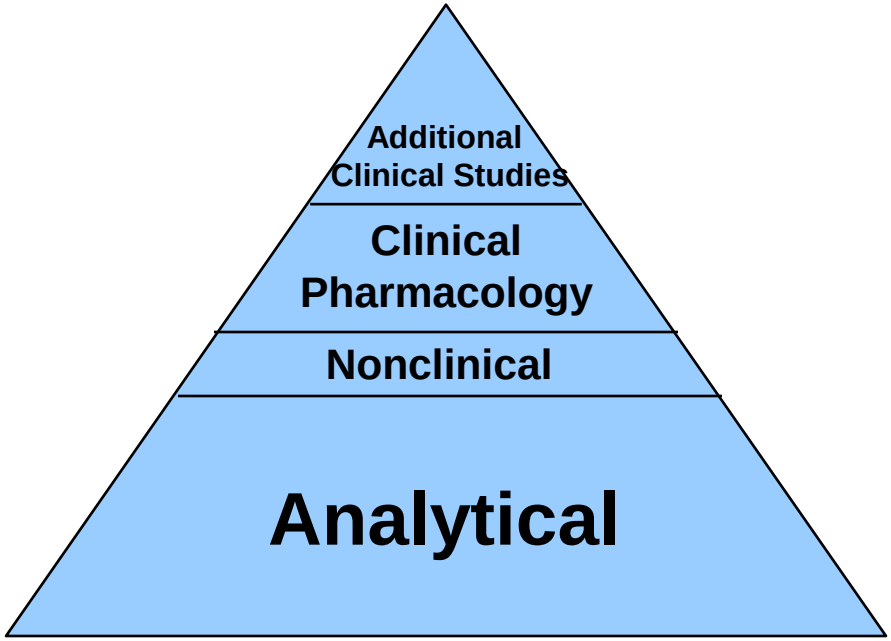
Key Development Concepts

Key Concept #1: Goals of "Stand-alone" and Biosimilar Development are Different

"Stand-alone" Development Program, 351(a)
Goal: To establish safety and efficacy of a new product

"Abbreviated" Development Program, 351(k)
Goal: To demonstrate biosimilarity (or interchangeability) to a reference product

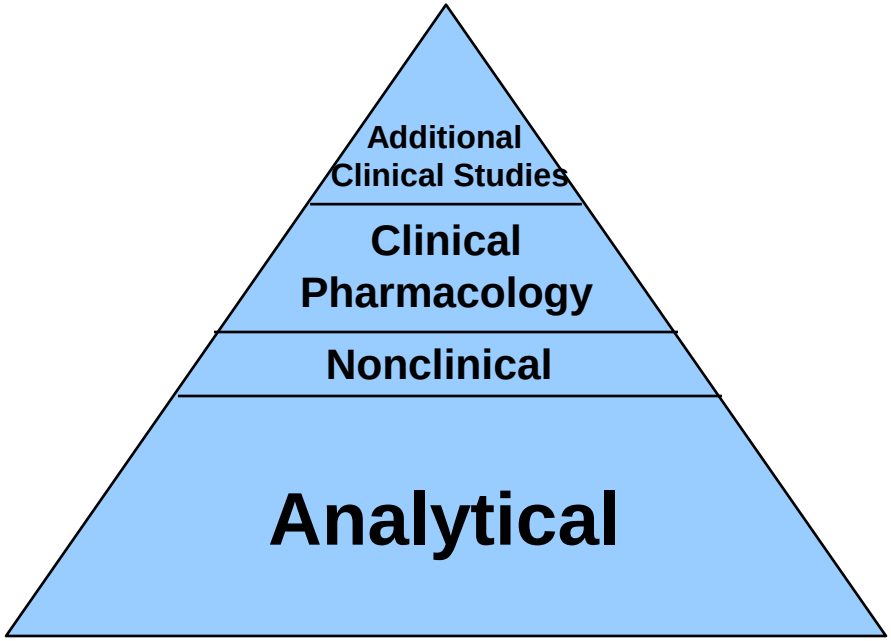


What does this difference mean from a development perspective?

Key Concept #2:
Stepwise Evidence Development

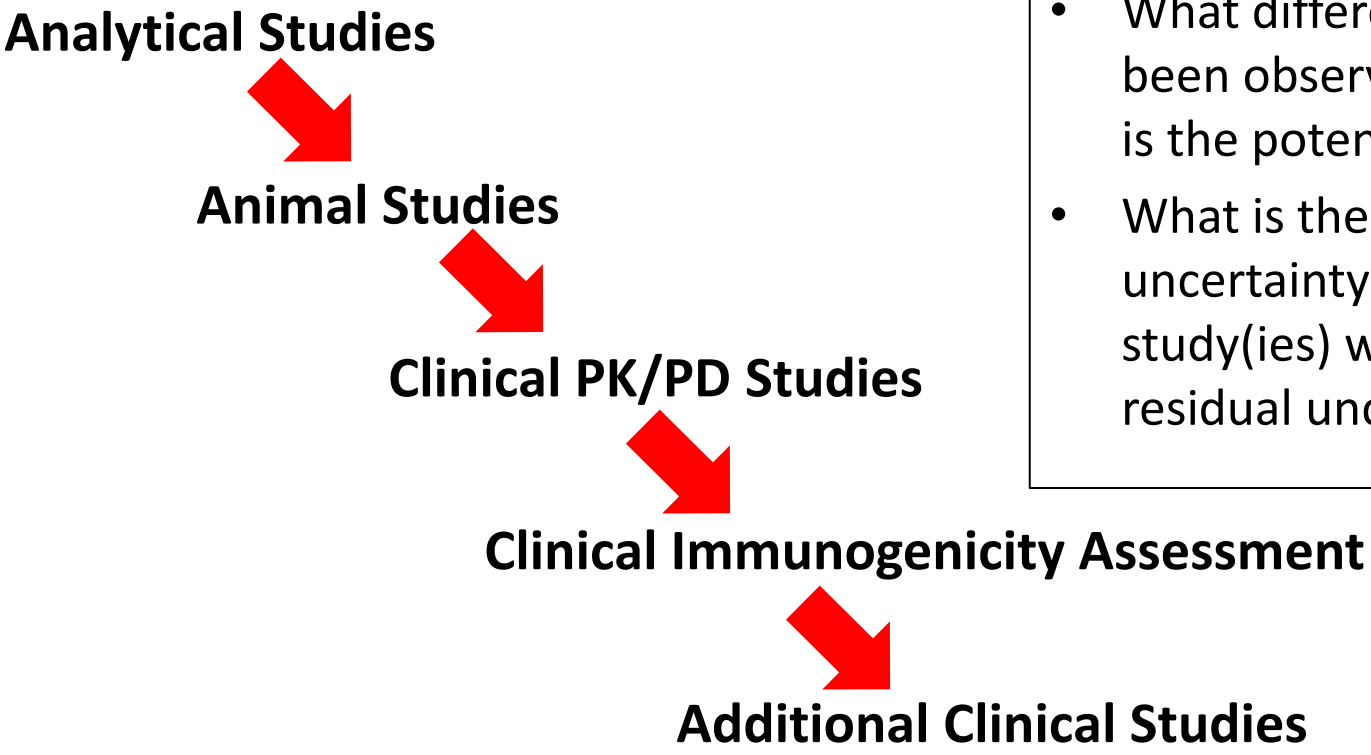
- FDA has outlined a **<u>stepwise approach</u>** to generate data in support of a demonstration of biosimilarity
- Evaluation of residual uncertainty at each step of data generation
- *Totality-of-the-evidence* approach in evaluating biosimilarity

- **There is no one "pivotal" study that demonstrates biosimilarity**



No "one size fits all" assessment

- Apply a step-wise approach to data generation and the evaluation of residual uncertainty*

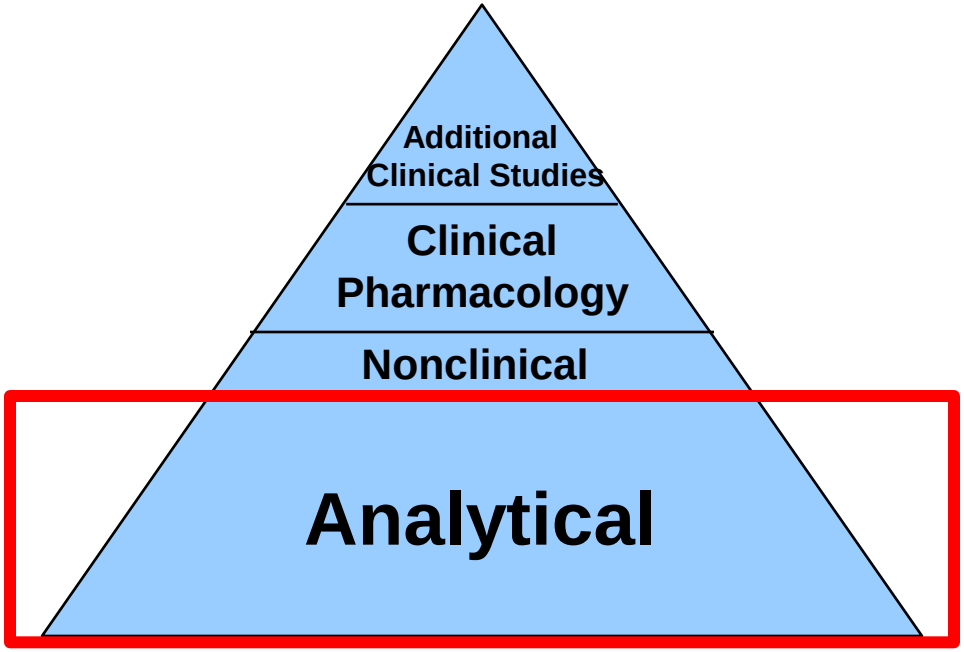


- What differences have been observed and what is the potential impact?
- What is the residual uncertainty and what study(ies) will address the residual uncertainty?

* The list is not intended to imply that all types of data described here are necessary for any given biosimilar development program. FDA may determine, in its discretion, that certain studies are unnecessary in a 351(k) application.

