U.S. Food and Drug Administration
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Overview of the Regulatory Pathway and FDA's Guidance for the Development and Approval of Biosimilar Products in the US

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Overview of Presentation

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

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

Overview

Background

- The **Biologics Price Competition and Innovation Act of 2009 (BPCI Act)** was passed as part of health reform (Affordable Care Act) that President Obama 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.

What is an Abbreviated Licensure Pathway for Biological Products?

- 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**.**

Definition: 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.

Definition: Reference Product

Reference Product means**:**

- 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.

Definition: Interchangeability

Interchangeable or **Interchangeability** means**:**

- 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.

Note: The 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 Requirements: 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.

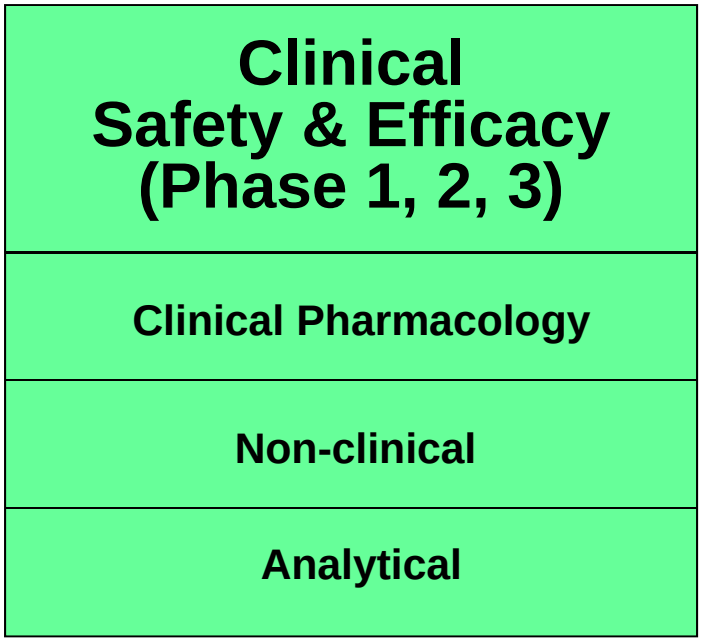
- A sponsor should justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product.

Overview of FDA's Approach to the Development of Biosimilars

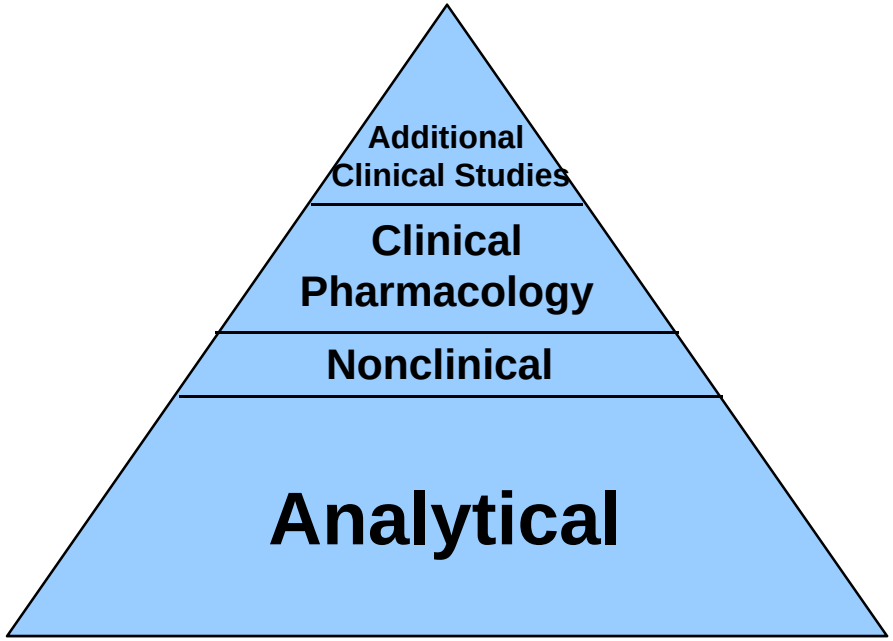
Key Development Concepts

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)



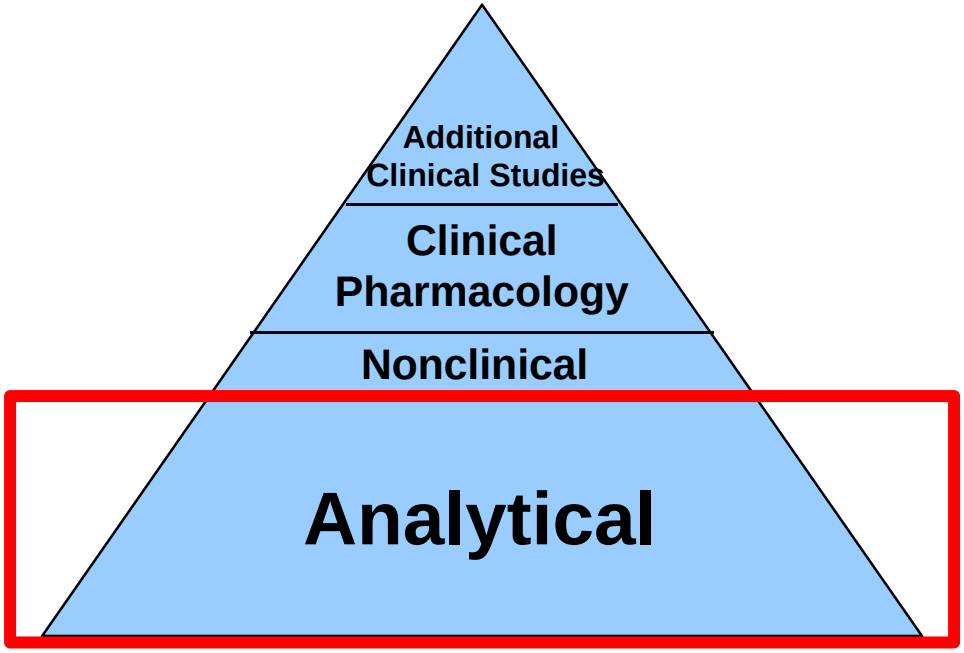
Key Concept #2:
Stepwise Evidence Development

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

- Apply a step-wise approach to data generation and the evaluation of residual uncertainty about biosimilarity
  - 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?
- There is no one "pivotal" study that demonstrates biosimilarity
- No "one size fits all" assessment

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

- Extensive **structural and functional characterization**



"Abbreviated" Development Program, 351(k) BLA

Assessing Analytical Similarity

- 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
  - Equivalence testing for certain highly critical attributes
  - Quality range (mean ± X SD) for other highly critical to low criticality attributes
  - Raw/graphical comparisons for other attributes with very low criticality or not amenable to other testing methodologies

Animal Data

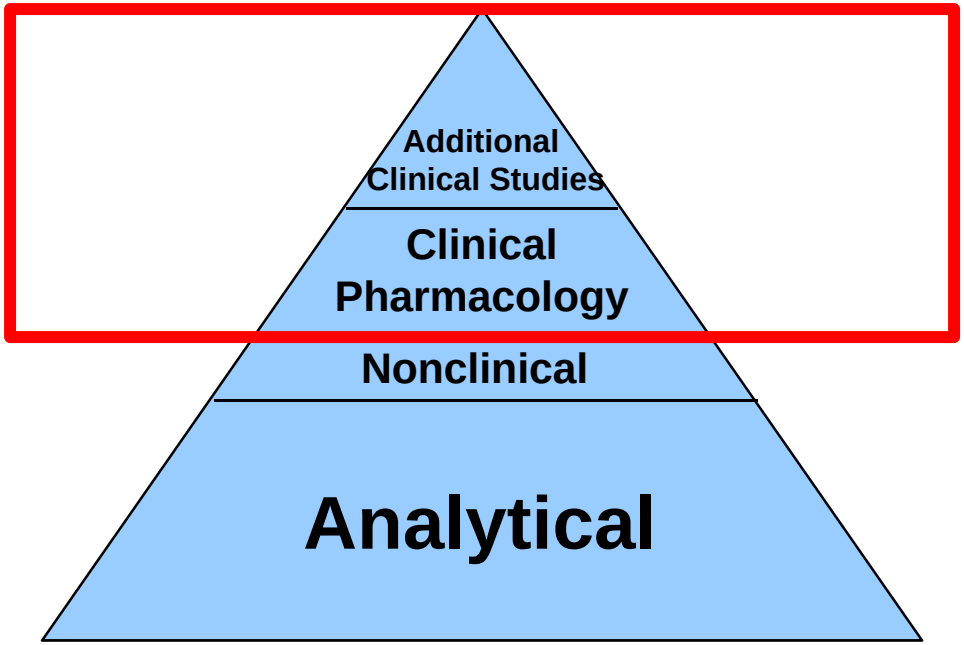
- Animal toxicity data are useful when uncertainties remain about the safety of the proposed product prior to initiating clinical studies

- 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

Extrapolation

- The potential exists for a biosimilar product to be approved for one or more conditions of use for which the US-licensed reference product is licensed based on extrapolation of data intended to support a demonstration of biosimilarity in one condition of use (e.g., indication) to other conditions of use.

- Sufficient scientific justification for extrapolating data is necessary.

Extrapolation Considerations

- FDA guidance outlines factors/issues that should be considered when providing scientific justification for extrapolation including, for example*,
  - The MOA(s) in each condition of use for which licensure is sought
  - The 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
- Differences between conditions of use do not necessarily preclude extrapolation
- Ensure totality of the evidence, including scientific justification for extrapolation, supports approach

*This list is a subset of the issues outlined in the FDA guidance document

Summary

- The content of a biosimilar development program is based on stepwise evidence development and the evaluation of residual uncertainty about biosimilarity between the proposed biosimilar product and the reference product.

- 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.

Thank you for your attention.

Introductory Remarks

351(k) BLA for GP2015, a Proposed Biosimilar to US-licensed Enbrel

Arthritis Advisory Committee

July 13, 2016

Nikolay P. Nikolov, MD
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration

Overview of the BLA

- Applicant: Sandoz
- Product: GP2015, proposed biosimilar to US-licensed Enbrel
- Dosing and route of administration: Same as the US-licensed Enbrel
- Indications for which GP2015 is developed:
  - Rheumatoid arthritis (RA)
  - Polyarticular Juvenile Idiopathic Arthritis (JIA)
  - Psoriatic arthritis (PsA)
  - Ankylosing spondylitis (AS)
  - Plaque psoriasis (PsO)

US: United States

Overview of GP2015 Development Program

- To support a demonstration that GP 2015 is **highly similar** to US-licensed Enbrel, Sandoz provided extensive data package that included analytical similarity assessment of:
  - Primary-, secondary-, and tertiary structure
  - Post-translational profile and *in vitro* functional characteristics
  - Purity and stability
  - TNF-α binding and potency

Overview of GP2015 Development Program

- To support a demonstration of **no clinically meaningful differences** between GP2015 and US-licensed Enbrel, Sandoz provided:
  - Studies to demonstrate similarity in exposure (i.e. PK) in healthy subjects
  - Comparative clinical efficacy and safety study in patients with PsO
  - Immunogenicity data in:
    - Patients with PsO and healthy subjects, and
    - Patients with PsO who were transitioned from EU-approved Enbrel to GP2015

Overview of GP2015 Clinical Program

Study ID	Design	Objectives	Subjects	Treatments	Endpoints
Clinical Pharmacology Studies					
Study 101	R, DB, 2-way cross-over	PK, safety, and immunogenicity	57 healthy subjects	SD 50 mg SC: • GP2015 • EU-Enbrel	C_{max}, AUC_t and AUC_{inf}
Study 102	R, DB, 2-way cross-over	PK, safety, and immunogenicity	54 healthy subjects	SD 50 mg SC: • GP2015 • US-Enbrel	C_{max}, AUC_t and AUC_{inf}
Study 104	R, DB, 2-way cross-over	PK, safety, and immunogenicity	54 healthy males	SD 50 mg SC: • GP2015 • EU-Enbrel	C_{max}, AUC_t and AUC_{inf}
Report 105	A cross-study comparison of studies 101 and 102				
Comparative Clinical Study					
Study 302	R, DB, PG Tx Period 1 (Wk 0-12)	Efficacy, safety, immunogenicity, PK	531 PsO patients	50 mg SC twice weekly: • GP2015 • EU-Enbrel	PASI 75
	R, DB, PG Tx Period 2 (switching) (Wk 12-30)	Safety, immunogenicity, PK	PsO patients re-randomized	50 mg SC Q weekly: • GP2015 cont'd • GP2015 switch • EU-Enbrel cont'd • EU-Enbrel switch	Safety, Immunogenicity

Overview of GP2015 Development Program

- To justify the relevance of the data generated using a non-US-licensed comparator, i.e. EU-approved Enbrel, Sandoz provided:
  - Extensive analytical bridging data between GP2015, US-licensed Enbrel, and EU-approved Enbrel, and
  - Clinical exposure (PK) bridging data between GP2015, US-licensed Enbrel, and EU-approved Enbrel in healthy subjects

Overview of GP2015 Development Program

- Sandoz also provided an extensive data package to address the scientific considerations* for extrapolation of data to support that there are no clinically meaningful differences for the additional indications sought for licensure:
  - The mechanism(s) of action (MOA) in each condition of use for which licensure is sought
  - The 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

*Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015

Discussion Questions

Discussion Question 1:

- Please discuss whether the evidence from analytical studies supports a demonstration that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components.

Discussion Question 2:

- Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in the studied condition of use (PsO).

Discussion Questions

Discussion Question 3:

- Please discuss whether the totality of the data provides adequate scientific justification to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel for the following additional indications for which US-licensed Enbrel is licensed:
  - RA
  - JIA
  - PsA
  - AS
- If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication, if relevant.

Voting Question

- Does the totality of the evidence support licensure of GP2015 as a biosimilar to US-licensed Enbrel for the following indications for which US-licensed Enbrel is currently licensed and for which Sandoz is seeking licensure (RA, JIA, AS, PsA, PsO)?

- Please explain the reason for your vote.

Product Quality Review

351(k) BLA for GP2015, a Proposed Biosimilar to US-licensed Enbrel

Arthritis Advisory Committee

July 13, 2016

Peter L. Adams, PhD
Product Quality Reviewer
Division of Biotechnology Review and Research 1
Office of Biotechnology Products

Outline

- Structure and Mechanism of Action
- GP2015 Manufacturing
- Studies to Support Biosimilarity
- Analytical Similarity Assessment

Etanercept Structure

- Reference Product : Enbrel®
- TNFR2 : Fc fusion
- 3 N-linked and 10 O-linked glycans
- Molecular weight: 150 kilodaltons
- 13 intrachain disulfide bonds (11 in TNFR2, 2 in Fc) and 3 interchain disulfide bonds (Fc hinge)
- Possesses heterogeneity typical of mammalian cell culture-derived mAbs and fusion proteins

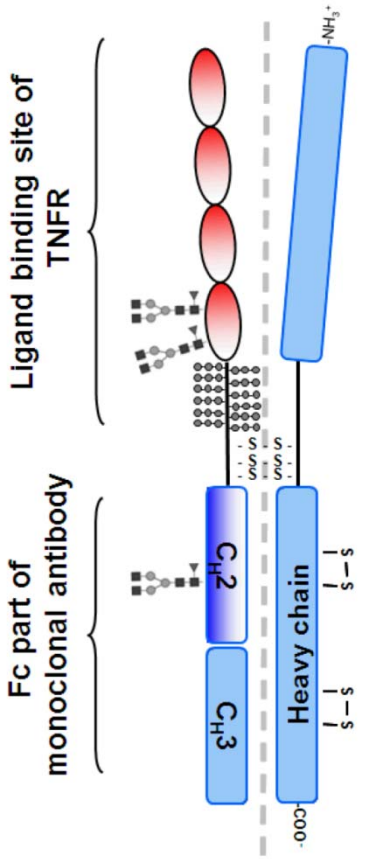
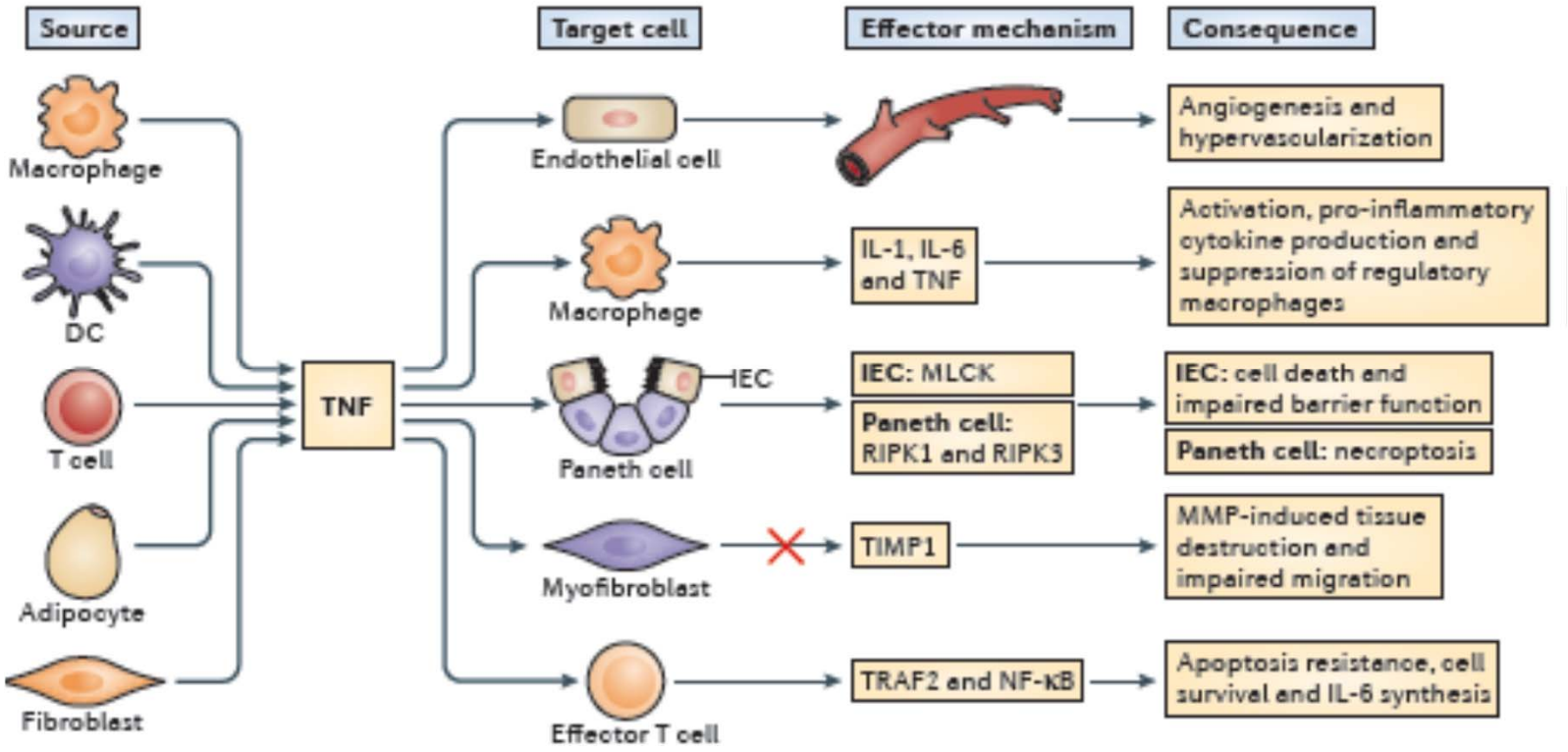


