

ACG Public Forum

Join ACG, the FDA, and EMA
for a discussion on biosimilars and IBD

Monday, 12:45 pm – 2:15 pm



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Biosimilars for IBD: What the Gastroenterologist Needs to Know

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Disclosures

- The views expressed in this presentation are my own and are not intended to convey official FDA policy.
- I have no financial conflicts of interest to disclose.
- The product specific details presented are used to exemplify the principles being discussed. All of this information is available in the public domain, and is not intended to promote any particular product.

What Questions Do Clinicians Have?

- What does biosimilarity mean to a clinician?
 - *How is this different from a “generic drug”?*
- Why was the biosimilar product not studied in IBD?
 - *What evidence is there that it will work for my patient?*
- Should I be concerned about immunogenicity that may occur with switching products?
- Do I have a choice in prescribing a biosimilar or not?
 - *What about an interchangeable product?*

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- Do I have a choice in prescribing a biosimilar or not?
 - What about an interchangeable product?
- Case study

Biosimilarity: Definition

Biosimilar or Biosimilarity means:

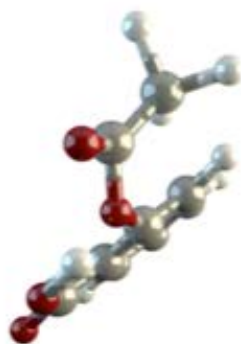
- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; **and**
- there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product

Framework to consider what “Biosimilar” means

	Small Molecule Drugs	Biological Products
Structure	<ul style="list-style-type: none"> • Smaller 	<ul style="list-style-type: none"> • Larger
Manufacturing	<ul style="list-style-type: none"> • Fewer critical process steps • Usually, organic/chemical synthesis • Homogenous drug substance 	<ul style="list-style-type: none"> • Multiple critical steps • Live cells/organisms with inherent contamination risk • Heterogeneous mixtures
Immunogenicity	<ul style="list-style-type: none"> • Usually not immunogenic 	<ul style="list-style-type: none"> • Often immunogenic

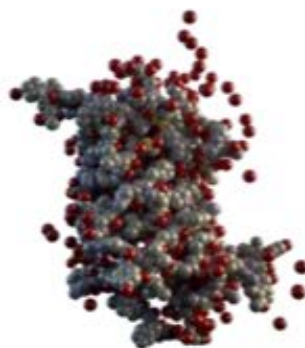
Comparison of small-molecule drugs and biologic products