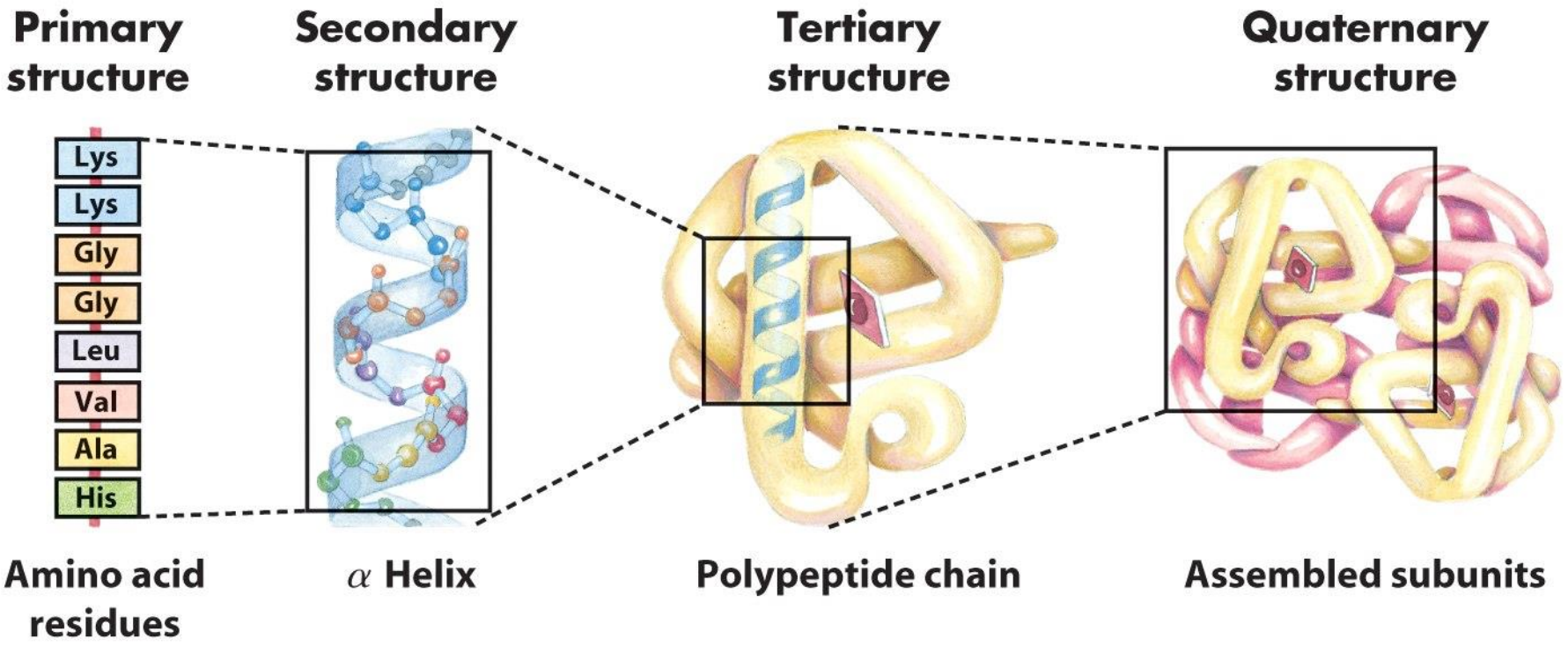
Key Concept #3:
Analytical Similarity Data -
The Foundation of a Biosimilar Development Program

- Extensive **structural and functional characterization**



"Abbreviated" Development Program, 351(k) BLA

Hierarchy of protein structure



- **Protein Heterogeneity**
- **Lot-to-lot variability**
- **All need to be evaluated as part of analytical similarity studies**

Assessing Analytical Similarity

- Comprehensive structural and functional analyses
- Comparative assessment of attributes including:
  - Amino acid sequence and modifications
  - Folding
  - Subunit interactions
  - Heterogeneity (size, aggregates, charge, hydrophobicity)
  - Glycosylation
  - Bioactivity
  - Impurities
- If a molecule is known to have multiple biological activities, where feasible, each should be demonstrated to be highly similar between the proposed biosimilar product and the reference product
- **Understand** the molecule and function and identify **critical quality attributes**

Generating Analytical Similarity Data

- Characterize reference product quality characteristics and product variability
- Manufacturing process for the proposed biosimilar product should be designed to produce a product with minimal or no difference in product quality characteristics compared to the reference product
- Identify and evaluate the potential impact of differences observed and what study(ies) will address the residual uncertainty
- **Understanding the relationship** between quality attributes and the clinical safety & efficacy profile aids ability to determine **residual uncertainty** about biosimilarity and to predict expected "clinical similarity" from the quality data.

Statistical Analysis of Analytical Similarity Data

- Statistical analyses of the analytical similarity data are conducted to support a demonstration that the proposed biosimilar product is highly similar to the reference product
- Quality attributes are ranking based on criticality with regard to their potential impact on activity, PK/PD, safety, immunogenicity, and other factors
- Data are then analyzed by various testing methodologies

Animal Data

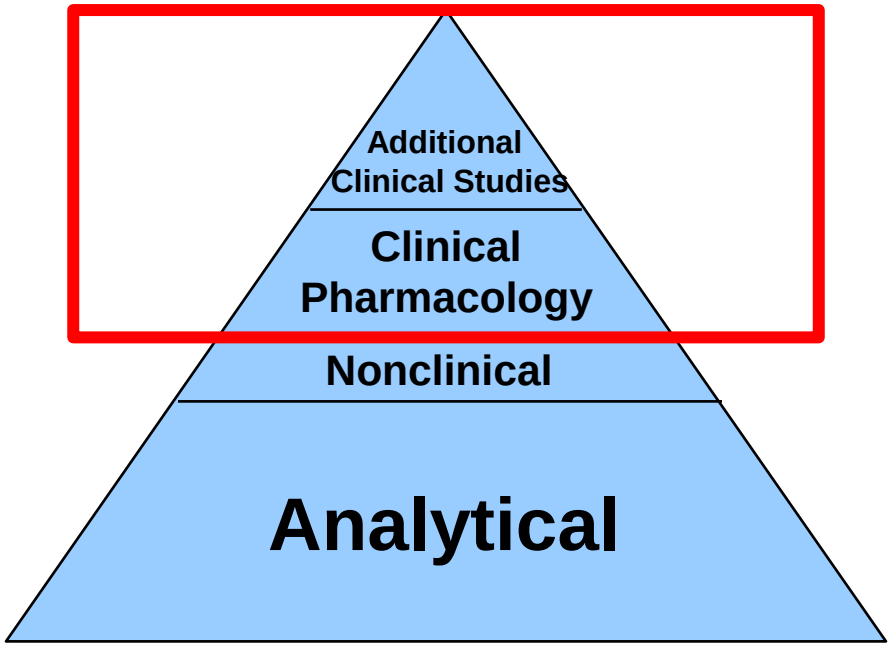
- Animal toxicity data are useful when uncertainties remain about the safety of the proposed product prior to initiating clinical studies

- The scope and extent of animal studies, including toxicity studies, will depend on publicly available information and/or data submitted in the biosimilar application regarding the reference product and the proposed biosimilar product, and the extent of known similarities or differences between the two

- A comparison of PK/PD in an animal model may be useful

Key Concept # 4:
Role of Clinical Studies

- The nature and scope of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products **after** conducting structural and functional characterization and, where relevant, animal studies.



"Abbreviated" Development Program, 351(k) BLA

Type of Clinical Data

- As a scientific matter, FDA expects an adequate clinical PK, and PD if relevant, comparison between the proposed biosimilar product and the reference product.

- As a scientific matter, at least 1 clinical study that includes a comparison of the immunogenicity of the proposed and reference product generally will be expected.

- As a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there are **residual uncertainties** about whether there are clinically meaningful differences between the proposed and reference products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.

Comparative Human PK and PD Data

- PK and/or PD is generally considered the most sensitive clinical study/assay in which to assess for differences between products, should they exist
- PK
  - Demonstrate PK **similarity** in an adequately sensitive population to detect any differences, should they exist
- PD
  - **Similar** PD using PD measure(s) that reflects the mechanism of action (MOA) or reflects the biological effect(s) of the drug

- **PK and PD similarity** data supports a demonstration of biosimilarity with the assumption that similar exposure (and pharmacodynamic response, if applicable) will provide **similar efficacy and safety** (i.e., an exposure-response relationship exists)

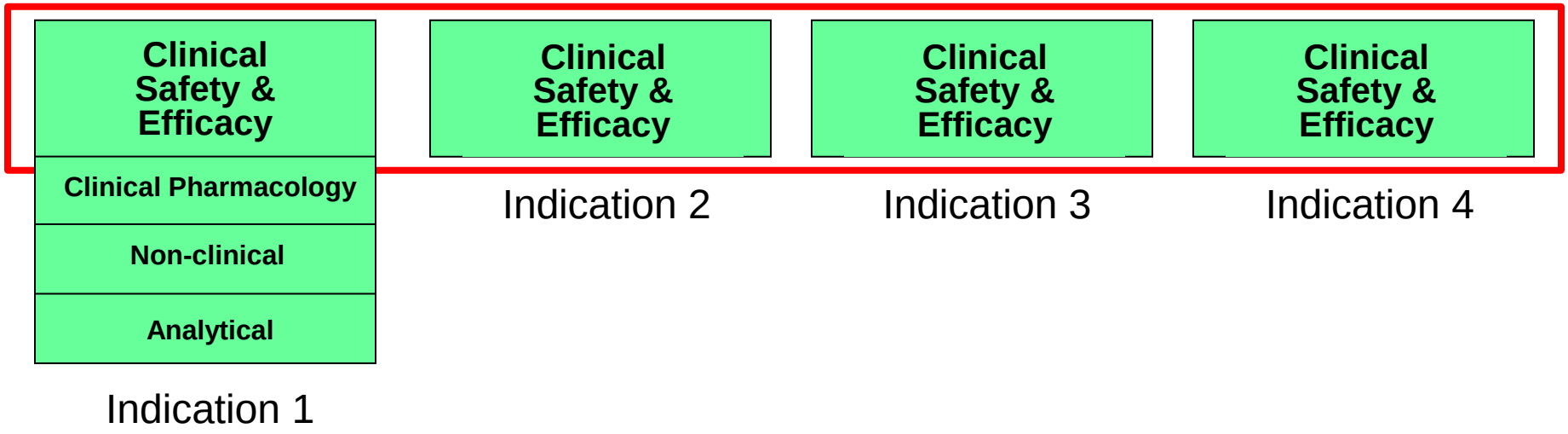
Comparative Clinical Study

- A comparative clinical study for a biosimilar development program should be designed to investigate whether there are clinically meaningful differences in safety and efficacy between the proposed product and the reference product.
- Population, endpoint, sample size and study duration should be adequately sensitive to detect differences, should they exist.
- Typically, an equivalence design would be used, but other designs may be justified depending on product-specific and program-specific considerations.
- Assessment of safety and immunogenicity