Figure taken from the Sandoz 351(k) BLA submission

TNF-α: A "Master" Cytokine

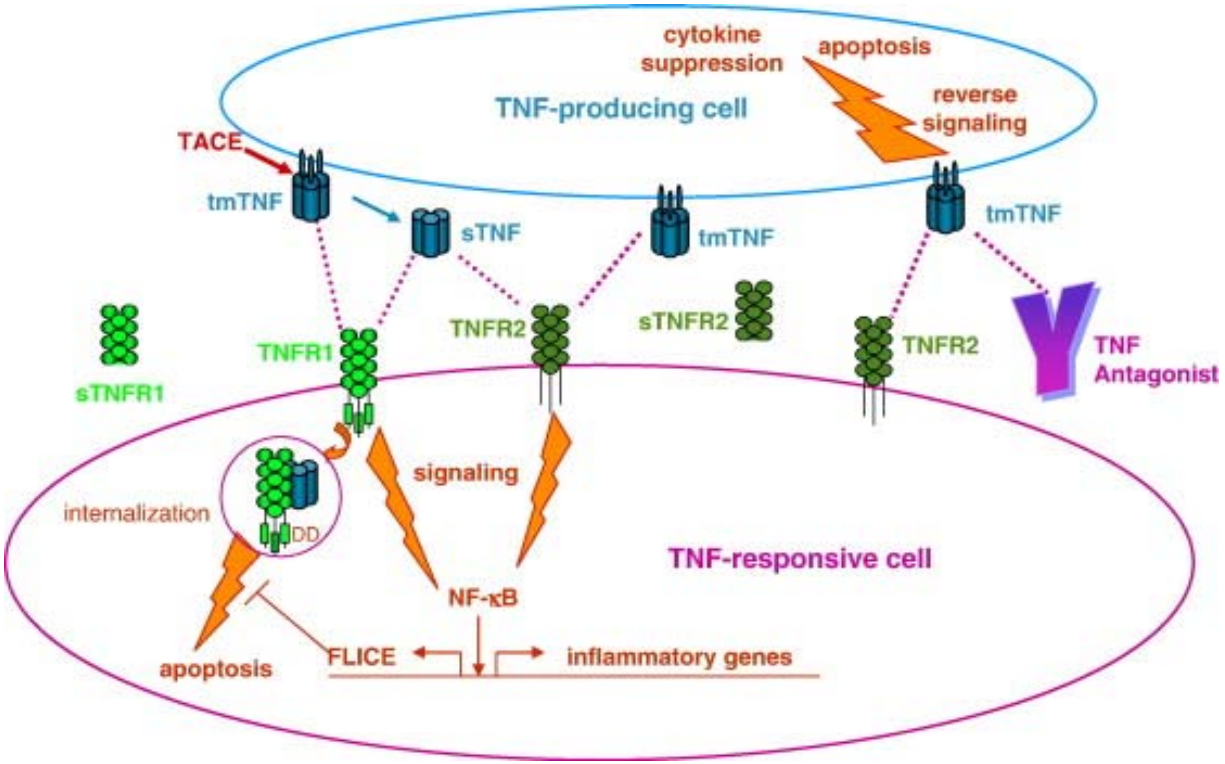
Membrane-bound (26kDa) and soluble (17kDa) forms

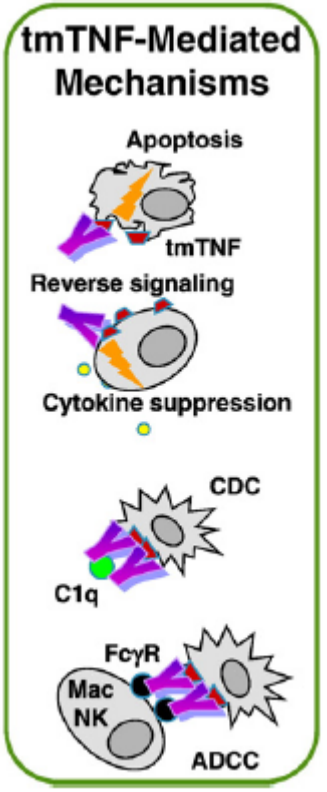


Neurath MF Nature Reviews Immunology 14, 329–342 (2014)

Mechanism of Action

- Neutralizes human tumor necrosis factor-α (TNF-α)
- Neutralizes human lymphotoxin-α (TNF-β)





Tracey, D., *et al* Pharmacology & Therapeutics 117, 244–279 (2008)

GP2015 Drug Substance

- Bioreactor production culture (mammalian cells)
- Standard biotechnology purification scheme
  - Viral safety procedures in place (testing and clearance)
  - Process related impurities (e.g., DNA, host cell proteins) adequately removed
- Drug substance lot history
  - Manufacturing lots since 2011, no changes in scale
  - Minor process changes: comparable product
- Critical Quality Attributes (CQA's) include potency, binding, aggregates, glycosylation, charge variants, host cell protein and viral safety
- Drug substance manufacturing facility inspected in Mar 2016

GP2015 Drug Product

- 50 mg/mL solution for injection
- Produced by aseptic processing and tested for sterility
- Container closure: prefilled syringe (25mg and 50mg)
- Same concentration, formulation differs from US-licensed Enbrel
- Expiry supported by stability studies

Component	25 mg/0.5mL	50 mg/1mL
Citric Acid	0.393	0.786
Sodium Citrate	6.76	13.52
Sodium Chloride	0.75	1.5
Sucrose	5	10
Lysine	2.3	4.6

Analytical Similarity

Analytical Similarity Evaluations

- An analytical comparison of GP2015 with US-licensed Enbrel is required to demonstrate that GP2015 is "highly similar" to US-licensed Enbrel

- Pair-wise comparisons of GP2015, US-licensed Enbrel, and EU-approved Enbrel are used to establish the analytical portion of the scientific bridge between the three products.

- An analytical bridge is needed
  - to justify the relevance of data generated using EU-approved Enbrel as the comparator in some clinical and non-clinical studies intended to support a demonstration of biosimilarity to US-licensed Enbrel

Methods Used to Evaluate Analytical Similarity

Quality Attribute	Method
Primary Structure	Peptide Mapping (MS/MS and UV)
	Amino Acid Analysis
	Intact Mass (MALDI)
	Disulfide bridging
	Free Cysteines
Content	Absorbance (A280nm)
Higher Order Structure	Near and Far UV Circular Dichroism
	Differential Scanning Calorimetry
	Hydrogen deuterium exchange
	FTIR
	1D-NMR
	X-ray crystallography
Higher molecular	Size exclusion chromatography (SEC)
weight species	SEC – MALLS
	Analytical Ultracentrifugation
	FFF-MALLS
Fragments	CE-SDS
	SEC

Quality Attribute	Method
Charge	Capillary Zone electrophoresis
	2D-DIGE
	cEIF
Hydrophobic variants	Reversed phase chromatography
Glycosylation and	N-linked NP-HPLC (Fc and TNFR)
Occupancy	O-linked (MALDI-TOF)
	Sialic acid (AEX, WAX and RP-HPLC labelled)
	Glycation (Boronate affinity chromatography)
In vitro Potency Assay	TNF-α reporter gene assay
	TNF-β reporter gene assay
	Apoptosis inhibition assay
Binding (TNF-α)	SPR
Binding (Fc)	FcRn SPR
	FcgRIa SPR
	FcgRIIa SPR
	FcgRIIIa & b SPR
	C1q binding
Bioassay	ADCC
	CDC

Analytical Methods: Studies to Support GP2015 High Similarity

Highly Critical Quality Attributes (QA) include:

- Amino acid identity
- Higher order structure
- In vitro TNF-α neutralization
- TNF-α binding

Analytical Results

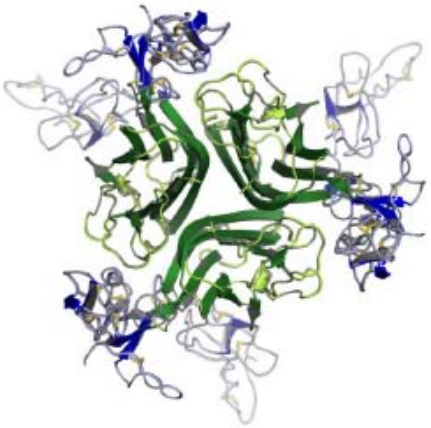
Product Lots Analyzed

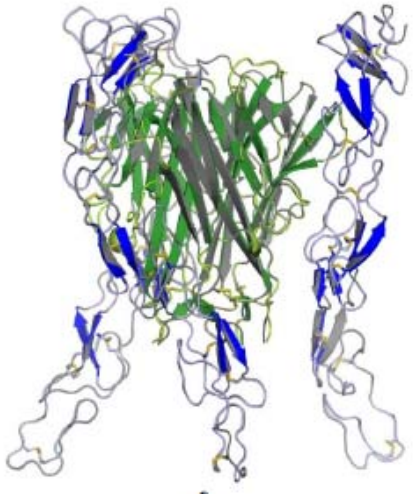
- 15 lots GP2015 DP
  - Clinical and commercial GP2015 drug product
  - Included lots used in clinical studies
- 21 lots GP2015 DS
- 34 lots US-licensed Enbrel
- 50 lots EU-approved Enbrel
- Not all lots tested for all attributes

Tertiary Structure

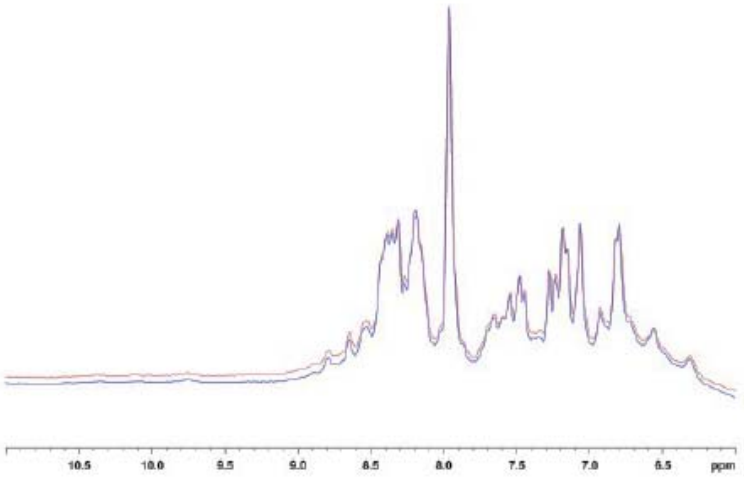
Higher Order Structural similarity demonstrated

i. X-ray Crystallography (TNFR2 co-crystallization with TNF-α)
- GP2015 DP (blue),US-Enbrel (grey) and TNF-α (green)
- rmsd =0.21Å





ii. 1D-NMR
- GP2015 DP (blue) and US-Enbrel (red)



Tertiary Structure

Higher Order Structural similarity demonstrated

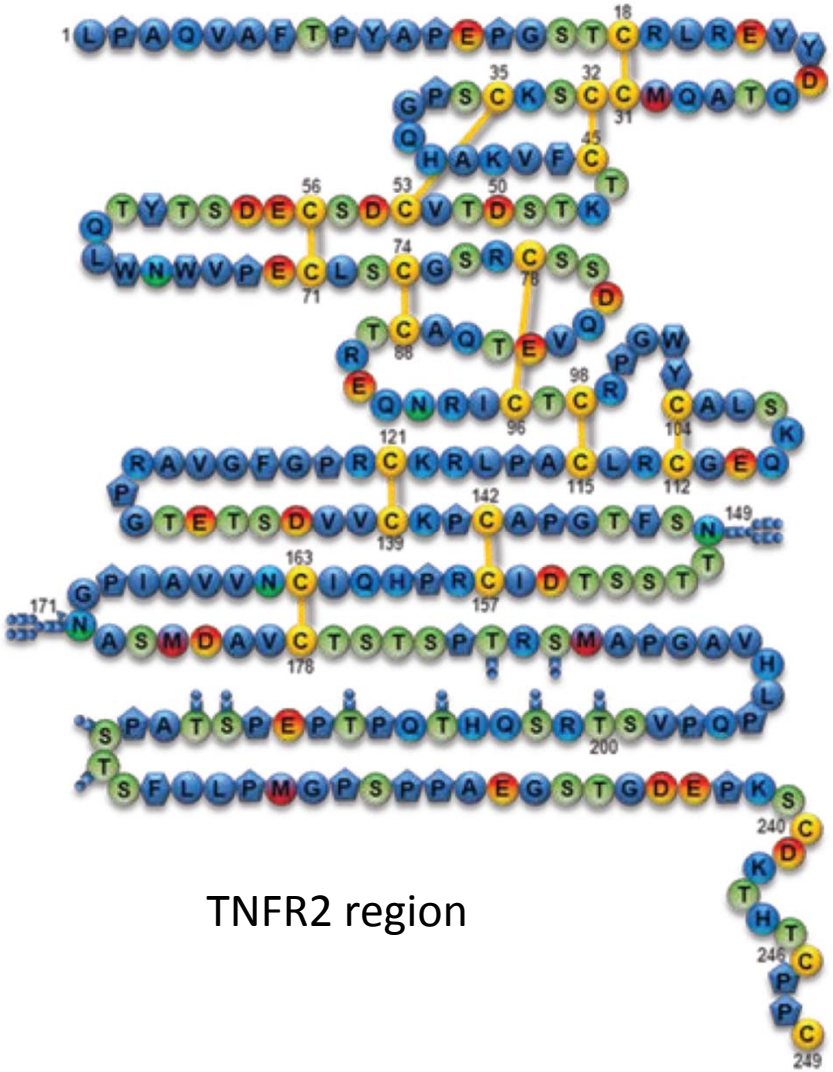
iii. Hydrogen-Deuterium Exchange

- Differences are < 1Da across the sequence

Heat map for hydrogen/deuterium exchange
GP2015 and Enbrel

Figure taken from the Sandoz 351(k) BLA submission

Disulfide Bonds



TNFR2 region

TNFR2:Fc disulfide bonds

13 intramolecular
(11 TNFR2, 2 Fc region)

3 intermolecular (Fc region)