Key Concept # 5: Extrapolation

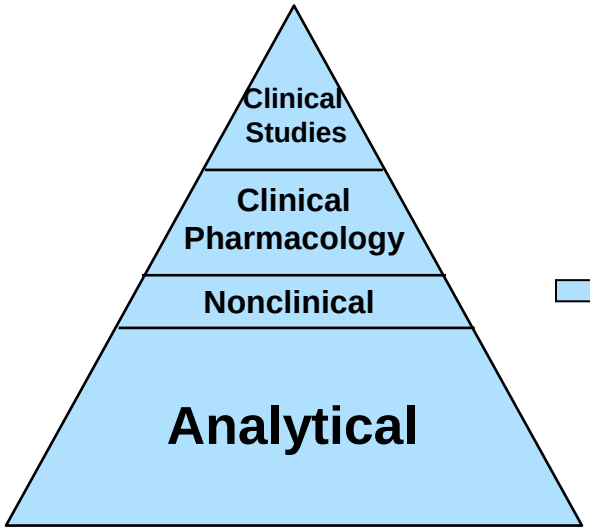
- The potential exists for a biosimilar product to be approved for one or more conditions of use for which the reference product is licensed based on extrapolation
- Sufficient scientific justification for extrapolation is necessary
- Differences between conditions of use (e.g., indications) do not necessarily preclude extrapolation
- FDA guidance outlines factors to consider, including:
  - MoA in each condition of use
  - PK and biodistribution in different patient populations
  - Immunogenicity in different patient populations
  - Differences in expected toxicities in each condition of use and patient population

Extrapolation Considerations: "Stand-alone" Drug Development



Extrapolation Considerations: "Stand-alone" vs. Biosimilar Development

Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy
Clinical Pharmacology	Indication 2	Indication 3	Indication 4
Non-clinical			
Analytical			



Extrapolation from information in 351(k) BLA and FDA's finding for the reference product to other indications previously approved for the reference product, considering for each indication:

- MOA(s)
- PK
- Immunogenicity
- Known toxicities

Biosimilar extrapolation is based on all available data in the 351(k) BLA and FDA's finding for the reference product, not from the indication(s) studied for biosimilar to other non-studied indications

Summary

- Development of a biosimilar product is different from "stand-alone" product development
  - Development goal is not to re-establish safety and effectiveness but to demonstrate the biosimilar product is **highly similar** to the reference product, and that there are **no clinically meaningful differences**
- Analytical comparisons are the foundation for determining whether the products are highly similar
- Clinical PK (and/or PD) is generally considered the most sensitive endpoint for detecting differences between products; an assessment of immunogenicity is needed and comparative clinical data are collected if questions remain
- Approval of a proposed biosimilar product is based on the **integration of various information and the totality of the evidence submitted** by the biosimilar sponsor to provide an overall assessment that the proposed product is biosimilar to the reference product.
- The FDA's high standard for approval of biosimilar and interchangeable products means that patients and health care professionals **can be confident of the safety and effectiveness of a biosimilar or interchangeable product**, just as they would for the reference product.

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Thank you for your attention.

Questions?

ABP215, a proposed biosimilar to US-licensed Avastin

BLA 761028

Oncologic Drugs Advisory Committee
July 13, 2017

U.S. Food and Drug Administration

FDA Review Team

Regulatory Project Management

Monica Hughes, M.A.
Leah Her, M.S., P.M.P.
CDR Keith Olin, Pharm.D. (OPQ)
CDR Latonia Ford, M.B.A., B.S.N., R.N. (OSE)
Neel Patel, Pharm.D. (TBBS)
Tyree Newman (TBBS)
Leila Hann (TBBS)

Product Quality

Joel Welch, Ph.D.
Chana Fuchs, Ph.D.
Jee Chung, Ph.D.

Product Quality Statistics

Yi Tsong, Ph.D.
Meiyu Shen, Ph.D.
Tianhua Wang, Ph.D.

Office of Process & Facility

Zhihao Peter Qiu, Ph.D.
Laura Fontan, Ph.D.
Patricia Hughes, Ph.D.
Scott Nichols, Ph.D.
Dupeh Palmer, Ph.D.

Labeling

CAPT Vicky Borders-Hemphill, Pharm.D

Clinical

Patricia Keegan, M.D.
Steven Lemery, M.D., M.H.S.
Sandra Casak, M.D.

Clinical Statistics

Rajeshwari Sridhara, Ph.D.
Thomas Gwise, Ph.D.
Kun He, Ph.D.
Lisa Rodriguez, Ph.D.
Weishi (Vivian) Yuan, Ph.D.

Clinical Pharmacology

NAM Atiqur Rahman, Ph.D.
Sarah Schrieber, Pharm.D.
Edwin Chow, Ph.D.

Pharmacology/Toxicology

John Leighton, Ph.D.
Whitney Helms, Ph.D.
Alex Putman, Ph.D.

Office of Scientific Investigations

Susan Thompson, M.D.
Lauren Iacono-Connor, Ph.D.
Damon Green, M.D., M.S.

Office of Study Integrity and Surveillance

Office of Surveillance and Epidemiology

Chi-Ming (Alice) Tu, Pharm.D.
Janine Stewart, Pharm.D.
Naomi Redd, Pharm.D.
Mei-Yean Chen, Pharm.D.
LCDR Steven Bird, Ph.D., Pharm.D.
Carolyn McCloskey, M.D.

Office of Regulatory Policy

Daniel Orr, J.D.

TBBS

Leah Christl, Ph.D.
Sue Lim, M.D.
Anne Rowzee, Ph.D.

Proposed Indications

- metastatic colorectal cancer (mCRC), in combination with intravenous (IV) 5-fluorouracil- (5-FU)-based chemotherapy for first- or second-line treatment
- mCRC, in combination with fluoropyrimidine-, irinotecan-, or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab containing regimen
- non-squamous non-small cell lung cancer (NSCLC), in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent, or metastatic disease
- glioblastoma multiforme (GBM), as a single agent for adult patients with progressive disease following prior therapy
- metastatic renal cell carcinoma (mRCC), in combination with interferon alfa
- cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease

FDA's Conclusions

- ABP215 and US-licensed Avastin are highly similar, notwithstanding minor differences in clinically inactive components.
- Clinical data obtained in healthy subjects (pharmacokinetic (PK)) and in patients with NSCLC support a demonstration that there are no clinically meaningful differences between ABP215 and US-licensed Avastin.
- **The totality of the data support the Applicant's claim that ABP215 is biosimilar to US-licensed Avastin.**

Presentation Outline

- Introduction
- Results
  - Product Quality
  - Clinical Pharmacology
  - Comparative Clinical Study
  - Summary of Safety, Extrapolation, and Summary of FDA's Analysis of Similarity
- Discussion Points and Questions for the Committee

Product Quality Review

Jee Chung, Ph.D.
Product Quality Reviewer
Office of Biotechnology Products, CDER
U.S. Food and Drug Administration

Tianhua Wang, Ph.D.
Product Quality Statistical Reviewer
Office of Biostatistics, CDER
U.S. Food and Drug Administration

Bevacizumab Structure Mechanism of Action

- US-licensed Avastin: Genentech, Inc
- Humanized IgG1 monoclonal antibody expressed in mammalian cell culture system
- Targets vascular endothelial growth factor family member A (VEGFA) and inhibits binding to VEGF receptors

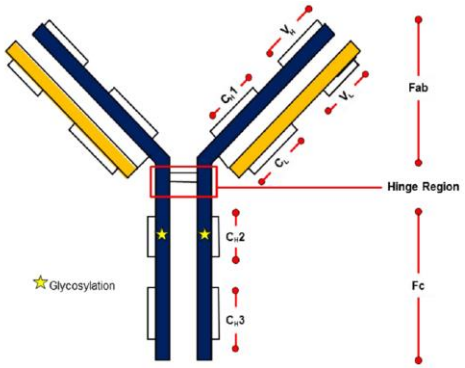


Figure excerpted from Applicant's 351 (k) BLA submission

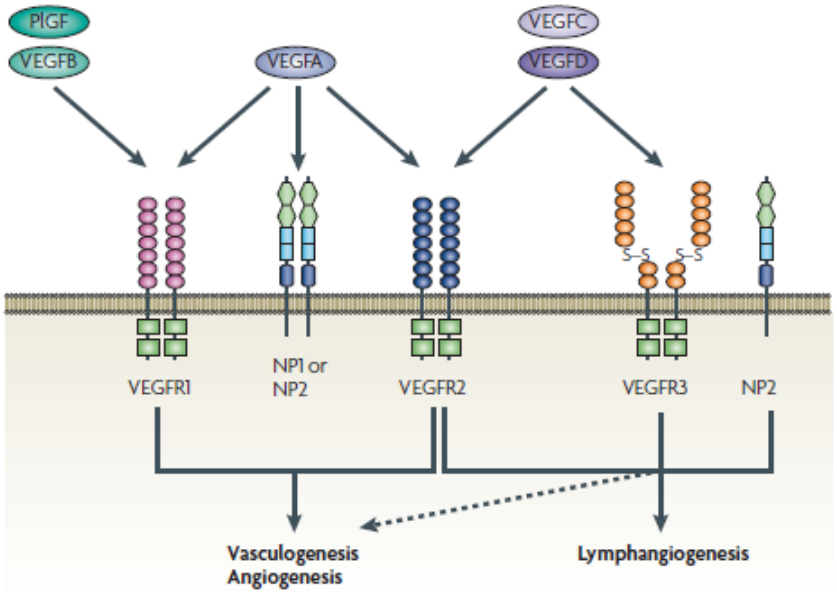


Figure excerpted from Ellis, L and Hicklin, D.J. 2008, Nat Rev Cancer 8: 579-591

Analytical Similarity Evaluations

- Analytical comparison of ABP215 and US-licensed Avastin to support a demonstration that ABP215 is “highly similar” to US-licensed Avastin

- Pairwise comparisons of ABP215, US-licensed Avastin, and EU-approved bevacizumab to support the analytical portion of the scientific bridge between the three products

The scientific bridge is needed to justify the relevance of data generated using EU-approved bevacizumab in the comparative clinical study in NSCLC to support a demonstration of biosimilarity to US-licensed Avastin.

Quality Attributes Evaluated

Primary structure

- Intact molecular weight
- Amino acid sequence
- Disulfide bonds

Higher order structure

- Secondary structure
- Tertiary structure
- Thermal Stability

Glycosylation

- Afucosylation
- Galactosylation
- High Mannose
- Sialylation

Drug product attributes

- Protein content
- Sub-visible particles
- Deliverable volume
- Appearance, pH, osmolality

Biological activities: Fab-Mediated

- Inhibition of Human Umbilical Vein Endothelial Cell (HUVEC) Proliferation
- VEGFA binding
- Binding kinetics for VEGFA isoforms (165, 121, and 111)
- Binding Specificity

Biological activities: Fc-Mediated

- FcRn
- Fcg Receptors [RIa, RIIa, RIIb, RIIIa (158V and 158F type), RIIIb]
- C1q
- Antibody-dependent cellular cytotoxicity (ADCC)
- Complement-dependent cytotoxicity (CDC)

Product related species

- Charge Variants
  - Acidic
  - Main
  - Basic
- Size Variants
  - Dimers and high-molecular weight species (HMW)
  - Heavy chain (HC) and light chain (LC) fragments

Stability

- Degradation profiles under accelerated and stress conditions

Multiple orthogonal methods were used for some attributes

Product Lots Used and Data Analysis

Product	Number of lots
ABP215 DP (DS)	19 (13)
US-licensed Avastin	27
EU-approved bevacizumab	29

Attribute Assessment	Statistical tools
Tier 1	Equivalence testing
Tier 2	Quality ranges
Tier 3	Graphical comparison

DP: Drug Product
DS: Drug Substance; 13 independent lots were used to derive 19 DP lots

- ABP215 lots used in clinical studies and from the proposed commercial process were included in analytical similarity assessment
- Applicant's comparative analysis was supported by statistical analysis
- FDA's evaluation also included independent statistical analysis

Statistical Equivalence Testing for Tier 1 Quality Attributes

Tianhua Wang, Ph.D.
Product Quality Statistical Reviewer
Office of Biostatistics, CDER
U.S. Food and Drug Administration

Tier 1 Quality Attributes for Statistical Equivalence Analysis

Assays that assessed the primary mechanism of action (**Tier 1 attributes**) were tested using **Equivalence Testing**.

1. % Relative Potency as assessed by Proliferation Inhibition Bioassay

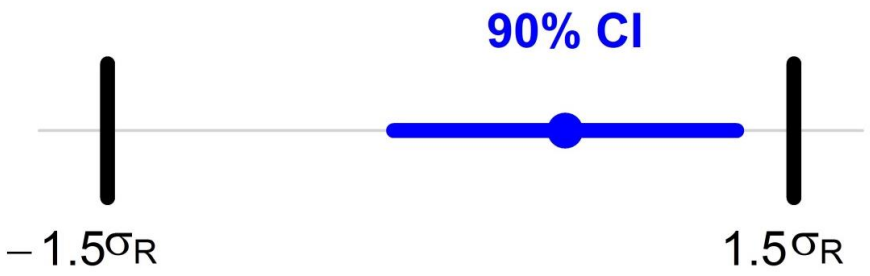
2. VEGF-A Binding by the enzyme-linked immunosorbent assay (ELISA)

Statistical Equivalence Test

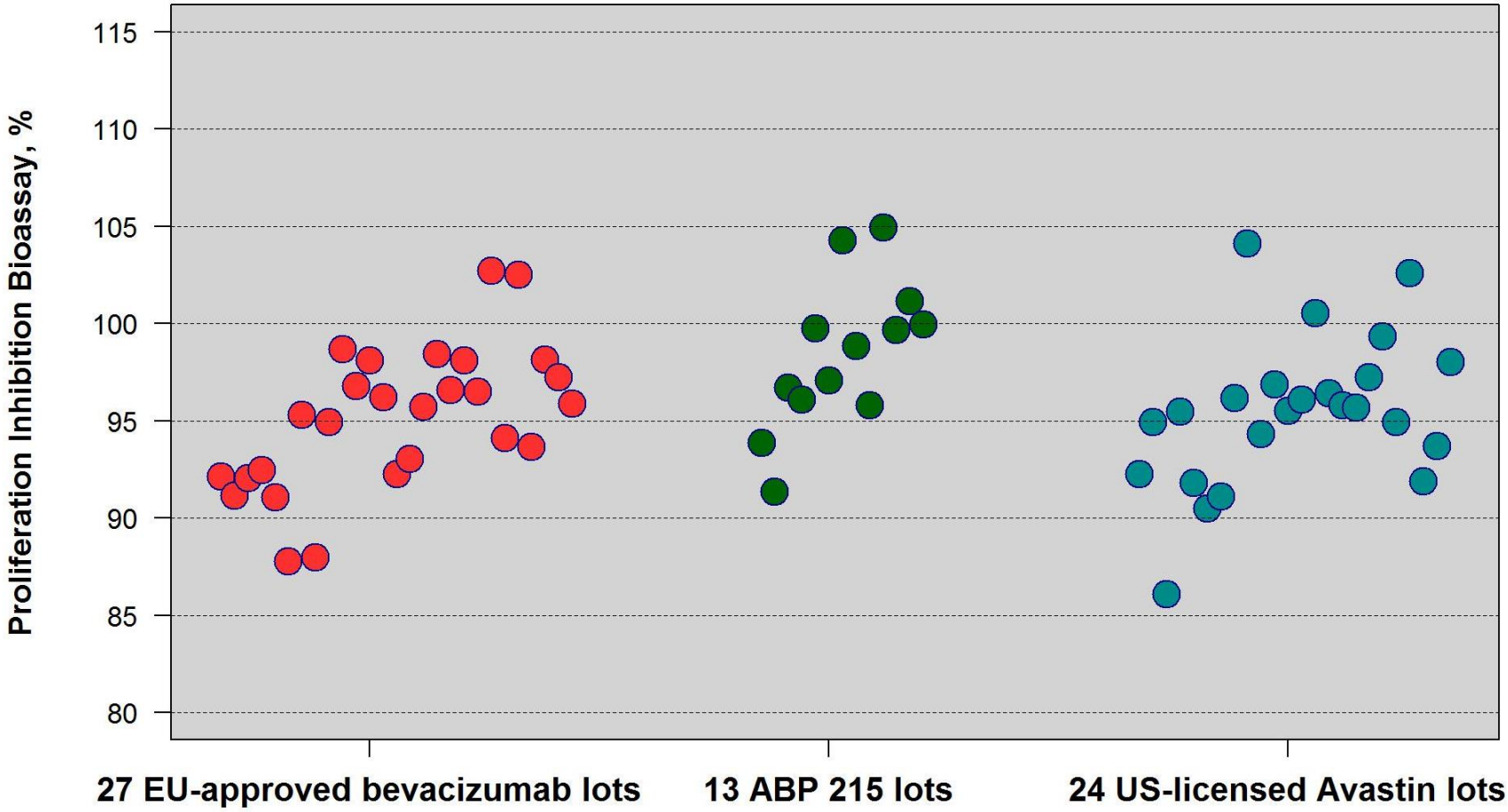
- **MeanDiff** = Mean(Test) – Mean(Reference)
- σ_R: standard deviation of reference product
- The hypotheses:

Null	**MeanDiff** $\leq -1.5\sigma_R$ **or MeanDiff** $\geq +1.5\sigma_R$
Alternative	$-1.5\sigma_R <$ **MeanDiff** $< +1.5\sigma_R$

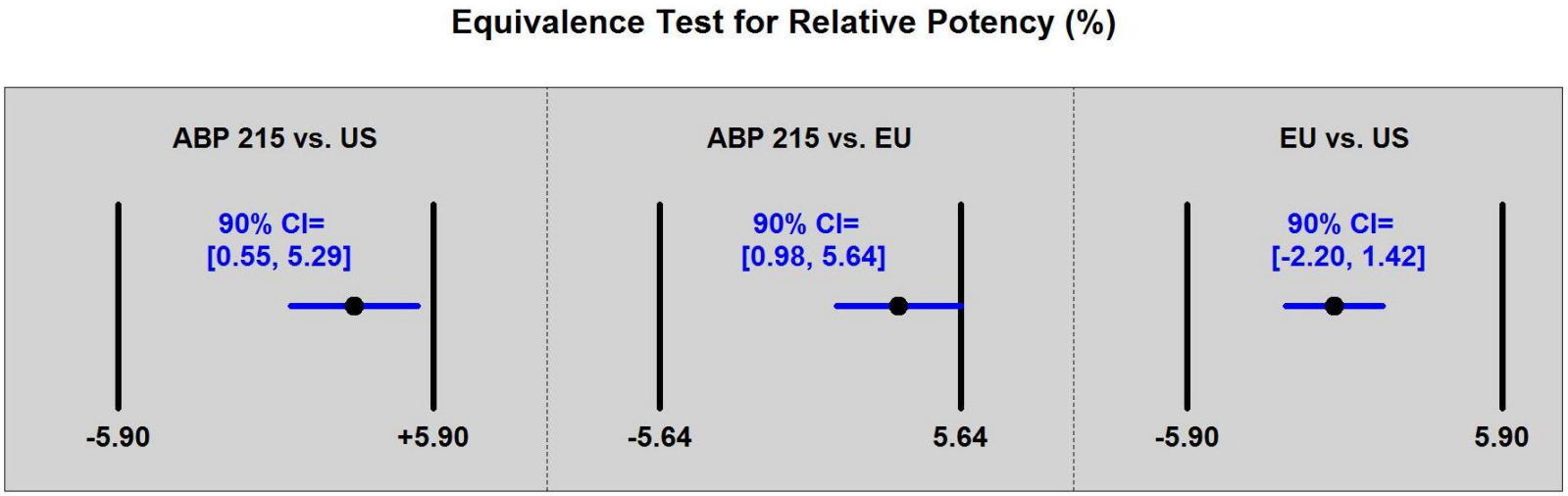
- Test and reference pass the equivalence test if