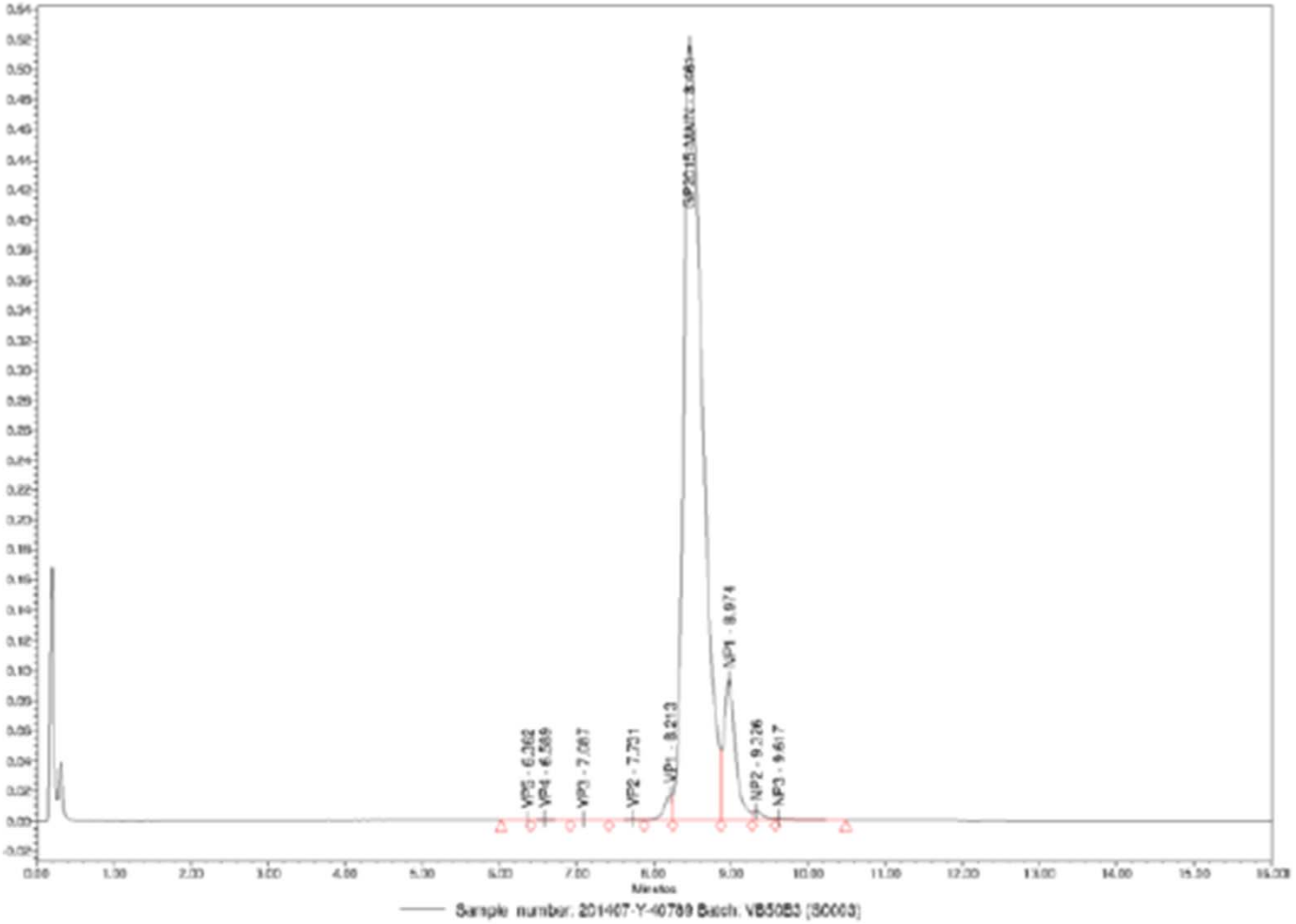
All disulfide bonds were identified in both GP2015, US-Enbrel and EU- Enbrel by non-reducing peptide mapping

Etanercept contains some misfolded protein due to wrongly bridged variants (WBV)

Figure taken from the Sandoz 351(k) BLA submission

Hydrophobic Variants

Reverse phase chromatography



ıent of the post-
ɔrotein, WBV

Figure taken from the Sandoz 351(k) BLA submission

Differences in Levels of Hydrophobic Variant by Reverse Phase Chromatography

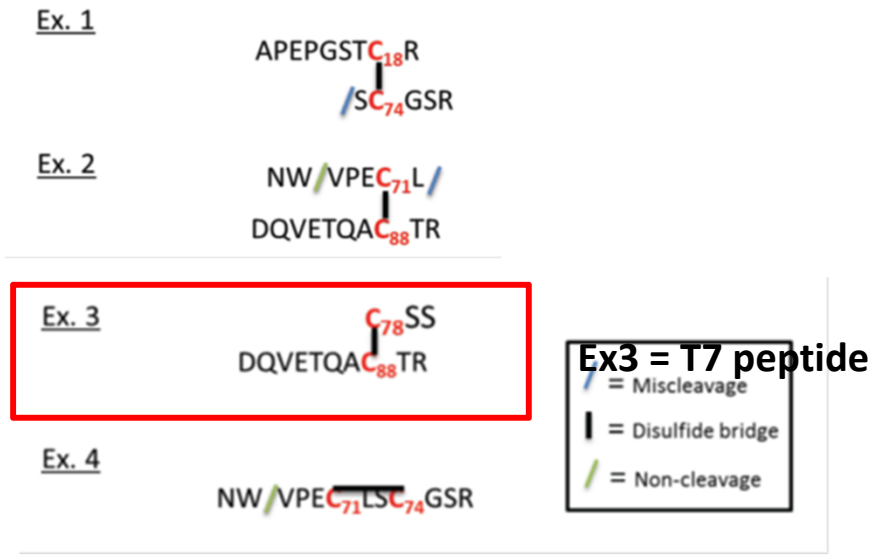
Product	# of lots	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
GP2015	19	10.73	0.62	9.6	11.8
US-licensed Enbrel	21	16.16	1.91	10.2	17.4
EU-approved Enbrel	26	17.54	2.01	12.3	19.8

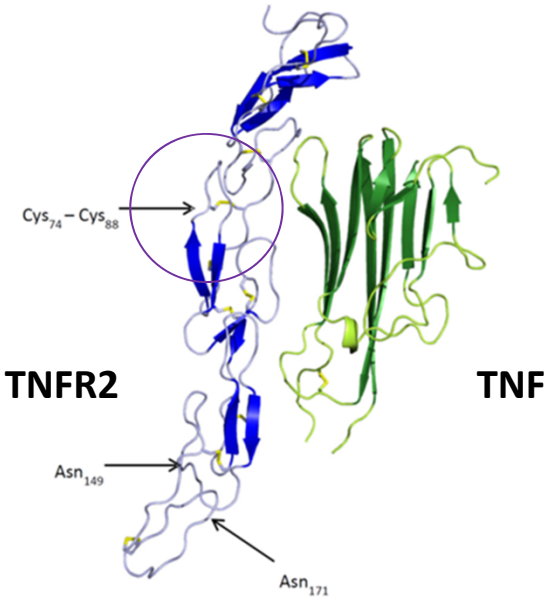
Source: FDA analysis of data from Sandoz 351(k) BLA submission

Misfolded Etanercept

- Enbrel contains a misfolded component, which can be identified by HIC or Reverse Phase Chromatography
  - Sandoz determined that US-licensed Enbrel and EU-Approved Enbrel have ~10-18% RPC post peak while GP2015 has ~9-12%

- The majority of the misfolded protein is disulfide scrambled (WBV) and has reduced activity in vitro





Figures taken from the Sandoz 351(k) BLA submission

Relationship Between WBV and Potency

- The T7 peptide can be used as a surrogate for misfolded etanercept
- There is an inverse relationship between % T7 peptide and potency
- Differences in WBV between GP2015 and US-Enbrel affect bioassay results
- Requested that Sandoz explore the possibility that WBV can correctly refold

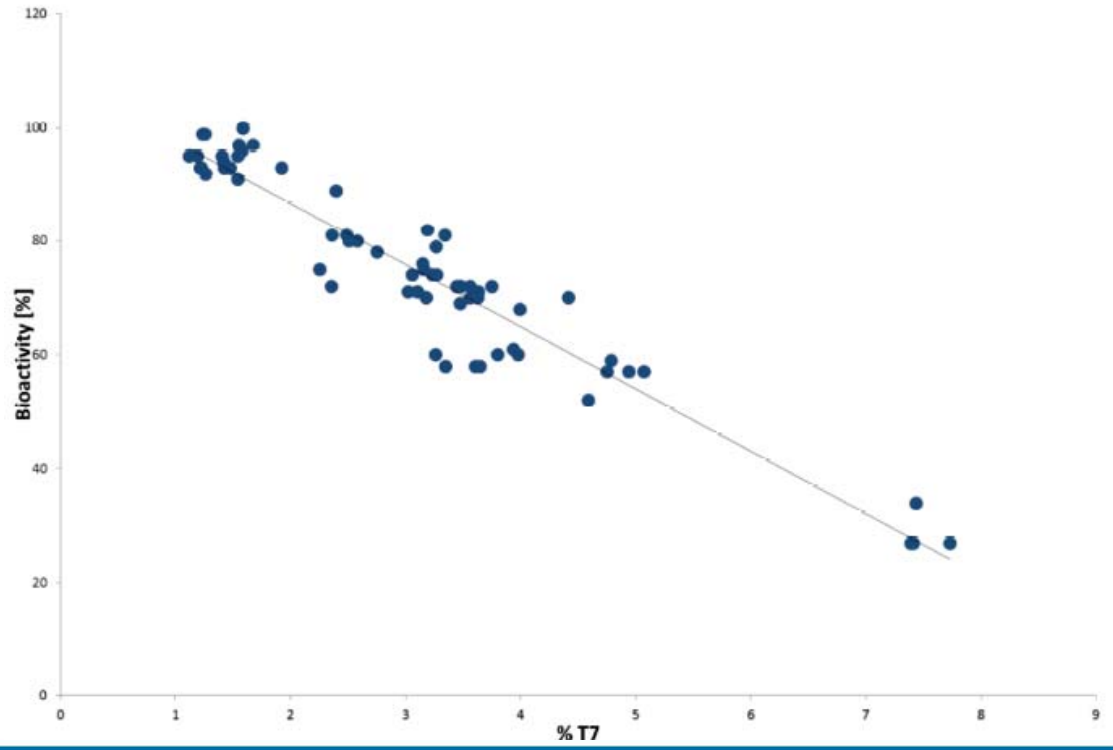
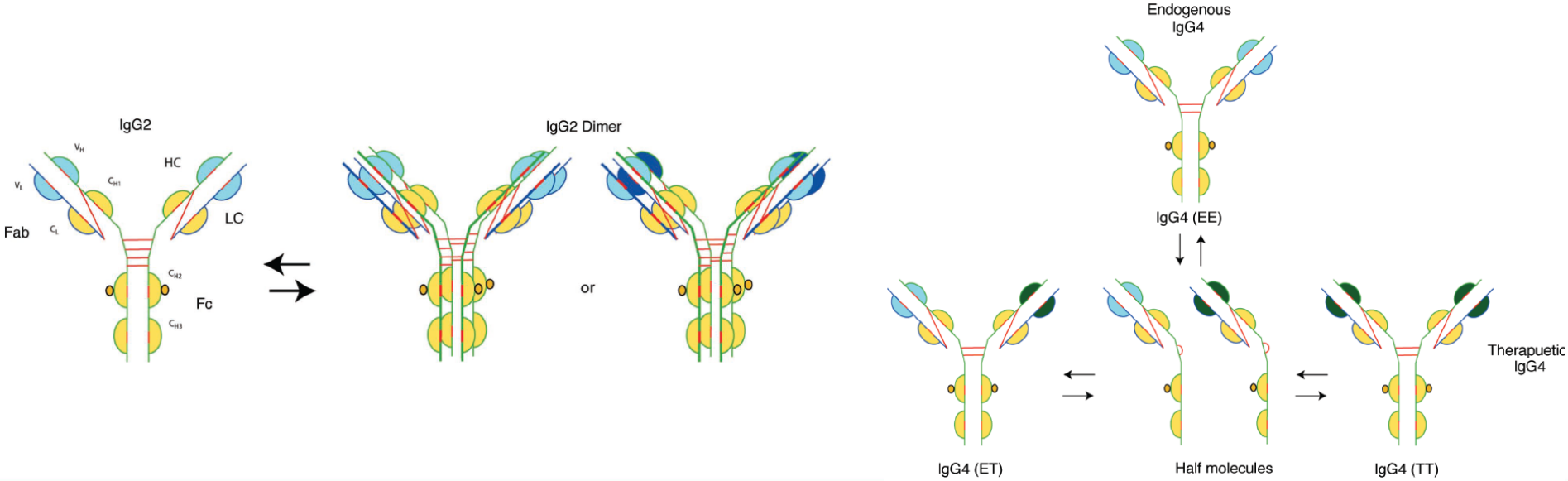


Figure from the Sandoz 351(k) BLA submission

Allosteric Disulfide Bonds

- Most disulfide bonds are structural and are important for the correct folding of a protein
- Some disulfide bonds are allosteric and control the function of a protein when they are reduced or oxidized
  - Changes in ligand binding, oligomer formation, substrate hydrolysis or proteolysis
- There is evidence that TNFR1, TNFR2 and other TNFR family members contain allosteric disulfide bonds
- IgG2 and IgG4 antibodies also have disulfide bonds that can reform in vivo



Restoration of *in vitro* Potency Under Redox Conditions

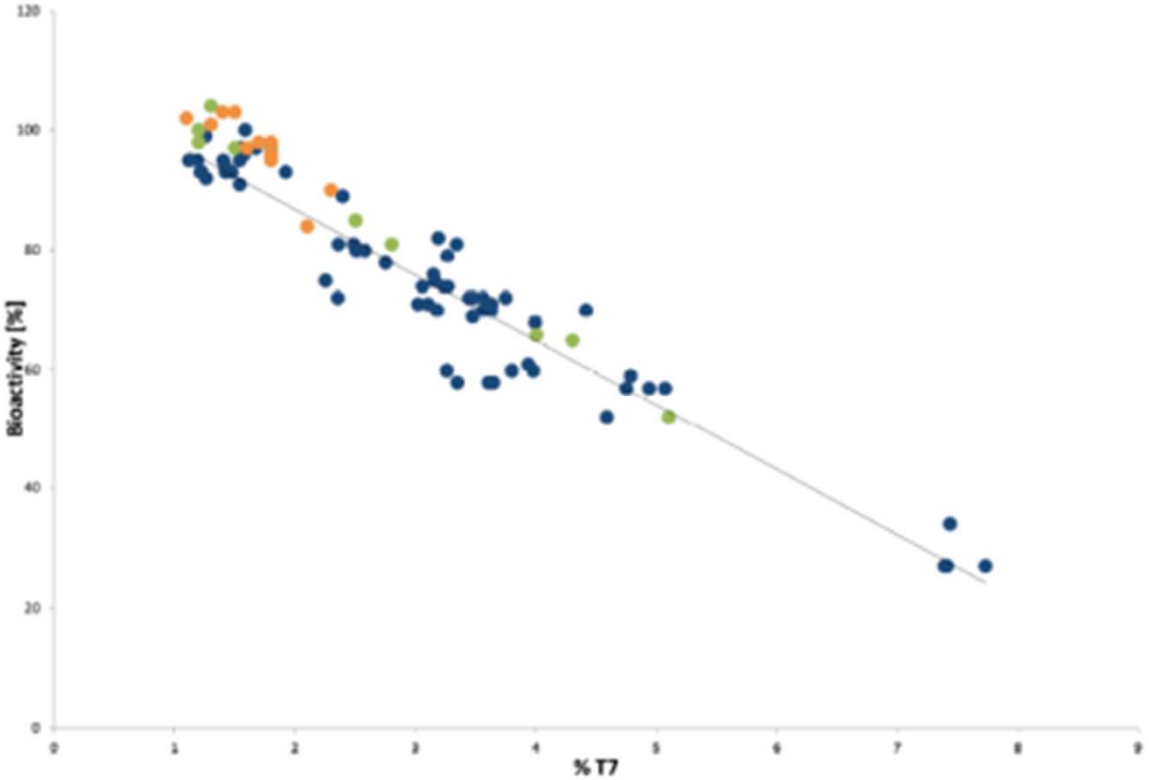
- Using redox conditions for the TNF-α reporter gene assay
  - There is a decrease in the % T7 peptide and an increase in the % potency

Sample	Control		Redox Incubation	
	T7 (% rel to standard peptide)	Potency (%)	T7 (% rel to standard peptide)	Potency (%)
GP2015 DS	1.0	99	1.2	103
GP2015 Process Intermediate 1	3.4	76	1.6	98
GP2015 Process Intermediate 2	5.5	58	2.0	93
DP2015 DP 1	1.2	98	1.5	103
DP2015 DP 2	1.8	97	1.3	101
DP2015 DP 3	1.2	100	1.7	98
Enbrel/US 1	2.6	89	1.7	107
Enbrel/US 2	2.5	85	1.8	98
Enbrel/US 3	2.8	81	1.8	96
Enbrel/US 4	2.5	85	1.8	95
Enbrel/EU 1	2.3	92	1.6	100

Data from the Sandoz 351(k) BLA submission

Relationship Between WBV and Potency After Redox Incubation

- Refolding of the WBV was demonstrated using in vitro conditions
- Based on relationship between T7 peptide and potency, Sandoz developed a "computed potency" model, which was used to reevaluate the TNF-α RGA data



blue: data points generated during development to establish structure-function relationship; green: control samples of redox experiments; orange: sample after redox incubation

Figure from the Sandoz 351(k) BLA submission

Methods to Assess Biological Activity

- TNF-α binding
  - Statistical equivalence
- TNF-α neutralization reporter gene assay (RGA)
  - Statistical equivalence
- TNF-α neutralization RGA after redox conditions (computed potency model)
  - Statistical equivalence
- TNF-α neutralization apoptosis
  - Quality range (Mean ± 3 SD)
- TNF-β neutralization RGA
  - Quality Range (Mean ± 3 SD)
- Antibody Dependent Cellular Cytotoxicity (ADCC)
  - Quality Range (Mean ± 3 SD)

Number of Lots Tested in Potency Methods Assessed by Statistical Equivalence

Assay	GP2015	US-Enbrel	EU-Enbrel
TNF-α Binding	8	11	12
TNF-α Neutralization	19	19	43
TNF-α Neutralization Computed Potency	9	11	11

Statistical Equivalence Testing for Bioactivity

351(k) BLA for GP2015, a Proposed Biosimilar to US-licensed Enbrel

Arthritis Advisory Committee
July 13, 2016

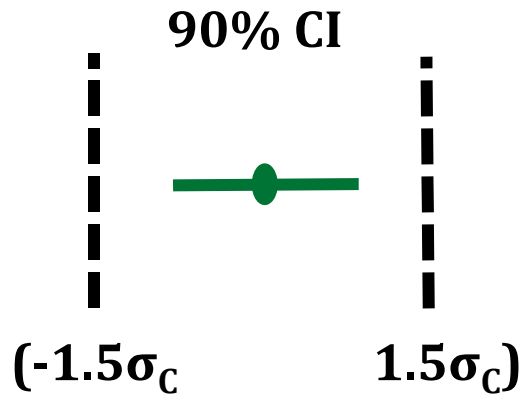
Meiyu Shen, PhD
Lead Mathematical Statistician
Office of Biostatistics, CDER
Food and Drug Administration

Highly Critical Quality Attributes for Statistical Equivalence Analysis

- Assays that assessed the primary mechanism of action that were tested using equivalence testing:
  - TNF-α binding
  - TNF-α neutralization reporter gene assay (RGA)
    - Determining bioactivity--potency
  - Computed TNF-α RGA

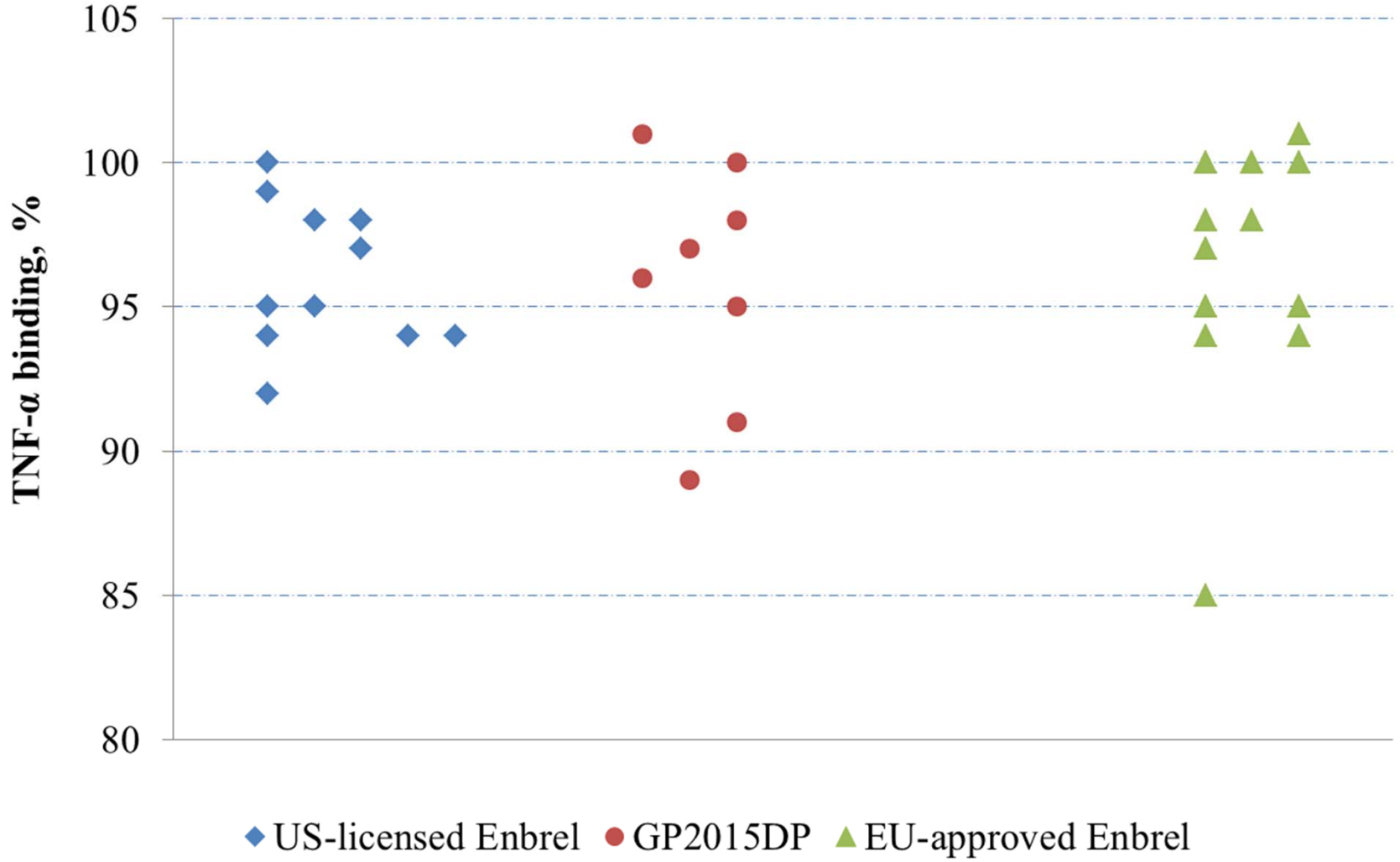
Statistical Equivalence Test

- The null hypothesis H0:
  - Mean(Test) – Mean (Comparator) $\geq 1.5\sigma_C$ or Mean(Test) – Mean (Comparator) $\leq -1.5\sigma_C$;
- Test and comparator are equivalent if



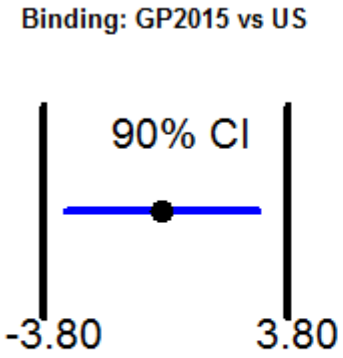
- Equivalence margin=$1.5\sigma_C$:
  - ➢ σ_C is estimated from comparator data measured by Sandoz.

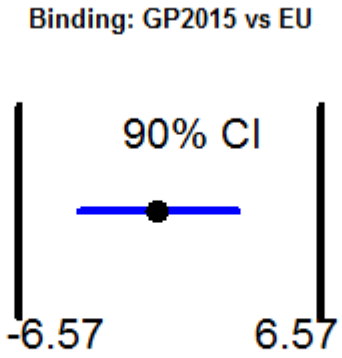
TNF-α Binding

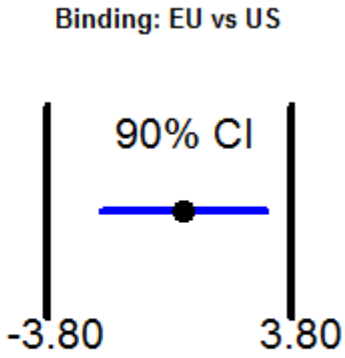


TNF-α Binding

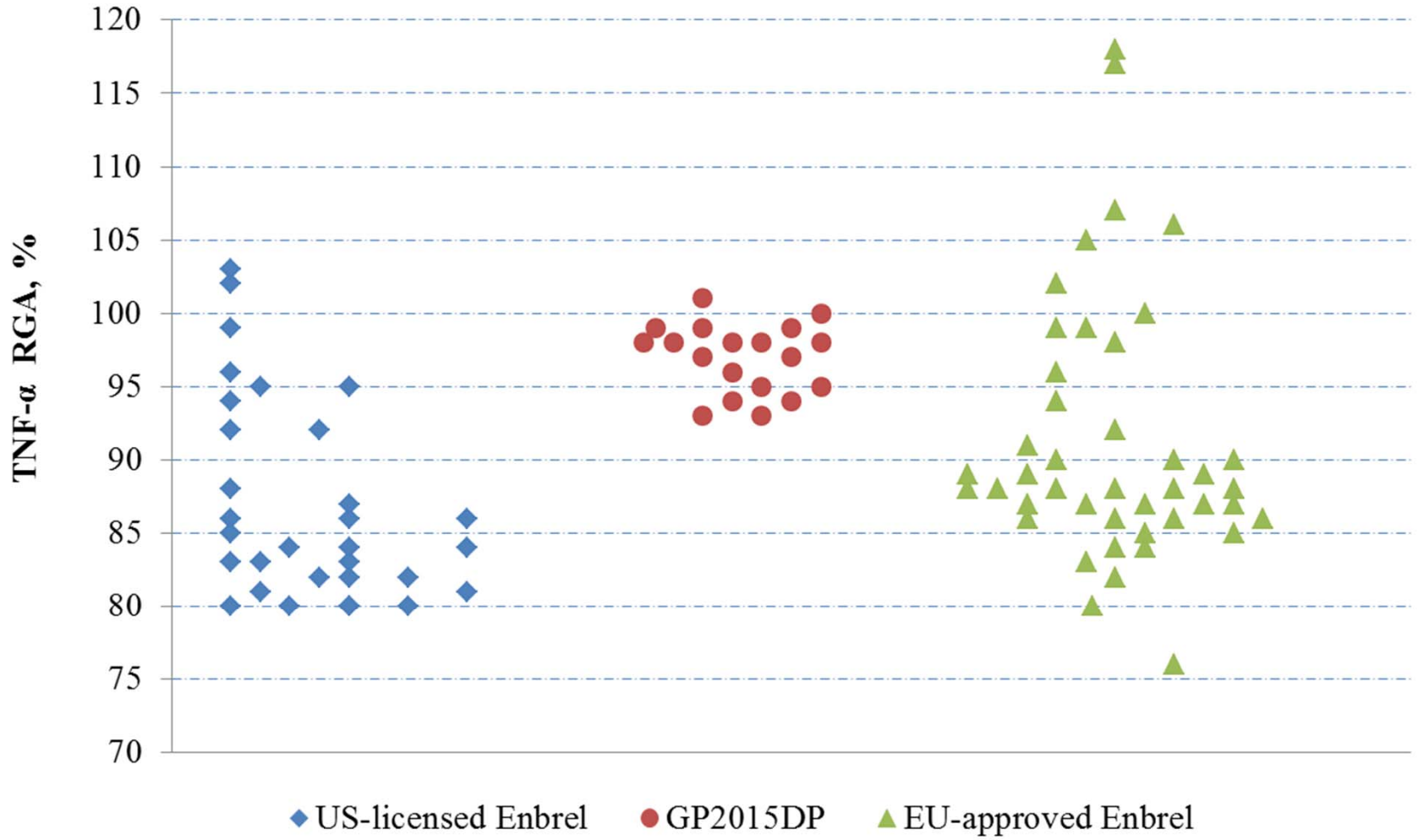
Comparison	# of lots	Mean difference, %	90% CI for mean difference, %	Equivalence margin, %	Pass equivalence test ?
GP2015 vs. US	(8, 11)	-0.125	(-3.11, 2.86)	(-3.80, 3.80)	Yes
GP2015 vs. EU	(8, 12)	-0.542	(-3.94, 2.94)	(-6.57, 6.57)	Yes
EU vs. US	(12, 11)	0.417	(-2.14,2.98)	(-3.80, 3.80)	Yes





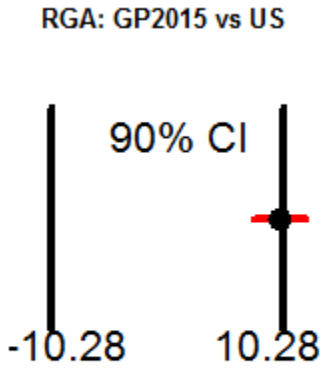


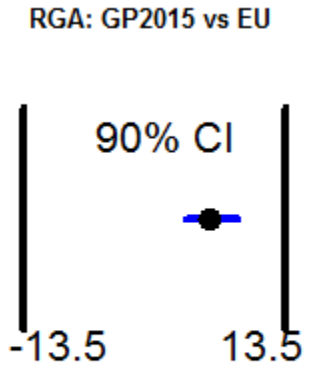
TNF-α Neutralization Reporter Gene Assay

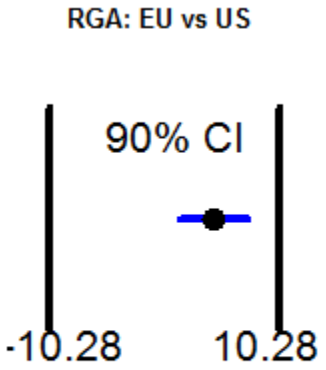


TNF-α RGA, %

Comparison	# of lots	Mean difference, %	90% confidence interval for mean difference, %	Equivalence margin, %	Pass equivalence test?
GP2015 vs. US	(19,31)	10.01	(7.62, 12.36)	(-10.28, 10.28)	No
GP2015 vs. EU	(19,43)	5.62	(3.15, 8.59)	(-13.50, 13.50)	Yes
EU vs. US	(43,31)	4.39	(1.32, 7.46)	(-10.28, 10.28)	Yes







* If $n_b < 1.5n_c$ 90% CI is adjusted by the imbalance of two groups' sample size

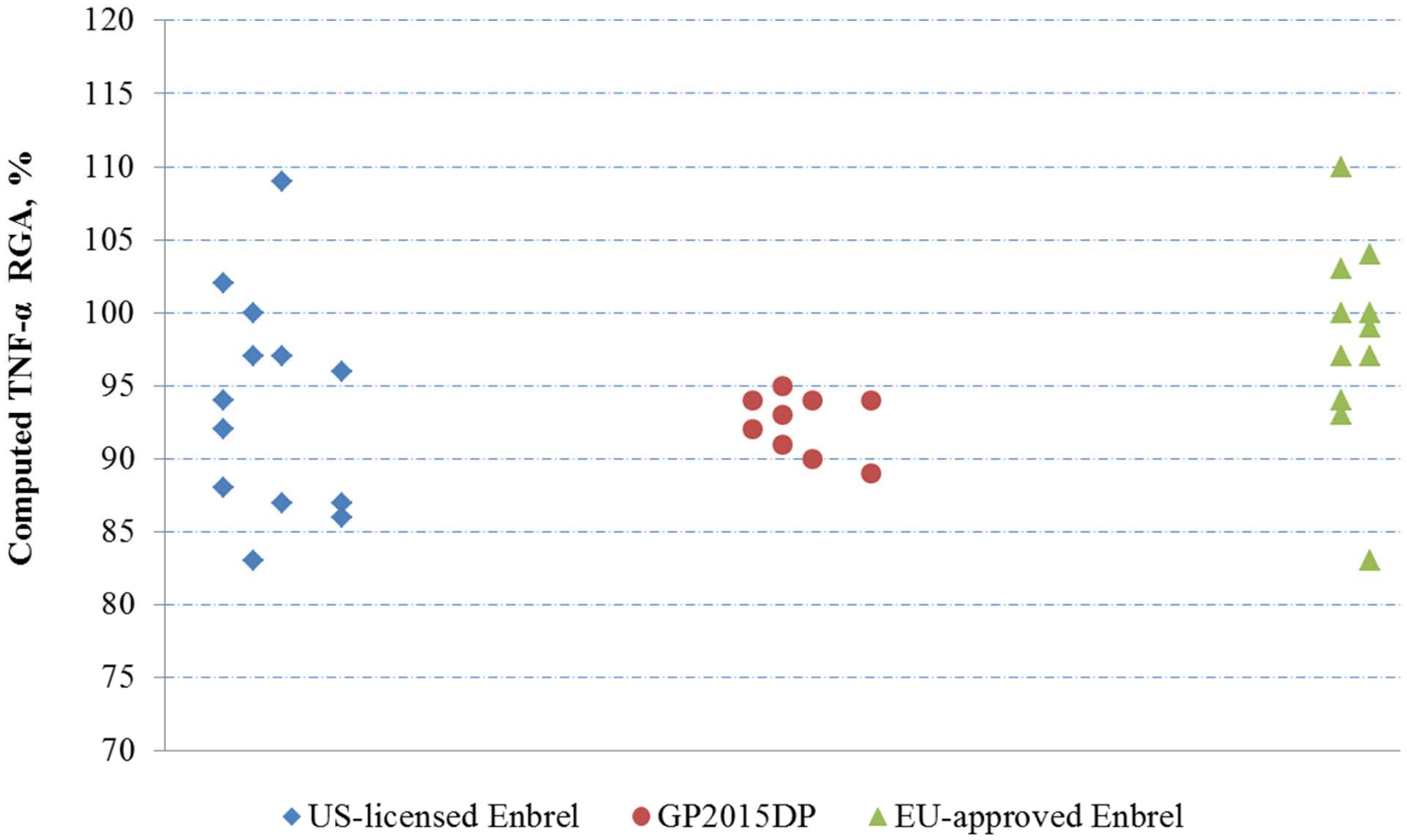
Mathematical Model for TNF-α RGA by Adjusting the Difference in %T7

- A negative correlation between wrongly bridged variant %T7 and TNF-alpha RGA exists

- %T7 differences (Sandoz's data)
  - US-licensed Enbrel and EU-Approved Enbrel have ~10-18% wrongly bridged disulfide bonds
  - GP2015 has ~9-12%

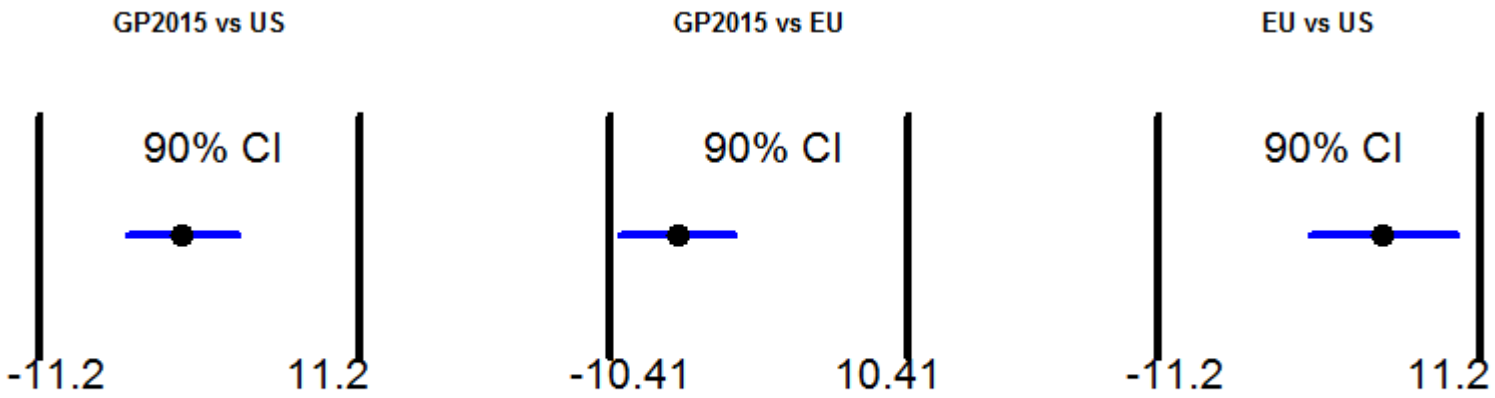
- To adjust the difference in %T7 between US-licensed Enbrel, EU-approved Enbrel and GP2015, a mathematical model is developed to convert the TNF-α RGA into the computed TNF-α RGA.