% Relative Potency as Assessed by Proliferation Inhibition Bioassay



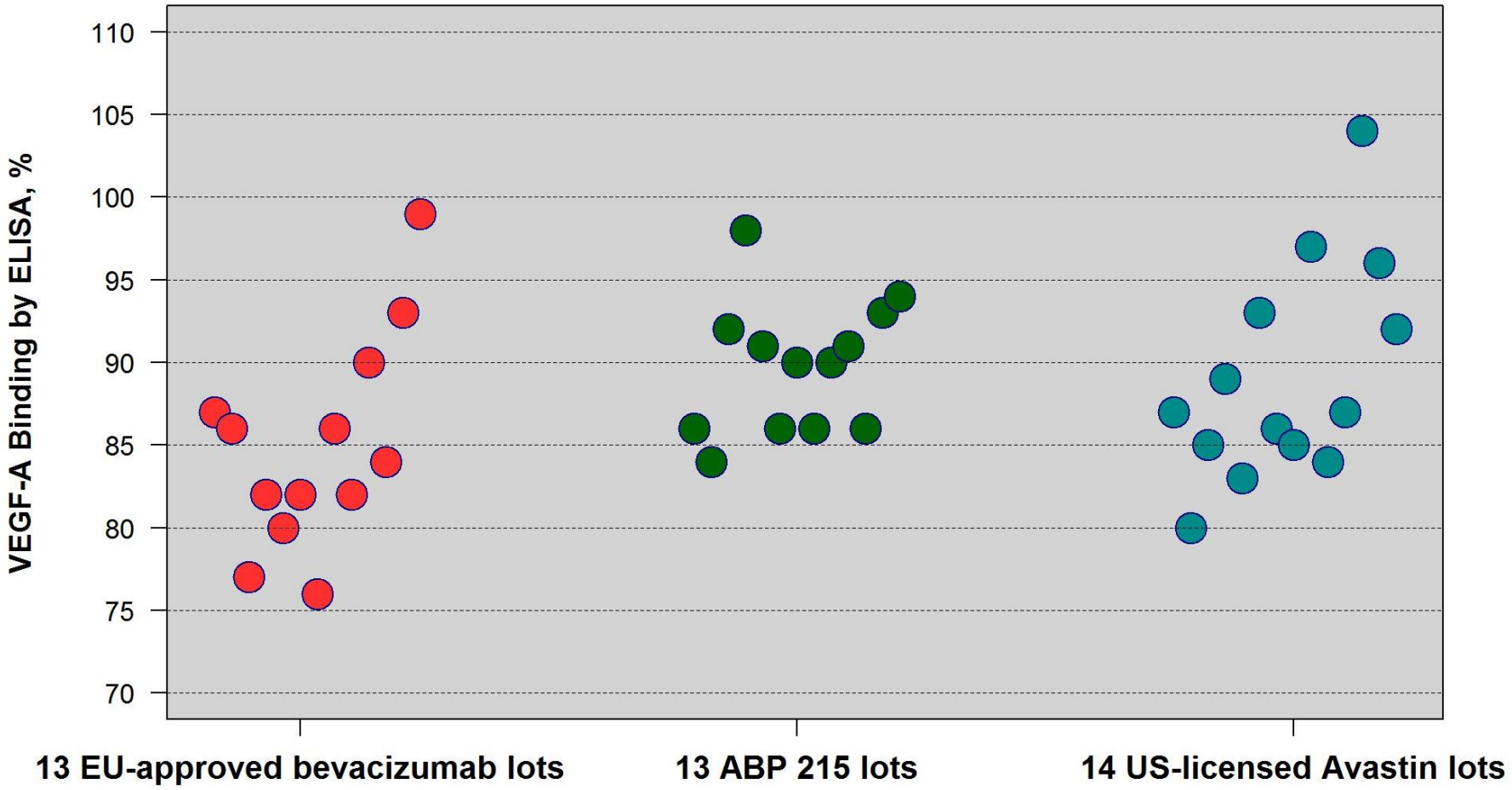
Equivalence Testing for Relative Potency (%)



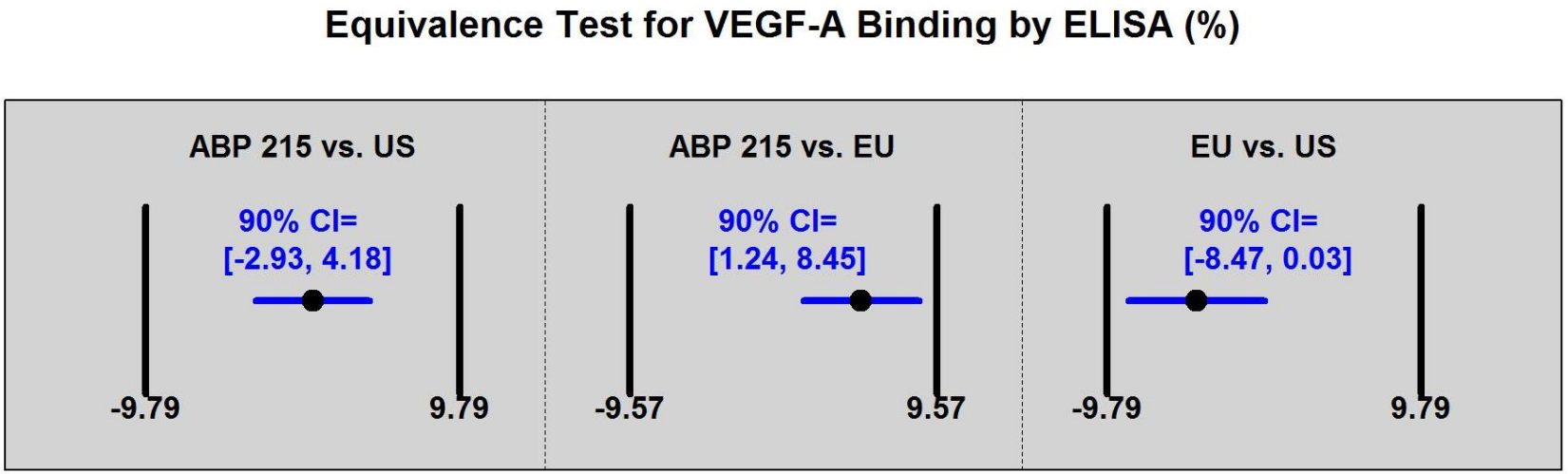
Comparison	# of lots	Mean Difference, %	90% Confidence Interval for Mean Difference, %	Equivalence Margin, %	Pass Equivalence Test?
ABP215 vs. **US**	(13,24)	2.92	(0.55, 5.29)	(-5.90, +5.90)	Yes
ABP215 vs. **EU**	(13,27)	3.31	(0.98, 5.64)	(-5.64, +5.64)	Yes
EU vs. **US**	(27,24)	-0.39	(-2.21, 1.42)	(-5.90, +5.90)	Yes

US = US-licensed Avastin; EU = EU-approved bevacizumab

VEGF-A Binding by ELISA



Equivalence Test for VEGF-A Binding by ELISA



Comparison	# of lots	Mean Difference, %	90% Confidence Interval for Mean Difference, %	Equivalence Margin, %	Pass Equivalence Test?
ABP215 vs. **US**	(13,14)	0.63	(-2.93, 4.18)	(-9.79, +9.79)	Yes
ABP215 vs. **EU**	(13,13)	4.85	(1.24, 8.45)	(-9.57, +9.57)	Yes
EU vs. **US**	(13,14)	-4.22	(-8.47, 0.03)	(-9.79, +9.79)	Yes

US = US-licensed Avastin; EU = EU-approved bevacizumab

Equivalence Testing Summary

Pairwise comparisons for both Tier 1 quality attributes pass equivalence testing.

1. Supports a demonstration that ABP215 is highly similar to US-licensed Avastin.

2. Supports the analytical portion of the scientific bridge to justify the relevance of EU-approved bevacizumab data from the comparative clinical study.