Computed TNF-α RGA



Computed TNF-α RGA

Comparison	# of lots	Mean difference, %	90% confidence interval for mean difference, %	Equivalence margin, %	Pass equivalence test?
GP2015 vs. US	(9,13)	-1.25	(-5.08, 2.59)	(-11.20, 11.20)	Yes
GP2015 vs. EU	(9,11)	-5.74	(-9.66, -1.81)	(-10.41, 10.41)	Yes
EU vs. US	(11,13)	4.49	(-0.57, 9.55)	(-11.20, 11.20)	Yes



Equivalence Testing Summary

- TNF-α binding
  - All 3-way comparisons passed equivalence testing
- Computed TNF-α RGA
  - All 3-way comparisons passed equivalence testing

Product Quality Review

351(k) BLA for GP2015, a Proposed Biosimilar to US-licensed Enbrel

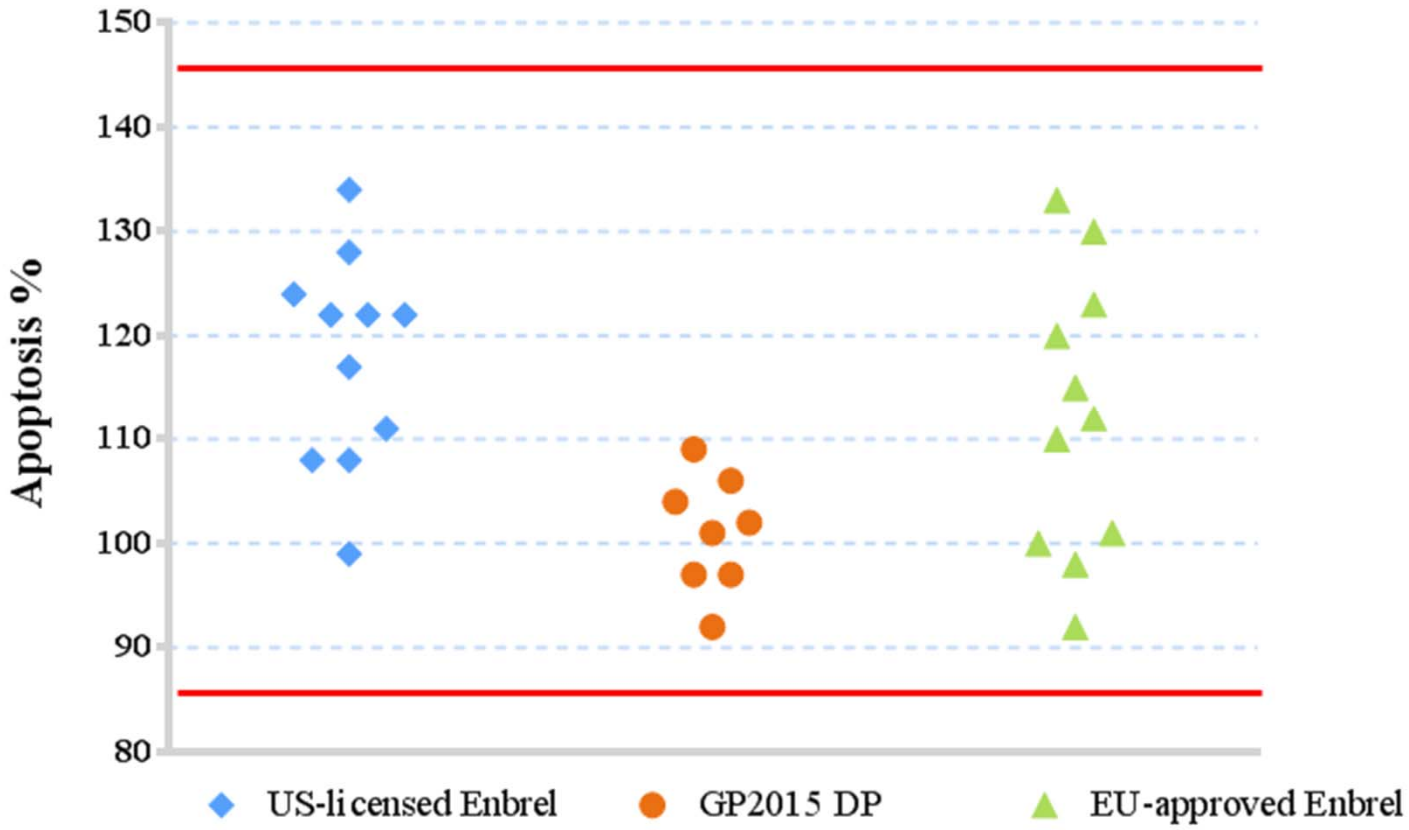
Arthritis Advisory Committee

July 13, 2016

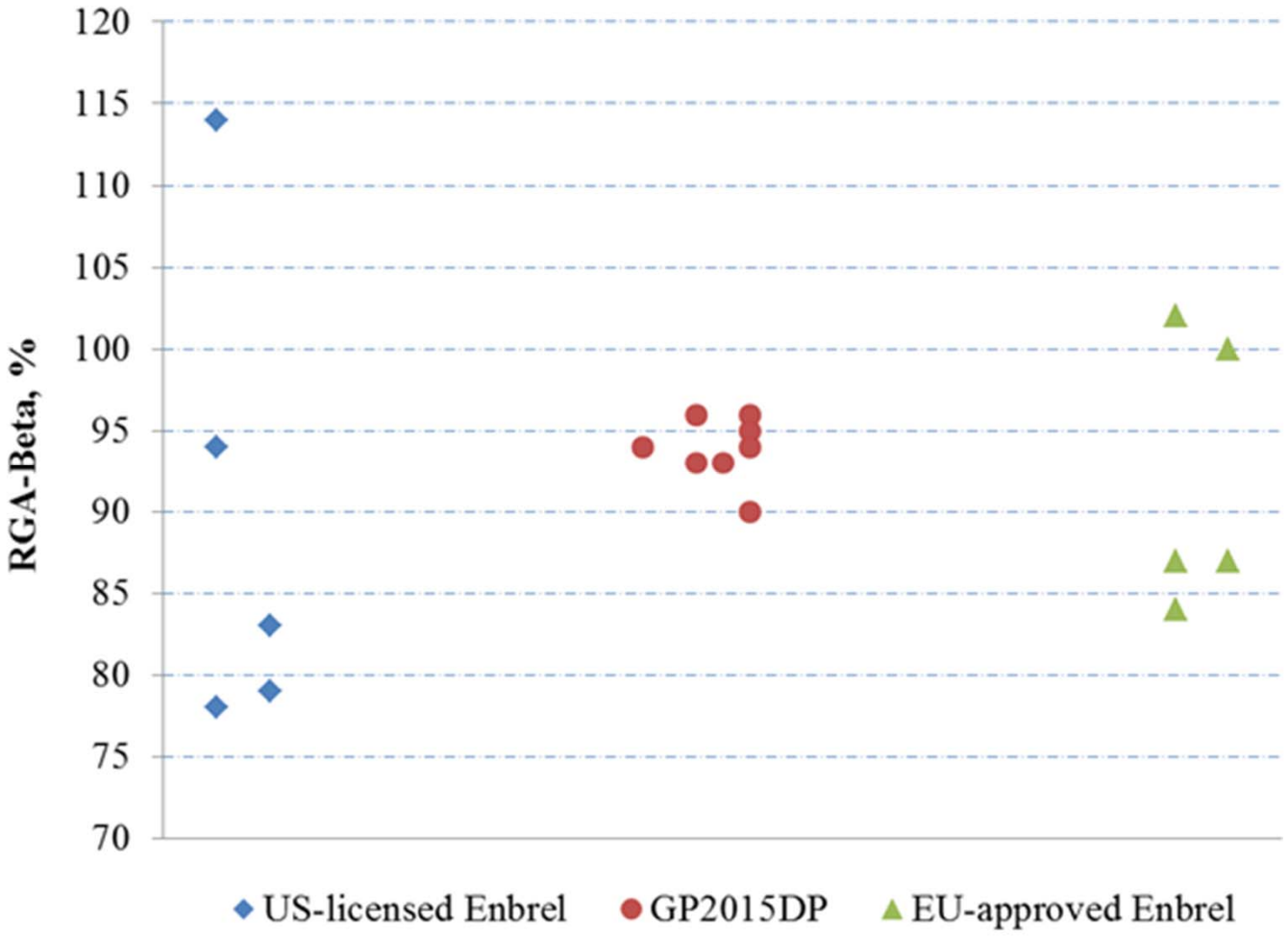
Peter L. Adams, PhD
Product Quality Reviewer
Division of Biotechnology Review and Research 1
Office of Biotechnology Products

Potency: Apoptosis Assay

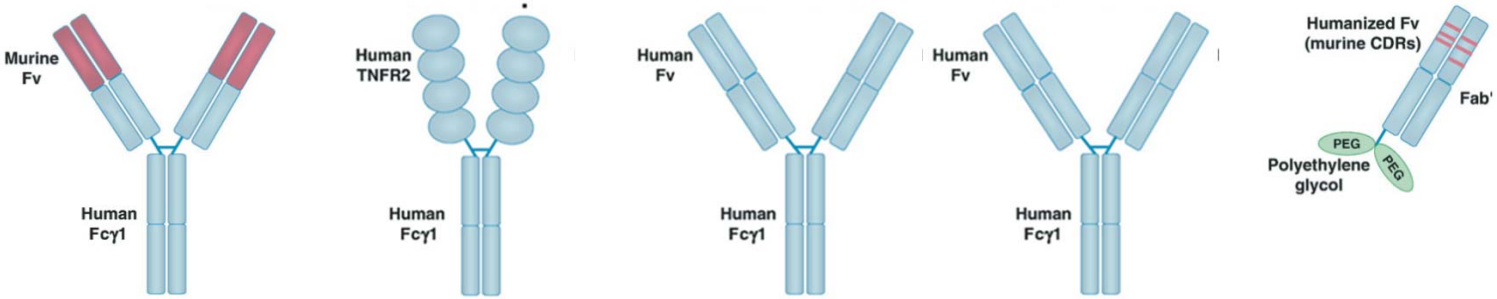
Neutralization of the TNF-α mediated apoptosis in U937 cells



Potency: TNF-β RGA



TNF Antagonists: Fc Effector Function



	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab
ADCC	Moderate	Low	Moderate	Moderate	None
CDC	Moderate	Low	Moderate	Moderate	None
RA	Yes	Yes	Yes	Yes	Yes

ADCC Assay: Comparing TNF Antagonists

- GP2015 had lower levels of afucosylated glycans, which correlates with lower levels of ADCC activity
- Highly sensitive assay includes target cells that over express mTNF
- ADCC is not considered to be a mechanism of action of etanercept

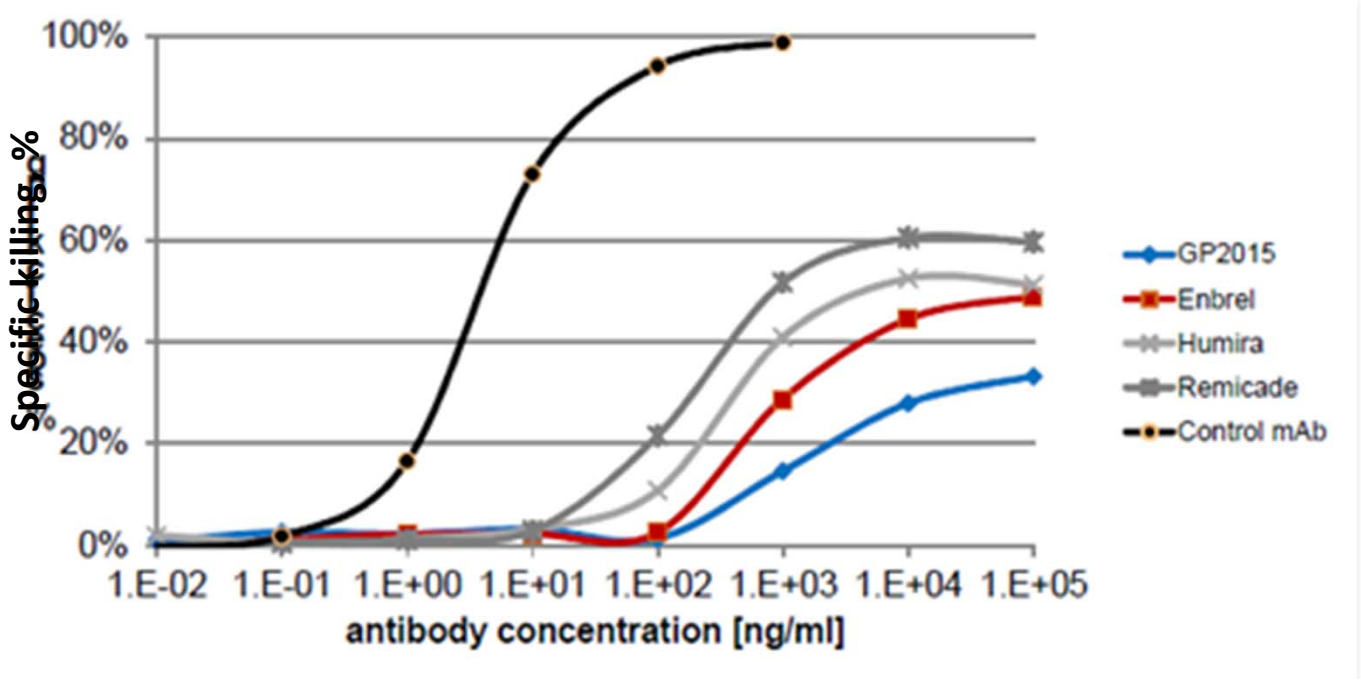
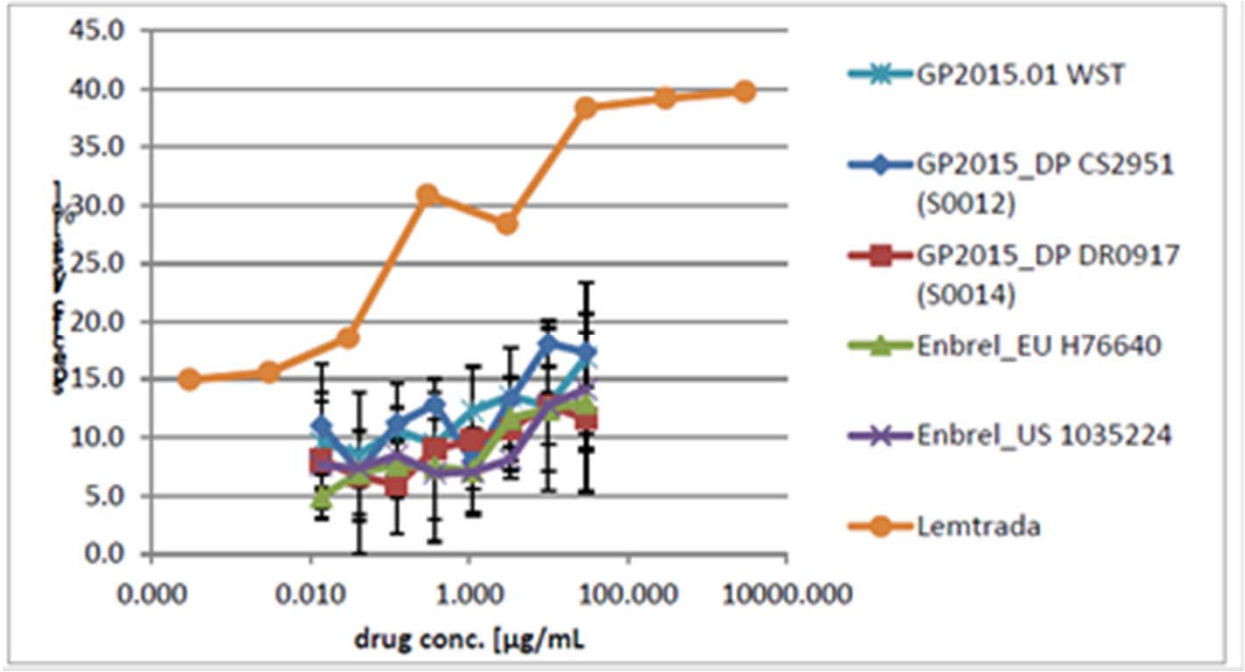