Product Quality Review Continued

Jee Chung, Ph.D.
Product Quality Reviewer
Office of Biotechnology Products, CDER
U.S. Food and Drug Administration

Analytical Similarity Summary

Quality Attribute	Supports a Demonstration of Highly Similar
Primary Structure	Yes
Higher Order Structure	Yes
Biological Activities • Inhibition of HUVEC Proliferation Bioassay • VEGFA Binding • FcRn • FcgRIa, FcgRIIa, FcgRIIb, FcgRIIIb, FcgRIIIa 158F type • FcgRIIIa 158V type • C1q Binding • Specificity for VEGFA • ADCC • CDC	Yes Yes Yes Yes Yes (#) Yes Yes Yes Yes

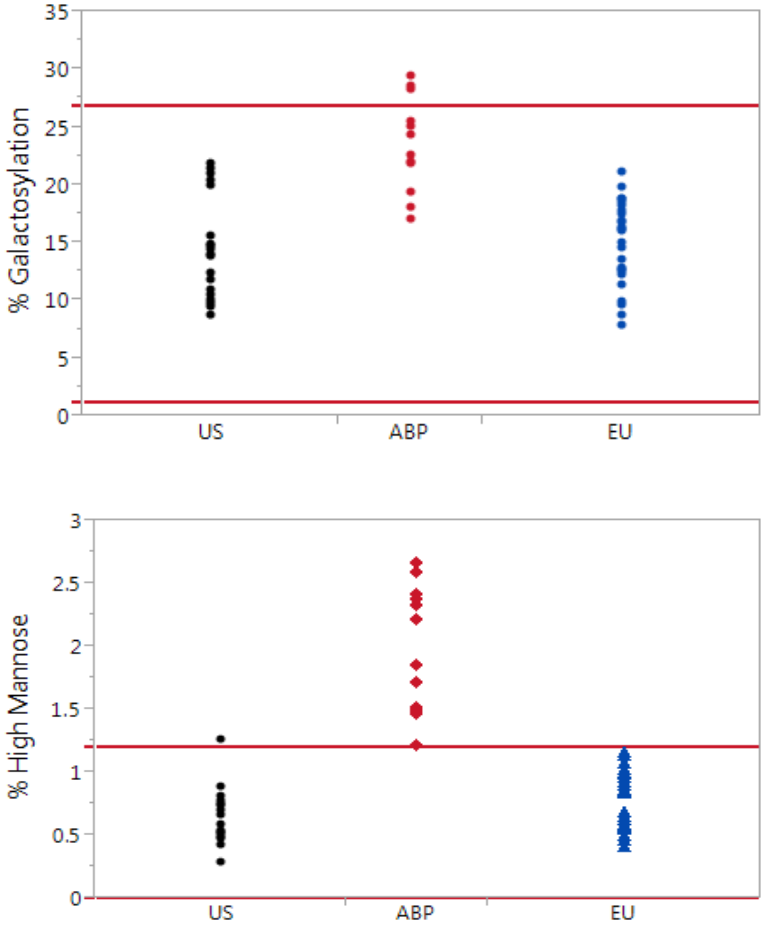
Quality Attribute	Supports a Demonstration of Highly Similar
Size Variants/Aggregates	Yes (#)
Size Variants/Fragments	Yes (#)
Charge Variants	Yes (#)
Glycosylation	Yes (#)
Sub-visible Particles	Yes
General Properties	Yes

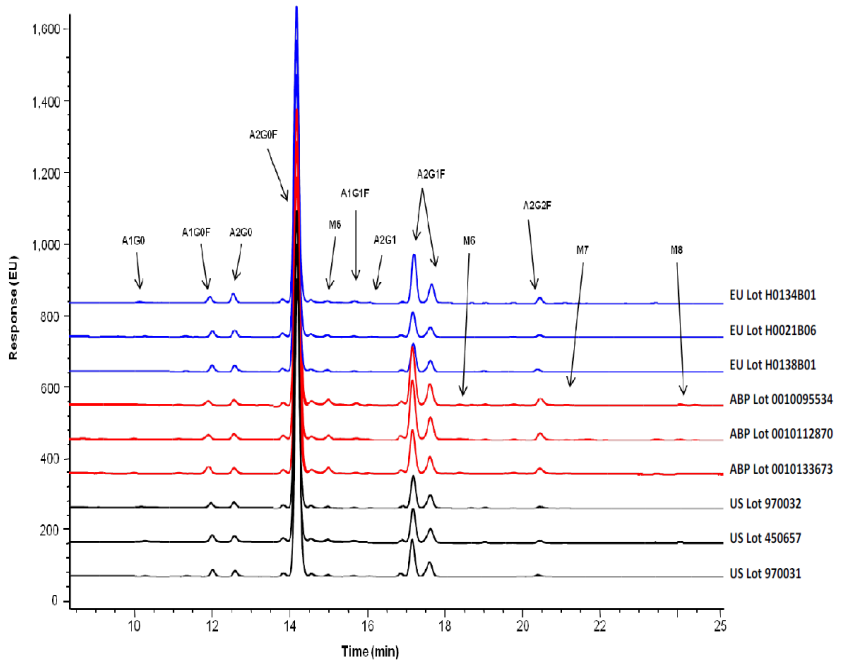
Differences in the indicated quality attributes did not preclude a demonstration that ABP215 is highly similar to US-licensed Avastin

Quality Attribute Differences

- Glycosylation Content
  - Galactosylation
  - High mannose
- FcgRIIIa (158V) Binding
- Product Related Species
  - Aggregates
  - Fragments
  - Charge variants

Differences in Glycosylation





Blue: EU-approved bevacizumab
Red: ABP215
Black: US-licensed Avastin

Red Lines are US Quality Ranges (QR)

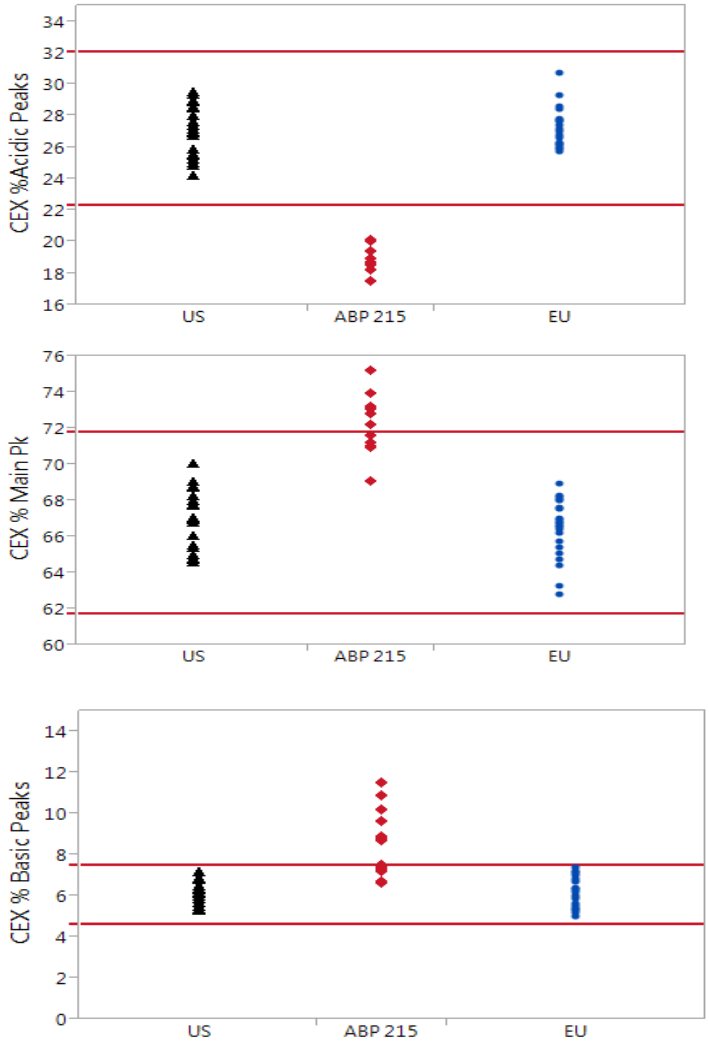
Addressing Glycosylation and FcγRIIIa (158V) Binding Differences

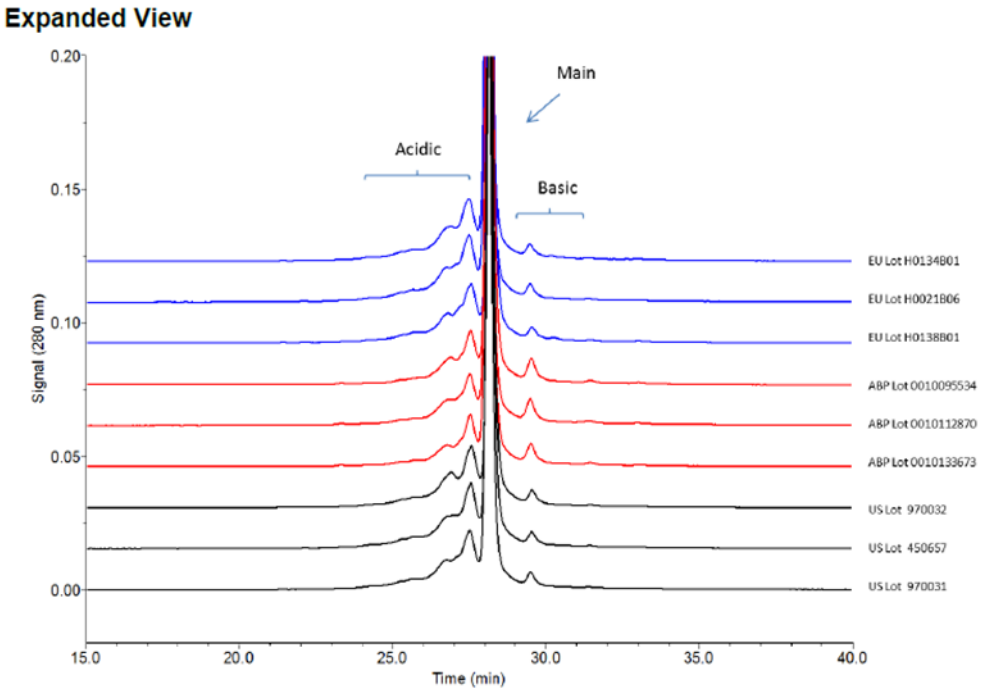
- Glycosylation of monoclonal antibodies can affect the in vivo biological activity
  - Galactosylation: Terminal galactose residues on N-linked glycans are known to affect binding to C1q and enhance CDC activity
  - High mannose: Increase monoclonal antibody clearance by binding to mannose receptors; have increased binding affinities for FcgRIIIa and enhanced ADCC activity

- In vitro cell based ADCC and CDC activities were assessed and were not detected for all three products

- Clinical pharmacokinetic data further addressed the residual uncertainty and showed that differences between the three products were unlikely to have clinical impact

Differences in Product Related Species: Charge Variants





Blue: EU-approved bevacizumab
Red: ABP215
Black: US-licensed Avastin

Red Lines are US QR

Addressing Differences in Charge Variants

- Post-translational modifications of monoclonal antibodies can lead to differences in charge variants
  - Acidic and Basic Peaks: consist of product degradants such as deamidated or oxidized species, sialylated glycan species, N-and C-terminal variants
- The Applicant isolated and characterized acidic and basic peaks and identified the same types of product variants in each peak for all three products, albeit in different amounts
- Carboxypeptidase treatment of ABP215 resulted in similar basic peak levels as US-licensed Avastin and EU-approved bevacizumab
  - Differences in the levels of C-terminal lysine residue of monoclonal antibodies were not considered relevant, as C-terminal lysine residues are known be removed in vivo shortly after administration, and removal does not impact product efficacy (Liu, H., et. al. Mabs 2015 Sept-Oct; 6(5): 1145-1154)
- Similar potency was demonstrated for all three products

Overall Conclusions for Analytical Similarity

- The totality of the analytical similarity data supports a conclusion that ABP215 is highly similar to US-licensed Avastin notwithstanding minor differences in clinically inactive components.