Figure from the Sandoz 351(k) BLA submission

ADCC:
Assessing Contribution to MOA

Primary human monocytes stimulated with LPS
US-Enbrel, EU-Enbrel, and GP2015 are compared to an anti-CD52 monoclonal antibody



Conclusion: ADCC is not a consideration for the mechanism of action of etanercept

Figure from the Sandoz 351(k) BLA submission

Analytical Similarity Summary

Analytical comparison between GP2015, US-Enbrel and EU-Enbrel

Quality Attribute	Supports a Demonstration of Highly Similar
Primary Structure	Yes -Same AA sequence
Secondary & Tertiary Structure	Yes
Protein content	Yes
Potency	Yes
TNF binding	Yes
Clarity	Yes
HMW variants /aggregates	Yes
Hydrophobic variants	#
Charged variants	Yes
Fragments	Yes

Quality Attribute	Supports a Demonstration of Highly Similar
Overall Glycosylation	Yes
Fc afucosylation	#
ADCC	#
CDC	Yes
Fc binding	Yes
FcRn binding	Yes

Differences in hydrophobic variants, Fc afucosylation and ADCC do not preclude a demonstration that GP2015 is highly similar to US-Enbrel

Stability profiles of the three products also support a demonstration that GP2015 is highly similar to US-Enbrel

Overall Analytical Conclusion

- Extensive analytical study to determine similarity:
  - Functional and Bioactivity Assays
  - Physicochemical Assays
  - Higher Order Structural Assays

- The analytical portion of the scientific bridge was established between EU-approved Enbrel, US-licensed Enbrel and GP2015

- The totality of the analytical similarity data supports the conclusion that GP2015 is highly similar to US-Licensed Enbrel

Clinical Pharmacology Review

351(k) BLA for GP2015, a Proposed Biosimilar to US-licensed Enbrel

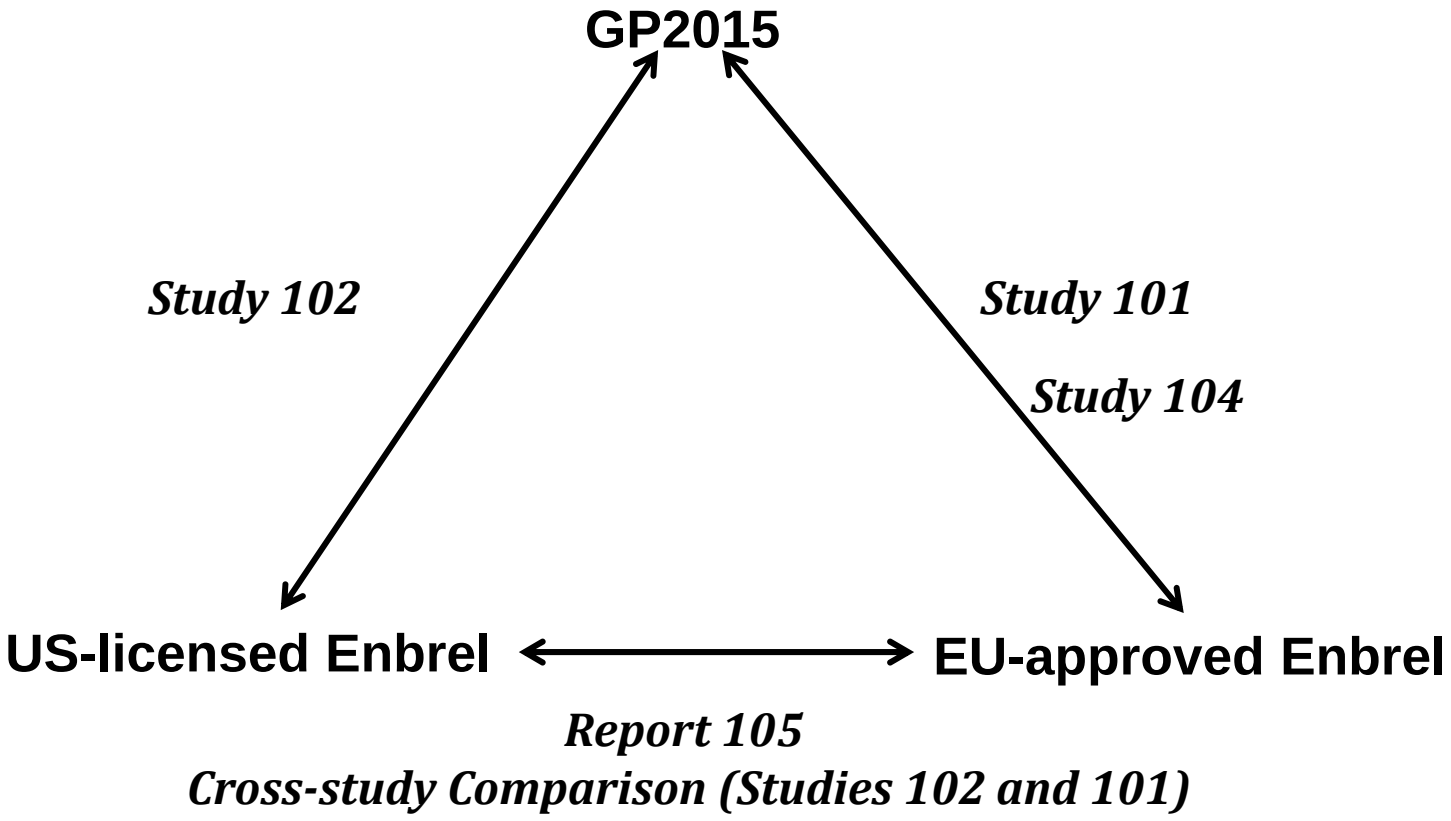
Arthritis Advisory Committee
July 13, 2016

Yunzhao Ren, MD, PhD
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology II
Office of Clinical Pharmacology
Food and Drug Administration

Overview of Clinical Pharmacology

- **The goals of the clinical pharmacology program are:**
  - To evaluate the pharmacokinetic (PK) similarity between GP2015 and US-licensed Enbrel
  - To assess the PK element of the scientific bridge between GP2015, US-licensed Enbrel, and EU-approved Enbrel
- **Clinical pharmacology program of GP2015:**
  - Three related PK studies
  - One cross-study PK comparison
  - C_{trough} comparison from comparative clinical study
- **Conclusions:**
  - PK similarity was demonstrated between GP2015 and US-licensed Enbrel
  - PK bridge was established between GP2015, US-licensed Enbrel, and EU-approved Enbrel

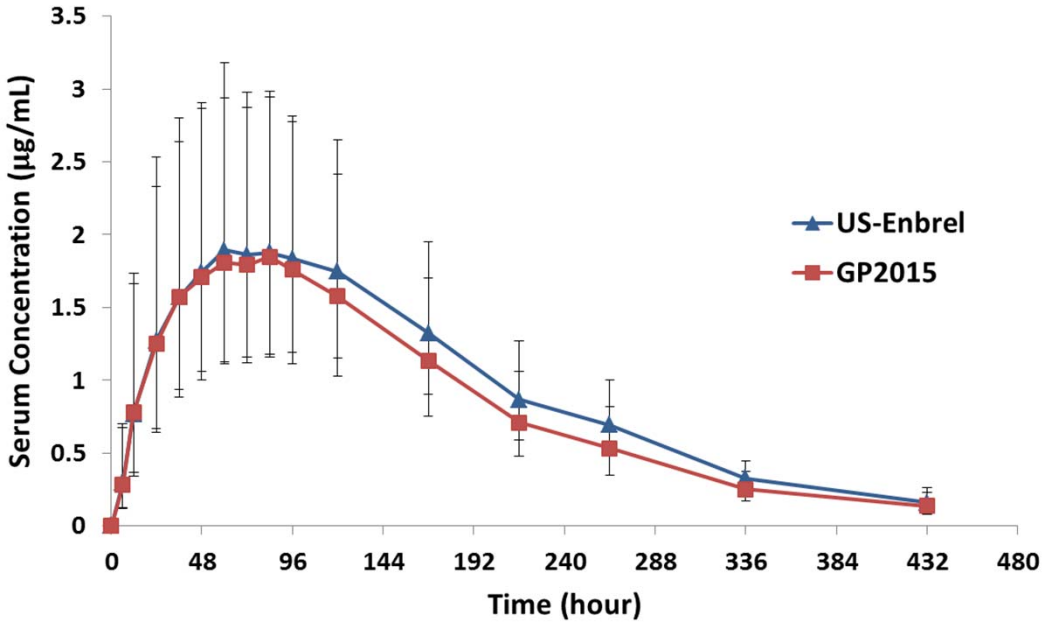
PK Similarity/Bridging Strategy



Studies 101, 102 and Report 105: Study Design

- **Study Design:** randomized, double-blind, two-way crossover, single dose in healthy subjects
  - Study 101: GP2015 vs. EU-approved Enbrel
  - Study 102: GP2015 vs. US-licensed Enbrel
  - Report 105: EU-approved Enbrel vs US-licensed Enbrel
- **Objectives:**
  - Primary: to compare PK ($AUC_{0\text{-tlast}}$ and C_{max}) between three products
  - Secondary: other PK parameters (including $AUC_{0\text{-inf}}$), overall safety and local tolerance, and immunogenicity
- **Treatments:**
  - Single dose of GP2015 50 mg PFS, subcutaneous
  - Single dose of US-licensed Enbrel: 50 mg PFS, subcutaneous
  - Single dose of EU-approved Enbrel: 50 mg PFS, subcutaneous
- **Subjects:**
  - 54 healthy males and females in Study 101
  - 57 healthy males and females in Study 102

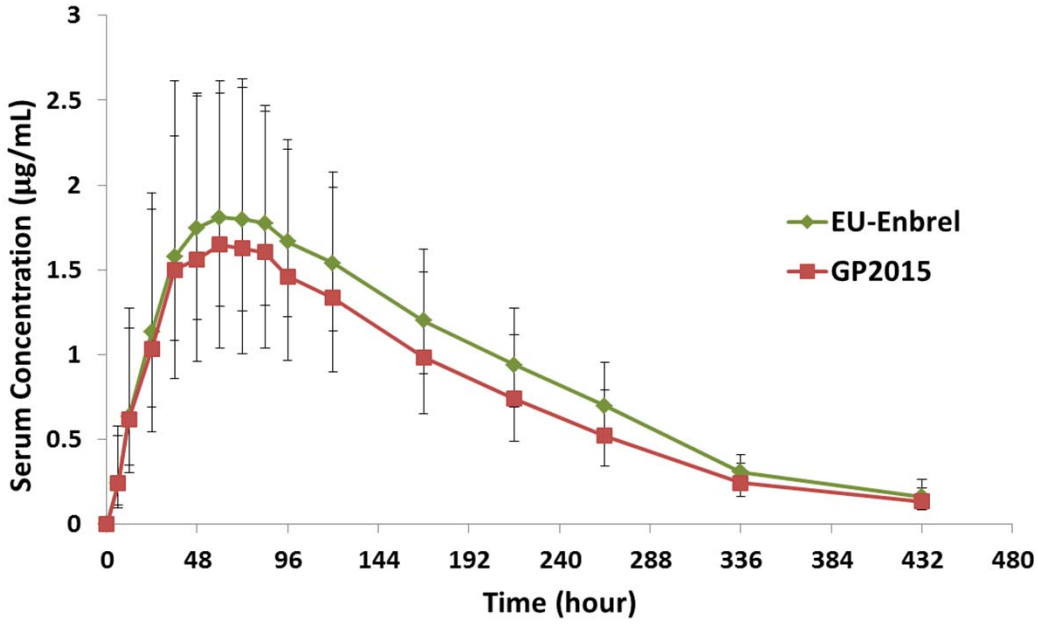
Study 102: GP2015 vs. US-Enbrel



	N	GP2015*	US-Enbrel*	Ratio GP/US (90% CI)	Intra-subject CV%
AUC_{0-t} (µg•h/mL)	53	369.8	415.0	0.89 (0.83, 0.96)	21.8%
AUC_{0-inf} (µg•h/mL)	54	390.3	439.7	0.89 (0.83, 0.95)	20.3%
C_{max} (µg/mL)	54	2.028	2.146	0.95 (0.87, 1.03)	26.3%

*** Least square mean**

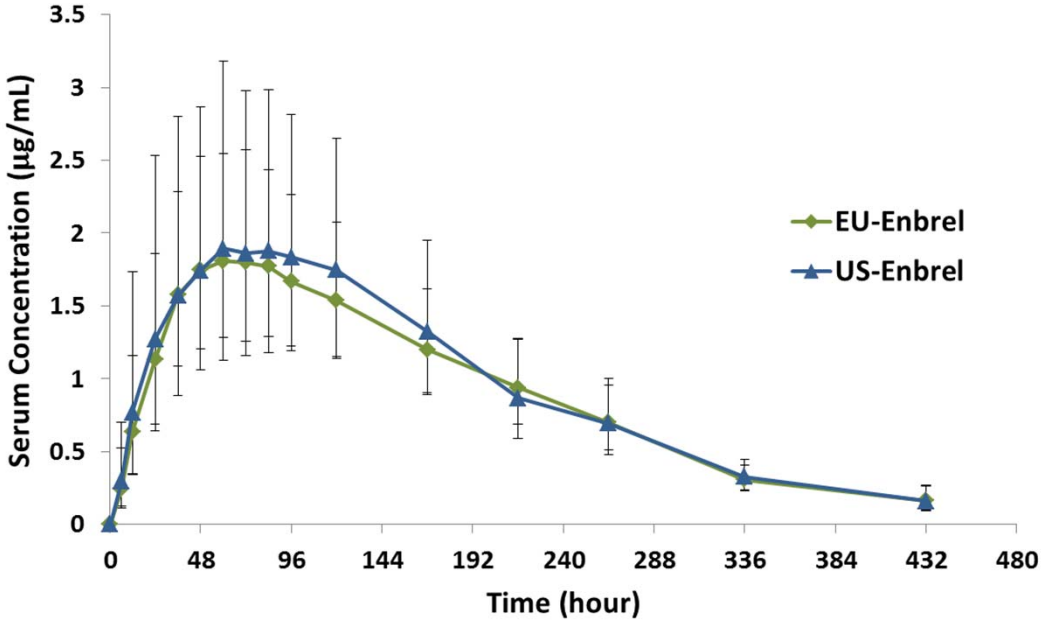
Study 101: GP2015 vs. EU-Enbrel



	N	GP2015*	EU-Enbrel*	Ratio GP/EU (90% CI)	Intra-subject CV%
AUC_{0-t} (µg•h/mL)	49	335.2	392.6	0.85 (0.78, 0.93)	25.9%
AUC_{0-inf} (µg•h/mL)	49	353.3	416.5	0.86 (0.78, 0.92)	25.0%
C_{max} (µg/mL)	50	1.808	1.982	0.91 (0.82, 1.01)	30.8%

*** Least square mean**

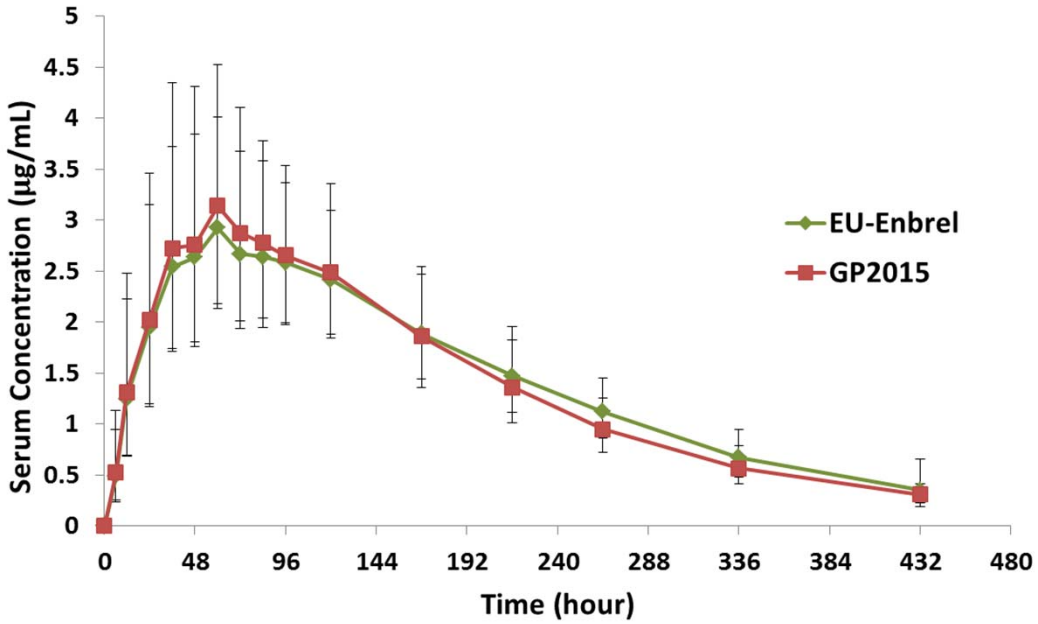
Report 105: EU-Enbrel vs. US-Enbrel



	EU-Enbrel*	US-Enbrel*	Ratio EU/US (90% CI)	Inter-subject CV%
$AUC_{0\text{-}t}$ (µg•h/mL)	392.6 (N=49)	415.2 (N=53)	0.95 (0.84, 1.06)	37.1%
$AUC_{0\text{-}inf}$ (µg•h/mL)	416.5 (N=49)	439.7 (N=54)	0.95 (0.85, 1.06)	44.4%
C_{max} (µg/mL)	1.980 (N=50)	2.146 (N=54)	0.92 (0.80, 1.06)	26.3%