- Adequate justification for the analytical portion of the scientific bridge between ABP215, US-licensed Avastin and EU-approved bevacizumab was provided.

Clinical Pharmacology

Edwin C.Y. Chow, Ph.D.
Clinical Pharmacology Reviewer
Office of Translational Sciences, CDER
U.S. Food and Drug Administration

Clinical Pharmacology Overview

The clinical pharmacology program aims to support the demonstration of no clinically meaningful differences between ABP215 and US-licensed Avastin by:

- Evaluating the single-dose pharmacokinetic (PK) similarity between ABP215 and US-licensed Avastin, and

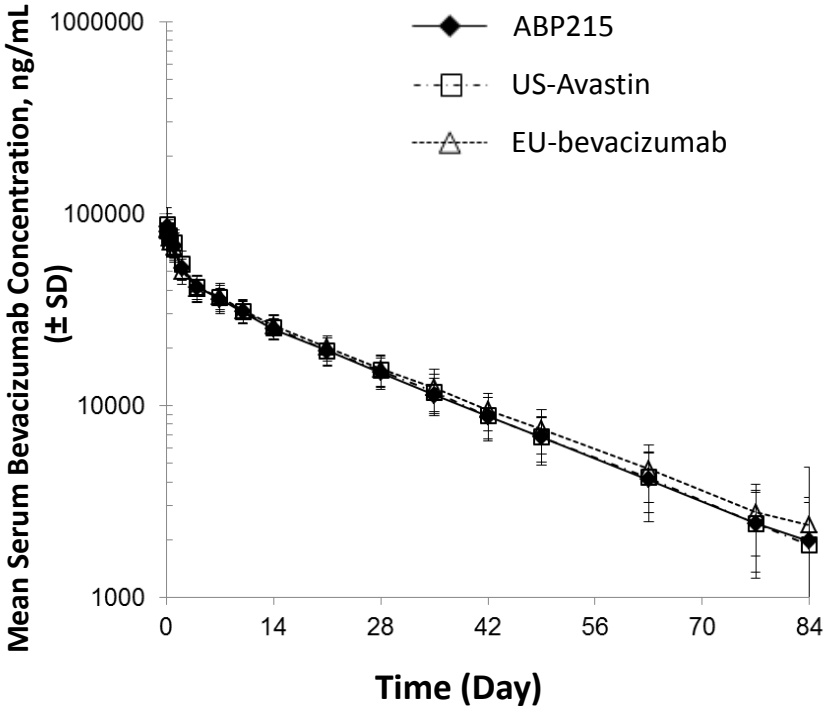
- Establishing the PK portion of the scientific bridge between ABP215, US-licensed Avastin and EU-approved bevacizumab.

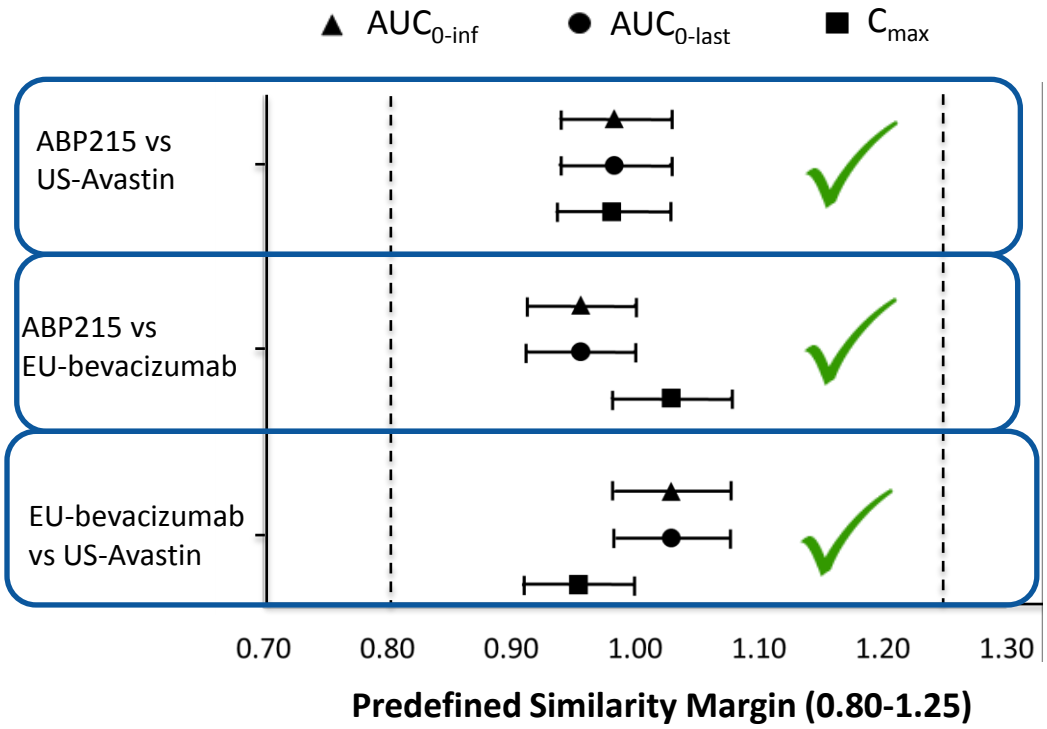
Clinical Studies

Study	Population	Design	Primary Endpoint	Dosing
20110216	Healthy subjects (N=202)	3-arm, parallel-group study of ABP215, US-licensed Avastin, and EU-approved bevacizumab	PK similarity	Single dose, 3 mg/kg IV
20120265	NSCLC patients (N=642)	Multicenter, randomized, double-blind, parallel-group study of ABP215, and EU-approved bevacizumab	ORR	15 mg/kg IV every 3 weeks for 18 weeks

IV: Intravenous; PK: pharmacokinetics; NSCLC: non-small cell lung cancer; ORR: Overall response rate

Study 20110216 Demonstrated PK Similarity





The geometric mean ratios and 90% CIs are within the pre-specified 0.80-1.25 range.

SD: standard deviation; AUC: area under curve; C_{max}: maximum concentration

Clinical Pharmacology Summary

Results of Study 216:

- Demonstrated PK similarity between ABP215 and US-licensed Avastin.

- Established the PK portion of the scientific bridge between ABP215, US-licensed Avastin, and EU-approved bevacizumab.
  - Justifies the relevance of the comparative clinical data generated with EU-approved bevacizumab.

Clinical Pharmacology Conclusion

The PK results support a demonstration of no clinically meaningful differences between ABP215 and US-licensed Avastin, and add to the totality of the evidence to support a demonstration of biosimilarity of ABP215 and US-licensed Avastin.

Comparative Clinical Study

Vivian Yuan, Ph.D.
Statistical Reviewer
Office of Biostatistics, CDER
U.S. Food and Drug Administration

Goal of the Study

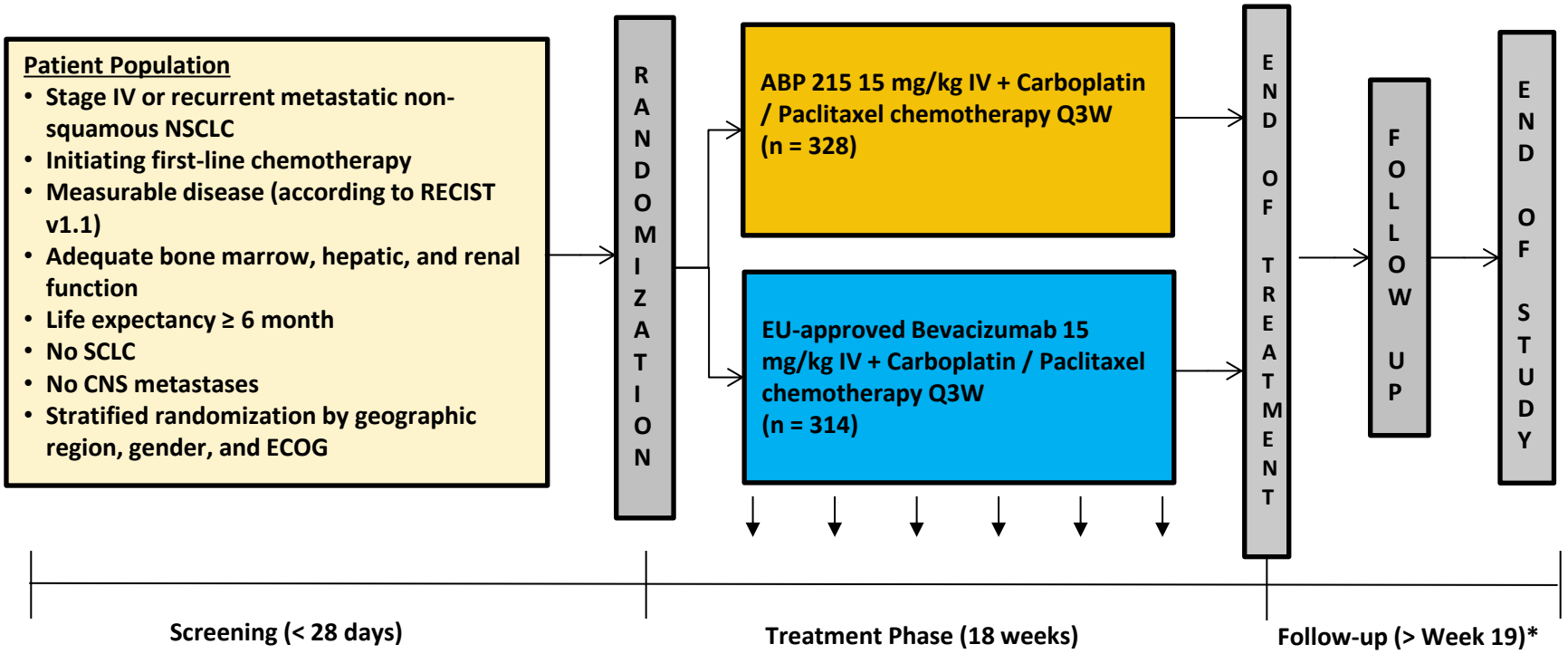
- Support a demonstration of no clinically meaningful differences
- Not to establish comparative efficacy
- Similarity test
  - Neither superior nor inferior
  - Pre-specified margins