*** Least square mean**

Study 104: GP2015 vs. EU-Enbrel



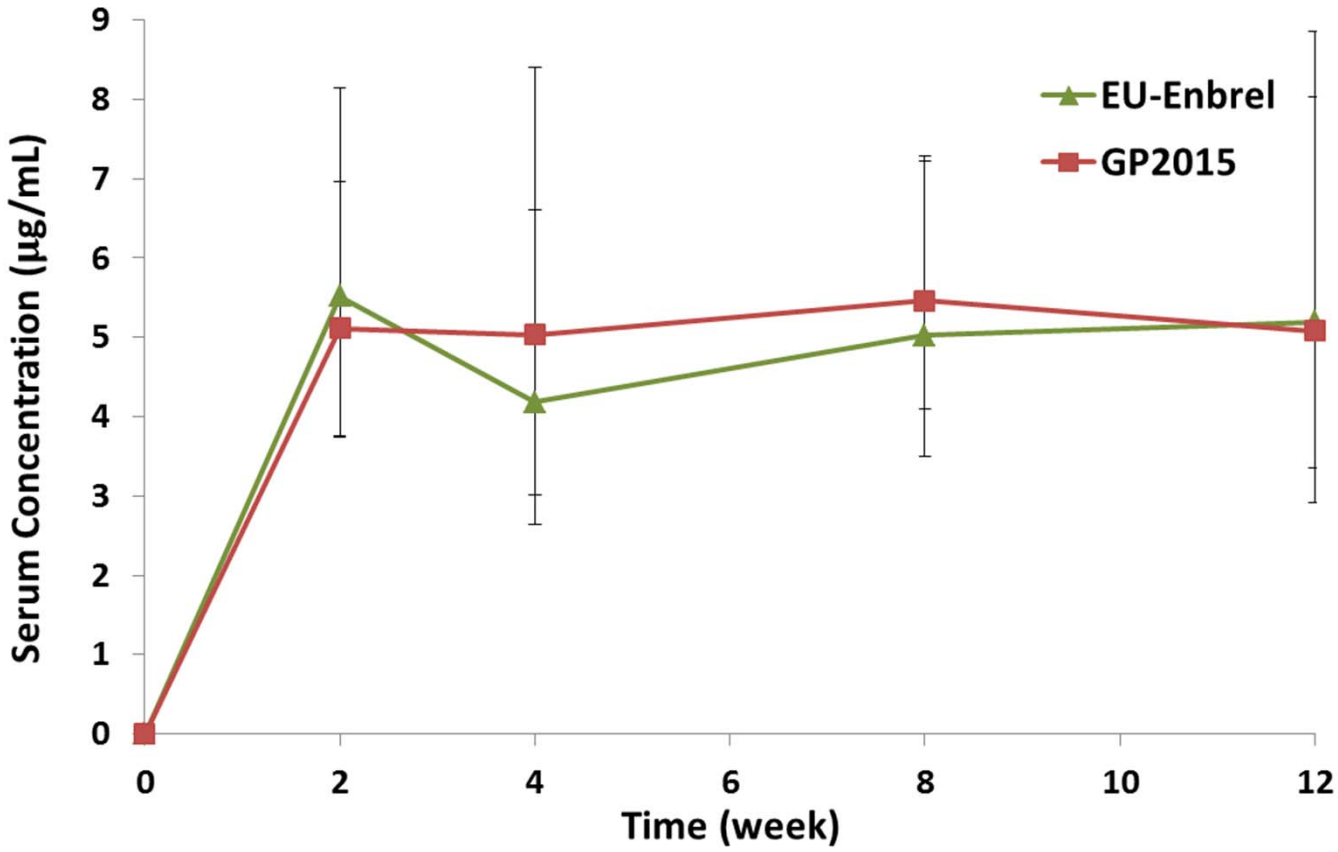
	N	GP2015*	EU-Enbrel*	Ratio GP/EU (90% CI)	Intra-subject CV%
AUC_{0-t} (µg•h/mL)	54	632.7	644.0	0.98 (0.94, 1.02)	12.1%
AUC_{0-inf} (µg•h/mL)	54	680.9	706.9	0.96 (0.93, 1.00)	12.2%
C_{max} (µg/mL)	54	3.416	3.087	1.11 (1.05, 1.17)	16.4%

*** Least square mean**

Study 302: Comparative Clinical Study

- **Study Design:** randomized, double-blind, multi-center, multi-dose in 531 patients with moderate to severe chronic plaque-type psoriasis
- **Secondary Objectives related to Clinical Pharmacology:**
  - Comparison of C_{trough} between GP2015 and EU-approved Enbrel
  - Immunogenicity
- **Treatments during Period 1 (Week 0 to Week 12):**
  - GP2015 50 mg PFS, subcutaneous, twice a week (batch# S0011, S0012, and S0014)
  - EU-approved Enbrel: 50 mg PFS, subcutaneous, twice a week (batch# G75422, H18066, H76640)
- **PK Samples:** pre-dose PK samples were collected from 147 PsO patients at Week 2, 4, 8, and 12

Study 302: C_{trough} Comparison



Clinical Pharmacology Conclusions

- PK similarity was demonstrated between GP2015 and the US-licensed Enbrel

- PK data support the scientific bridge between GP2015, US-licensed Enbrel, and EU-approved Enbrel to justify the relevance of comparative data generated using EU-approved Enbrel

Clinical Efficacy Review

351(k) BLA for GP2015, a Proposed Biosimilar to US-licensed Enbrel

Arthritis Advisory Committee
July 13, 2016

Kathleen Fritsch, PhD
Mathematical Statistician
DBIII/OB/OTS/CDER
Food and Drug Administration

Study 302
Comparative Clinical Study in Plaque Psoriasis
GP2015 vs. EU-approved Enbrel

Part 1: Similarity (Week 0 to 12)

- 531 subjects with moderate to severe psoriasis
- GP2015 vs. EU-appr. Enbrel
- Primary endpoint: PASI 75 at Week 12
- Secondary endpoints: Percent change in PASI and IGA response

Part 2: Switching (Week 12 to 30)

- Subjects with PASI >50 at Week 12 continue study
- Subjects randomized to continue original treatment or switch at 6-week intervals (3 switches)

Part 3: Extension (Week 30 to 52)

- Subjects continue on last-assigned treatment through Week 52

PASI = Psoriasis Area Severity Index, IGA = Investigator's Global Assessment

Statistical Analysis Plan

- Primary Endpoint – PASI 75 at Week 12
  - Statistical model:
    - Exact confidence interval (protocol)
    - Logistic regression adjusted for body weight and prior therapy (statistical analysis plan)
  - 95% and 90% confidence intervals
  - Similarity margin: ± 18%
  - Analysis Population
    - Primary: Per protocol set (PPS)
    - Supportive: Full analysis set (FAS) with non-responder imputation

Key Analysis Issue: Classification of Prior Therapies

- One of the randomization stratification factors was 'prior systemic therapies for psoriasis' ('None', 'Any except TNF', 'TNF')
  - Insufficient guidance to investigators on how to classify subjects into these categories leading to inconsistencies between stratum and therapies recorded on case report form
  - Change in viewpoint by the applicant about whether certain therapies were 'systemic psoriasis therapies' (e.g. phototherapy, analgesics for pain due to psoriasis)
  - Applicant used two versions of the 'actual' prior therapy classification: one with the original study report (Week 12 database lock) and one with the updated study report (Week 30 database lock)

Subject Disposition (Treatment Period 1)

	GP2015 N=264	EU-approved Enbrel N=267
Discontinued	8 (3.0%)	12 (4.5%)
Adverse event	4 (1.5%)	3 (1.1%)
Subject decision	2 (0.8%)	5 (1.9%)
Other	2 (0.8%)	4 (1.5%)

PASI 75 at Week 12
Exact Confidence Intervals
(No Covariate Adjustments)

Population	GP2015	EU-approved Enbrel	Difference	90% Conf. Int.
FAS	N=264 70.5%	N=267 71.5%	-1.1%	(-8.3%, 6.0%)
PPS	N=239 73.6%	N=241 75.5%	-1.9%	(-9.4%, 5.6%)

FAS = Full Analysis Set (Non-responder imputation); PPS = Per Protocol Set

PASI 75 at Week 12
Covariate-Adjusted Confidence Intervals (FAS)

Prior Therapy Definition	GP2015 N=264	EU-appr. Enbrel N=267	Difference[a]	90% Conf. Int.
Stratification	70.4%	71.6%	-1.1%	(-7.5%, 5.3%)
First reclassification	70.3%	71.7%	-1.4%	(-7.7%, 5.0%)
Second reclassification	70.4%	71.6%	-1.2%	(-7.5%, 5.2%)

[a] Model Estimate adjusted for prior therapy and weight classification

FAS = Full Analysis Set (Non-responder imputation)

Secondary Endpoints (Week 12)

	GP2015 N=256	EU-approved Enbrel N=256	Difference
Percent Improvement in PASI	82.6%	81.7%	0.9%
IGA response	58.2%	55.1%	3.1%

Full Analysis Set using Observed Cases

Interpretation of Study 302

- Key assumptions
  - Assay sensitivity (ability to detect meaningful differences if they exist)
  - Appropriate quality of study conduct
  - Appropriateness of margin
    - Percent preservation of treatment effect
    - Study power

Published Enbrel Studies in Psoriasis

	Leonardi (2003)	Papp (2005)	Study 302
Selected inclusion criteria	BSA ≥ 10 PASI ≥ 10	BSA ≥ 10 PASI ≥ 10	BSA ≥ 10 PASI ≥ 10 IGA ≥ Mod
Location	US	US, Canada, Western Europe	Europe, South Africa
Sample size *Enbrel* *Placebo*	 164 162	 194 196	 267 --
PASI 75 *Enbrel* *Placebo*	 49% 4%	 49% 3%	 71.5% --
Difference	45%	46%	

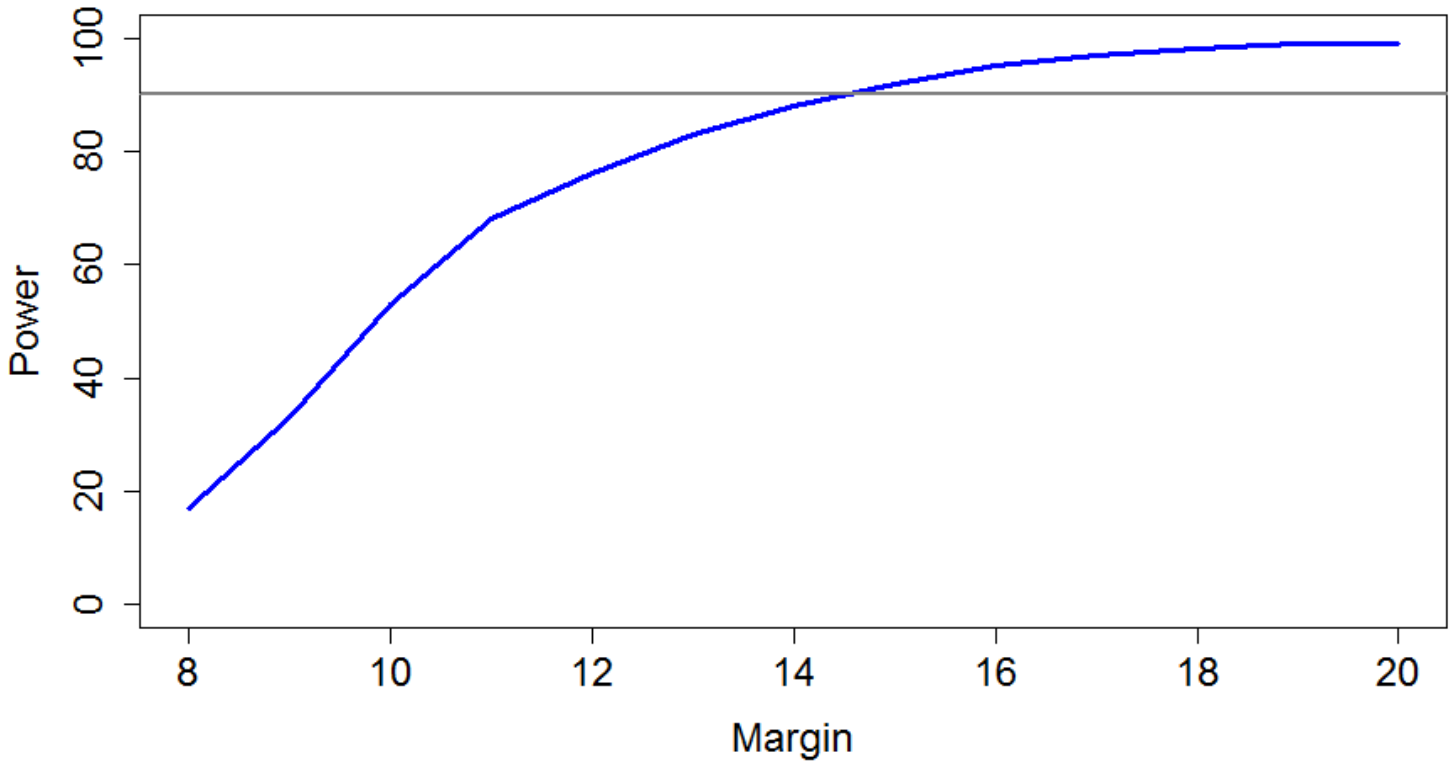
- Assay sensitivity assumption appears reasonable
- No loss of efficacy relative to historical studies

Leonardi CL et al, N Engl J of Med. 2003; 349:2014-22
Papp KA et al, Br J of Dermatol. 2005; 152:1304-12.

Margin Selection

- Percent preservation of treatment effect
  - 18% corresponds to retention of ~60% of treatment effect of Enbrel relative to placebo from published studies (using point estimate of 45%)
- Power
  - Under study design characteristics (N=546, expected PASI 75 response rates of 49%), explore relationship between various margins and study power

Power under Various Margins (assuming true treatment difference is 0) N=546 / PASI 75 = 49%



Summary of Efficacy Results in Study 302

- Primary Endpoint: PASI 75
  - Treatment difference: -1.1%
  - 90% exact confidence interval: (-8.3%, 6.0%)
  - Study met pre-specified similarity criteria (± 18% margin)
  - Consistent results under handling of prior therapy stratification variable
- Secondary endpoints are consistent with the primary endpoint
- Study 302 supports a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel

References

- Leonardi CL et al, N Engl J of Med. 2003; 349:2014-22
- Papp KA et al, Br J of Dermatol. 2005; 152:1304-12

Safety and Immunogenicity

351(k) BLA for GP2015, a Proposed Biosimilar to US-licensed Enbrel

Arthritis Advisory Committee

July 13, 2016

Rachel Glaser, MD
Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration

Overview of Safety

- Safety population
  - 747 subjects (patients and healthy subjects) exposed to at least one dose of GP2015
- No new safety signals
  - Types and incidence of TEAEs, SAEs, AE leading to discontinuation were similar
  - Most common TEAEs were infections
  - AEs leading to discontinuation were single occurrences
- One death occurred across the GP2015 development program:
  - Cardiopulmonary failure in EU-approved Enbrel treatment group (Study 302)
- No cases of anaphylaxis by Sampson criteria*
- Immunogenicity
  - Low incidence of ADA in GP2015 and EU-approved Enbrel groups
  - ADA incidence did not increase following transition from EU-approved Enbrel to GP2015

*Sampson et.al. J Allergy Clin Immunol 2006; 117:391-7

Overview of Safety

	Plaque Psoriasis Study 302						Healthy Subjects Studies 101, 102, 104		
	Treatment Period 1		Treatment Period 2						
	GP2015 N=264	EU-Enbrel N=267	Cont'd GP2015 N=150	Cont'd EU-Enbrel N=151	Switched EU-Enbrel N=96	Switched GP2015 N=100	GP2015 N = 162	US-Enbrel N = 56	EU-Enbrel N = 107
# of pts with ≥1 TEAE, n(%)	99 (38)	96 (36)	47 (31)	52 (34)	35 (37)	32 (32)	87 (64)	28 (50)	55 (51)
# of pts with ≥1 SAE, n(%)	4 (2)	3 (1)	1 (<1)	2 (1)	3 (3)	3 (3)	--	--	--
Discont. due to AE, n(%)	5 (2)	4 (2)	1 (<1)	2 (1)	5 (5)	1 (1)	2 (1)	--	1 (<1)
AESI	9 (3)	5 (2)	7 (5)	3(2)	2 (2)	3 (3)	n/a	n/a	n/a
Injection site reaction	13 (5)	38 (14)	6 (4)	7 (5)	4 (4)	5 (5)	11 (7)	3 (5)	5 (5)
Hypersensitivity	1 (<1)	--	--	1 (<1)	--	--	--	--	--
Death	--	1 (<1)	--	--	--	--	--	--	--