Margin Selection

- Reference product effect size from meta-analysis
- Constancy: clinical implications of margin size
- Study design characteristics

Study 20120265

Study of ABP 215 Compared with EU-approved Bevacizumab in Subjects with Advanced NSCLC



*Maintenance monotherapy not included
CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; Q3W = once every 3 weeks

Source: BLA files

Study Endpoints

- Primary: objective response rate (ORR) by RECIST v1.1, as assessed by central, independent, blinded radiologists

- Secondary:
  - Duration of response (DOR), and
  - Progression-free survival (PFS)

Primary Objective

- Applicant's proposal: Compare the 2-sided 90% CI of the ORR risk ratio (RR) between ABP215 and EU-approved bevacizumab with similarity margin (0.67, 1.5)

- 95% power

- FDA's calculated margin is different from the Applicant's

- The study result was compared to both the Applicant's and FDA's margins

FDA's Margin

- Meta-analysis: Four trials were included to estimate the historical effect of the reference product: E4599, JO19907, AVF07571, and AVAiL

N (CT/BCT)	CT	BCT	RR (95% CI*)
810/865	19.3%	**37.7%**	0.53 (0.45, 0.63)

*CI = Confidence Interval; CT= chemotherapy; BCT = bevacizumab with chemotherapy; RR = risk ratio

- The Null hypothesis

$$\frac{\text{ORR}_{\text{ABP215}}}{\text{ORR}_{\text{EU-approved bevacizumab}}} \leq 0.73, or \frac{\text{ORR}_{\text{ABP215}}}{\text{ORR}_{\text{EU-approved bevacizumab}}} \geq 1.36$$

- The alternative hypothesis

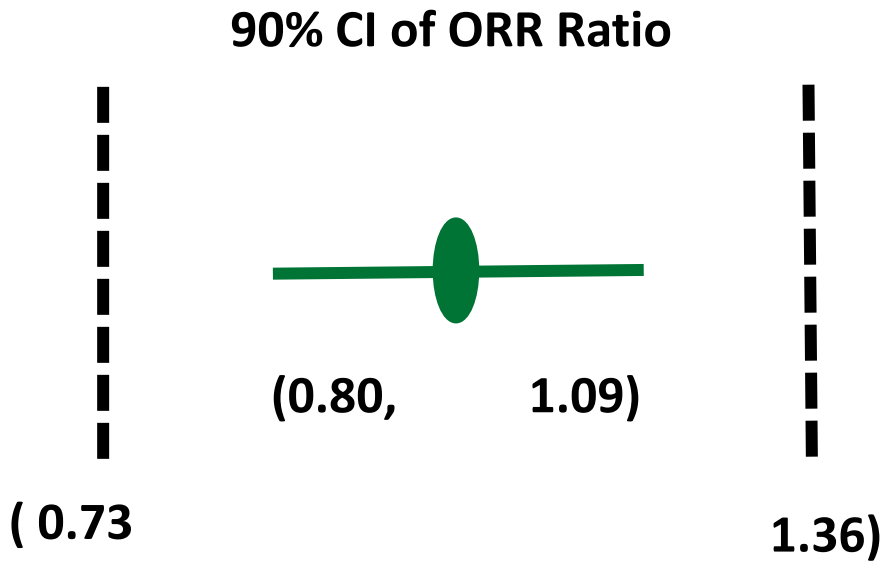
$$0.73 < \frac{\text{ORR}_{\text{ABP215}}}{\text{ORR}_{\text{EU-approved bevacizumab}}} < 1.36$$

Primary Results

	ABP215	EU-approved bevacizumab
N	328	314
Response	128	131
Complete	2	2
Partial	126	129
ORR	39.0%	41.7%
ORR 95%CI	(33.7%, 44.5%)	(36.2%, 47.4%)
RR, 90% CI	0.93 (0.80, 1.09)	
Applicant's margin	(0.67, 1.50)	
FDA margin	(0.73, 1.36)	

Test for Similarity

Similarity margin per ORR ratio: (0.73, 1.36)



Summary

- ORR accepted by FDA as the primary endpoint.
- Similarity margin was calculated based on historical data and clinical considerations.
- The results of the comparative clinical study support a demonstration of no clinically meaningful differences between ABP215 and US-licensed Avastin.

- **Summary of Safety**
- **Extrapolation**
- **Summary of FDA Analysis of Similarity**

Sandra Casak, M.D.
Clinical Reviewer
Office of Hematology and Oncology Products, CDER
U.S. Food and Drug Administration

Study 20120265: Summary of Safety

- FDA agrees with the Applicant's analysis.
- There were no new safety signals.
- FDA agrees that there were no meaningful differences in safety between the study treatment arms.

Avastin Indications

- metastatic colorectal cancer (mCRC), in combination with intravenous (IV) 5-fluorouracil- (5-FU)-based chemotherapy for first- or second-line treatment
- mCRC, in combination with fluoropyrimidine-, irinotecan-, or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab containing regimen
- non-squamous non-small cell lung cancer (NSCLC), in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent, or metastatic disease
- glioblastoma multiforme (GBM), as a single agent for adult patients with progressive disease following prior therapy
- metastatic renal cell carcinoma (mRCC), in combination with interferon alfa
- cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease
- platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan
- platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer , in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine

Extrapolation

It may be appropriate for a biosimilar product to be licensed for one or more conditions of use (e.g., indications) for which the reference product is licensed, based on data supporting a demonstration of biosimilarity, including, e.g., data from clinical study(ies) performed in another condition of use.

Also see FDA Guidance for Industry “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product”

Scientific Justification for Extrapolation

If a biological product meets the statutory requirements for licensure as a biosimilar product … the Applicant needs to provide sufficient scientific justification for extrapolation, which should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action (MOA), if known or can reasonably be determined, in each condition of use for which licensure is sought,
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations,
- The immunogenicity of the product in different patient populations,
- Differences in expected toxicities in each condition of use and patient population,
- Any other factor that may affect the safety and efficacy of the product in each condition of use and patient population for which licensure is sought.

Mechanism of Action

- Bevacizumab binds VEGF-A and prevents its interaction with VEGFR-1 and VEGFR-2 on the surface of endothelial cells.

- In all conditions of use, angiogenesis is a crucial component for growth and invasiveness of the primary tumor and metastases.

- The MOA of bevacizumab in all indications is inhibition of angiogenesis and normalization of the tumor vasculature.

- There is no evidence in the literature to support claims of a unique MOA in a specific condition of use.

PK and Biodistribution

- PK characteristics of bevacizumab are similar between indications approved for US-licensed Avastin.
- There are no relevant PK-related interactions when bevacizumab is administered concurrently with chemotherapy.
- Body weight and gender are the covariates related to inter-patient variability irrespective of the type of cancer.
- Study 216 demonstrated PK similarity between ABP215 and EU-approved bevacizumab, ABP215 and US-licensed Avastin, and US-licensed Avastin and EU-approved bevacizumab.
- Study 265 supports the finding of the PK Study 216.

Immunogenicity

- Avastin USPI: incidence of anti-drug antibody (ADA) is low (0.6%)
- No ADAs in Study 216
- Study 265: similar low rates in the formation of ADAs

Toxicity

- Bevacizumab has a well characterized safety profile.
- Risk of a particular toxicity may differ by disease setting (i.e., fistula formation is more common in cervical cancer and hemoptysis is more common in NSCLC) but are present in all disease settings.
- Safety profile observed in Study 265 is very similar to the profile observed in randomized controlled studies (RCTs) of bevacizumab in NSCLC.
- There were no meaningful differences between arms in Study 265.

Extrapolation: Conclusions

- Based on the totality of the data, including analytical and PK similarity as well as no meaningful differences in anti-tumor activity, safety, and immunogenicity

AND

- Considering that there are no known differences in the MOA, PK, immunogenicity, and safety across different indications for US-licensed Avastin,

Extrapolation of similarity from ABP215 to all US-Avastin indications is scientifically justified.

Summary

- ABP215 and US-licensed Avastin are highly similar, notwithstanding minor differences in clinically inactive components;
- Adequate bridging data (analytical and PK) justifies the relevance of data obtained using EU-approved bevacizumab to support a demonstration of biosimilarity of ABP215 to US-licensed Avastin;
- PK data support the conclusion of biosimilarity;
- Clinical data obtained in patients with NSCLC support a demonstration that there are no clinically meaningful differences between ABP215 and US-licensed Avastin;
- Extrapolation of the data obtained scientifically justifies extrapolation to all US-approved Avastin indications;
- **The totality of the data support the Applicant's claim that ABP215 is biosimilar to US-licensed Avastin.**

Discussion Points

Discussion point 1: Please discuss whether the evidence supports a demonstration that ABP215 is highly similar to US-licensed Avastin, notwithstanding minor differences in clinically inactive components.

Discussion point 2: Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between ABP215 and US-licensed Avastin in the studied condition of use.

Discussion point 3: Please discuss whether there is adequate scientific justification to support licensure for all of the proposed indications.

Voting Question

Does the totality of the evidence support licensure of ABP215 as a biosimilar product to US-licensed Avastin for each of the indications for which US-licensed Avastin is currently licensed and for which the Applicant is seeking licensure as listed below:

- Metastatic colorectal cancer, with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment.
- Metastatic colorectal cancer, with fluoropyrimidine-irinotecan- or fluoropyrimidine oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen.
- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease.
- Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy.
- Metastatic renal cell carcinoma with interferon alfa.
- Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease.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