SAE: serious adverse event, TEAE: treatment-emergent adverse event, AESI: adverse event of special interest
AESI not defined for PK studies
Source: FDA safety analysis of data from Sandoz 351(k) BLA submission

SAEs: Study 302

	Treatment Period 1		Treatment Period 2			
System Organ Class	GP2015 N=264 n (%)	EU-Enbrel N=267 n (%)	Cont'd GP2015 N=150 n (%)	Cont'd EU-Enbrel N=151 n (%)	Switched EU-Enbrel N=96 n (%)	Switched GP2015 N=100 n (%)
Number of patients with SAEs	4 (2)	3 (1)	1 (<1)	2 (1)	3 (3)	3 (3)
Infections and infestations	1 (<1)	--	--	1 (<1)	2 (2)	--
Injury, poisoning, procedural complications	1 (<1)	--	1 (<1)	1 (<1)	--	--
Hepatobiliary disorders	--	1 (<1)	--	--	--	1 (1)
Cardiac disorders	--	1 (<1)	--	--	--	--
Eye disorders	--	1 (<1)	--	--	--	--
Gastrointestinal disorders	--	--	--	--	--	1 (1)
Immune system disorders	1 (<1)	--	--	--	--	--
Musculoskeletal, connective tissue disorders	--	--	--	--	--	1 (1)
Neoplasms benign, malignant, unspecified	1 (<1)	--	--	--	--	--
Respiratory, thoracic, mediastinal disorders	--	--	--	--	1 (1)	--
Skin and subcutaneous tissue disorders	--	--	--	--	--	1 (1)

Source: FDA analysis of data from Sandoz's 351(k) BLA submission

Adverse Events of Special Interest: Study 302

	Treatment Period 1		Treatment Period 2			
System Organ Class	**GP2015 N=264 n (%)**	**EU-Enbrel N=267 n (%)**	**Cont'd GP2015 N=150 n (%)**	**Cont 'd EU-Enbrel N=151 n (%)**	**Switched EU-Enbrel N=96 n (%)**	**Switched GP2015 N=100 n (%)**
# of pts with ≥1 TEAE, n (%)	9 (3)	5 (2)	7 (5)	3 (2)	2 (2)	3 (3)
Neoplasms benign, malignant, unspecified	5 (2)	1 (<1)	1 (<1)	--	--	--
Infections and infestations	3 (1)	3 (1)	4 (3)	--	2 (2)	1 (1)
Skin and subcutaneous tissue disorders	--	1 (<1)	--	2 (1)	--	2 (2)
Blood and lymphatic system disorders	--	--	2 (1)	--	--	--
Immune system disorders	1 (<1)	--	--	1 (<1)	--	--
Investigations	1 (<1)	--	--	--	--	--

Source: FDA safety analysis of data from Sandoz 351(k) BLA submission

Immunogenicity Assessment

- Generally, immunogenicity assessment of a proposed biosimilar product is a component of 351(k) applications
- ADA against etanercept have no apparent correlation with clinical response or adverse events*
- Similar immunogenicity between GP2015 and EU-Enbrel

Study 302						
	Treatment Period 1		Treatment Period 2			
# ADA positive subjects	GP2015 N=264	EU-Enbrel N=267	Cont'd GP2015 N=150	Cont'd EU-Enbrel N=151	Switched EU-Enbrel N=96	Switched GP2015 N=100
Baseline	--	--				
Week 2	--	**1**				
Week 4	--	**5**				
Week 8	--	--				
Week 12	--	--				
Week 18			--	--	--	--
Week 30			--	--	--	--

*FDA-approved Enbrel labeling

Summary of Safety and Immunogenicity

- Safety outcomes, including immunogenicity, were similar between patients treated with GP2015 or comparator products
- No new safety signals were identified in the GP2015 clinical program
- The safety and immunogenicity results support the demonstration of no clinically meaningful differences between GP2015 and the US-licensed Enbrel

Considerations for Extrapolation

Extrapolation Considerations: Indications Being Sought for Licensure of GP2015

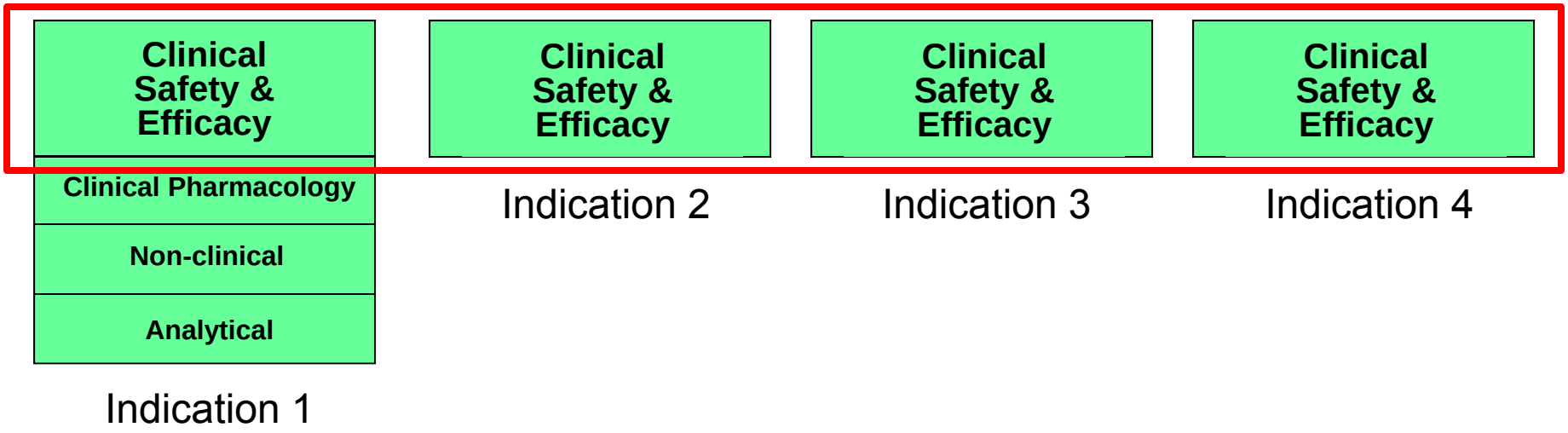
Indication studied in GP2015 clinical program:

- Plaque Psoriasis (PsO)

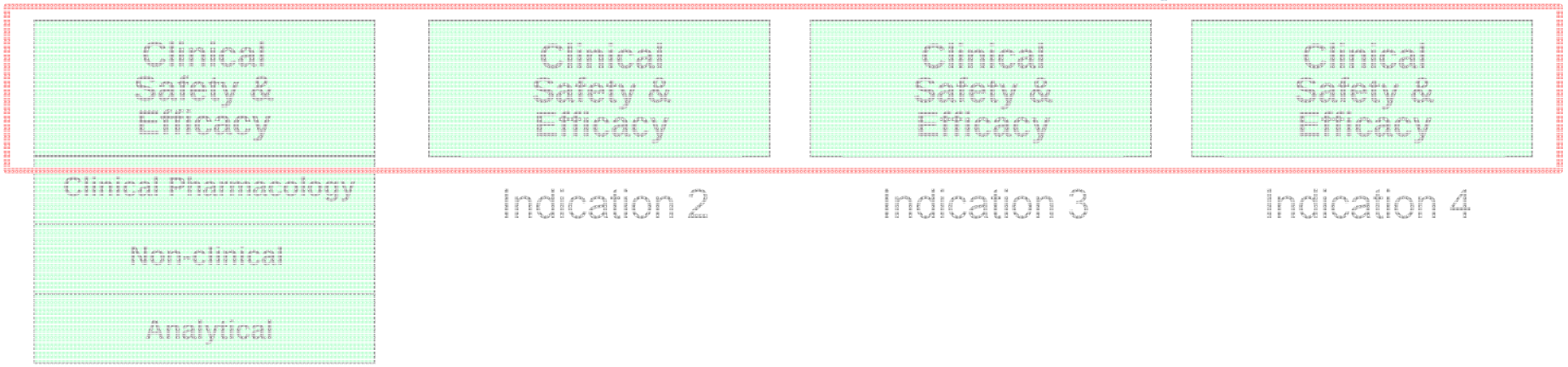
No clinical data on the use of GP2015 in:

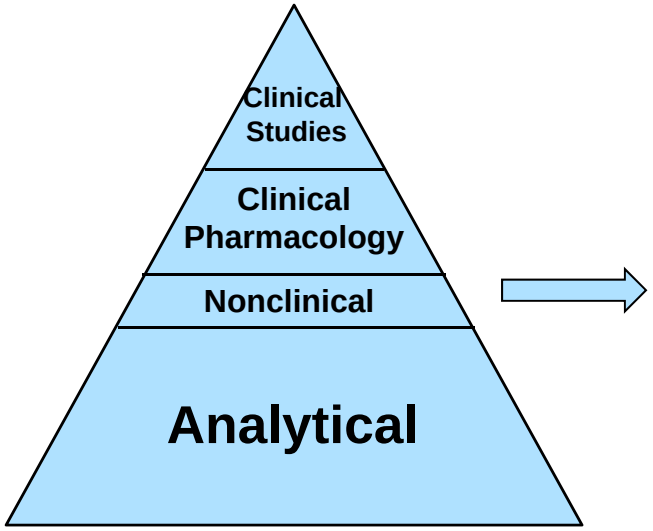
- Rheumatoid Arthritis (RA)
- Polyarticular Juvenile Idiopathic Arthritis (JIA)
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)

"Stand-alone" Drug Development



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



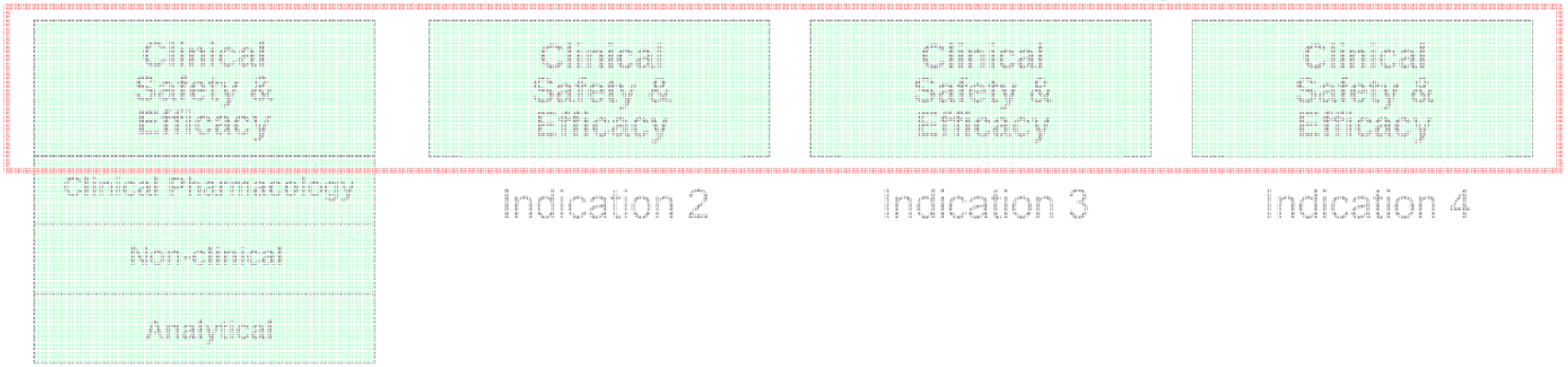


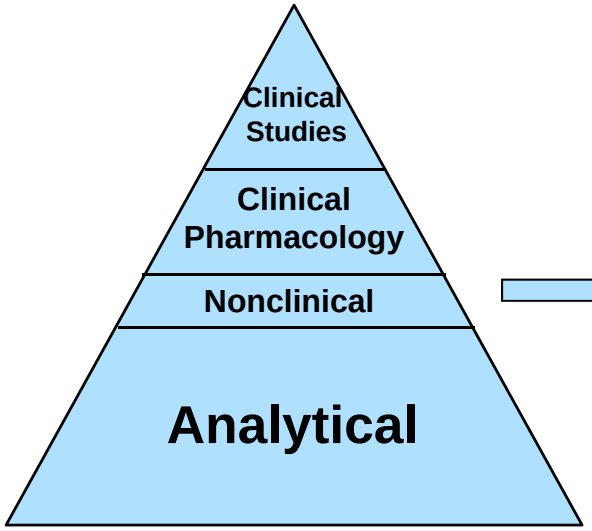
Demonstrate:

- High similarity
- NCMD to the reference product in one or more indications

NCMD: no clinically meaningful differences

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





Demonstrate:
- High similarity
- NCMD to the reference product in one or more indications

Demonstration may include extrapolation of data, considering for each indication:
- MOA(s)
- PK
- Immunogenicity
- Toxicities

NCMD: no clinically meaningful differences

Extrapolation Considerations: Totality of the Evidence

Sandoz provided evidence to support a demonstration that:

- GP2015 is highly similar to US-licensed Enbrel:
  - Primary-, secondary-, and tertiary structure
  - Post-translational profile and *in vitro* functional characteristics
  - Purity and stability
  - Potency, including TNF-α binding and neutralization
- There are no clinically meaningful differences between GP2015 and US-licensed Enbrel based on:
  - Similar clinical pharmacokinetics
  - Similar efficacy, safety, and immunogenicity in PsO

Sandoz also provided scientific justification to support that there are no clinically meaningful differences for the additional indications sought for licensure

Extrapolation Considerations: RA, PsA, AS, JIA

- High analytical similarity between GP2015 and US-licensed Enbrel
- The primary MOA of etanercept in RA, PsA, AS, and JIA , i.e. TNF-α binding and neutralization, is similar between GP2015 and US-licensed Enbrel, supporting the demonstration of the same MOA for the indications being sought
- Clinical data support the demonstration of no clinically meaningful differences in patients with PsO
- It is reasonable to extrapolate data to support that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in RA, PsA, AS, and JIA

Summary

- The totality of the evidence, provided by Applicant, supports:
  - A demonstration that GP2015 is biosimilar to US-licensed Enbrel based on data demonstrating:
    - GP2015 is highly similar to US-licensed Enbrel
    - No clinically meaningful differences exist between GP2015 and US-licensed Enbrel
  - Licensure of GP2015 for the indications for which US-licensed Enbrel is licensed and for which Sandoz is seeking licensure

Thank you!

Charge to the Committee

351(k) BLA for GP2015, a Proposed Biosimilar to US-licensed Enbrel

Arthritis Advisory Committee

July 13, 2016

Nikolay P. Nikolov, MD
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration

Biosimilarity Definition: Section 351(k) of the PHS Act

- "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."

Issues for Consideration

Amgen provided evidence to support a demonstration that:

- GP2015 is highly similar to US-licensed Enbrel:
  - Primary-, secondary-, and tertiary structure
  - Post-translational profile and *in vitro* functional characteristics
  - Purity and stability
  - Potency, including TNF-α binding and neutralization
- There are no clinically meaningful differences between GP2015 and US-licensed Enbrel based on:
  - Similar clinical pharmacokinetics
  - Similar efficacy, safety, and immunogenicity in patients with PsO

Sandoz also provided scientific justification to support that there are no clinically meaningful differences for the additional indications sought for licensure

Discussion Question 1

- Please discuss whether the evidence from analytical studies supports a demonstration that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components.

Discussion Question 2

- Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel in the studied condition of use (PsO).

Discussion Question 3

- Please discuss whether the totality of the data provides adequate scientific justification to support a demonstration of no clinically meaningful differences between GP2015 and US-licensed Enbrel for the following additional indications for which US-licensed Enbrel is licensed:
  - RA
  - JIA
  - PsA
  - AS
- If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication, if relevant.

Voting Question

- Does the totality of the evidence support licensure of GP2015 as a biosimilar to US-licensed Enbrel for the following indications for which US-licensed Enbrel is currently licensed and for which Sandoz is seeking licensure (RA, JIA, AS, PsA, PsO)?

- Please explain the reason for your vote.

Backup Slide Shown

Bioanalytical Method SOP PV05102

The bioanalytical methods are acceptable based on method validation results.

	Version 02	Version 03	
Applied Clinical Studies	Studies 101 and 102	Studies 103 and104	Study 302
Capture Antibody	Peprotech 500-P168 rabbit anti-human soluble TNFR2 polyclonal antibody		
Detection Antibody	R&D Systems BAF726 biotinylated goat anti-human TNFR2 polyclonal antibody	Becton Dickinson 552477 biotinylated rat anti-human TNFR2 monoclonal antibody	
Streptavidin-HRP	Invitrogen SNN4004		
Quality Control	Sandoz GP2015.01REF 9.59 mg/mL	Sandoz GP2015.02REF 9.7 mg/mL	
Minimal Required Dilution in Blocking Buffer	1:3	1:20	1:100
Quantification range of the calibration curve (ng/mL)	1.0 to 120.0	6.7 to 800.0	33.3 to 4000.0
Lower Limit of Quantitation of Sample (ng/mL)	8.0	6.7	33.3