SMALL MOLECULE DRUG



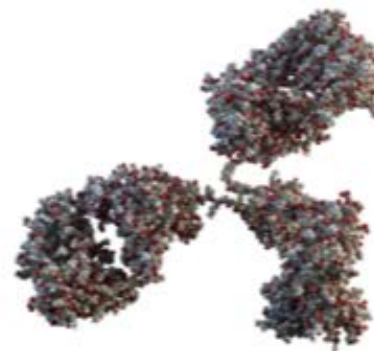
Aspirin
21 atoms

SMALL BIOLOGIC



Human Growth Hormone
~ 3000 atoms

LARGE BIOLOGIC



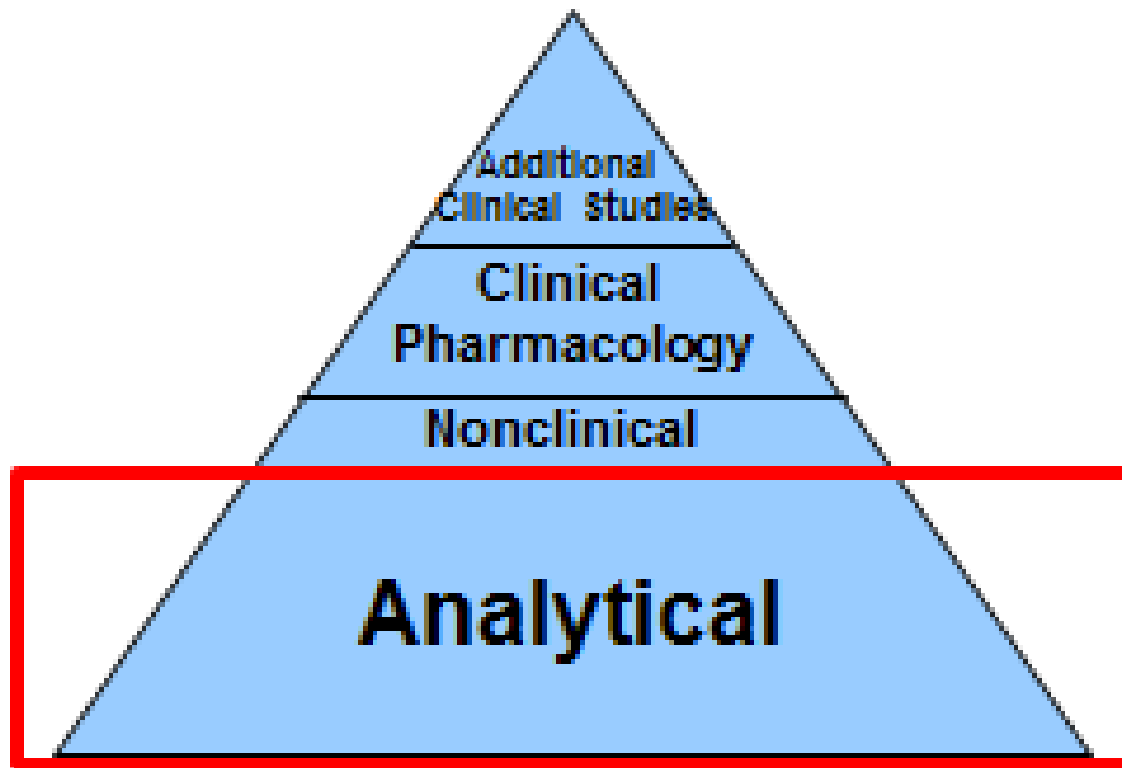
Monoclonal antibody
~ 25,000 atoms

INCREASING COMPLEXITY

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Stepwise Approach to Demonstrating Similarity



"Abbreviated" Development Program, 351(k) BLA

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 clinical data intended to demonstrate biosimilarity in one condition of use
- Sufficient scientific justification for extrapolating data is necessary

Scientific Justification

- Mechanism of Action (MOA) if known, in each condition of use for which licensure is sought
- PK and bio-distribution of the product in different patient populations
- 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 or efficacy of the product in each condition of use and patient population

Extrapolation Example

- Inflectra (infliximab-dyyb) developed as CT-P13 (Celltrion)
- First biosimilar to a TNF blocker approved by FDA
- Application included controlled clinical studies in Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS)
- Did receive all the (eligible) indications as the US-licensed reference product (Remicade).
 - Psoriatic Arthritis
 - Plaque Psoriasis
 - Adult and Pediatric Crohn's Disease
 - Adult Ulcerative Colitis*



Known and Potential MOA of Infliximab

MOA of infliximab	RA	AS	PsA	PsO	CD Pediatric CD	UC Pediatric UC	Similarity Criteria Met
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF							
	Yes	Yes	Yes	Yes	Likely	Likely	✓
Reverse (outside-to-inside) signaling via tmTNF:							
Apoptosis of lamina propria activated T cells	-	-	-	-	Likely	Likely	✓
Suppression of cytokine secretion	-	-	-	-	Likely	Likely	✓
Mechanisms involving the Fc region of the antibody:							
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible	✓
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible	✓*
Induction of regulatory MΦ in mucosal healing	-	-	-	-	Plausible	Plausible	✓

* Modest shift in mean activity of CT-P13 vs. reference product, within the established quality range

PK / Biodistribution

- PK is known to be similar across various patient populations*
- For this reason, since the applicant demonstrated PK similarity between CT-P13 and EU approved Remicade in multiple usage scenarios, the Agency accepted the rationale that PK differences would not be expected in the IBD population.
- *as described in the reference product labelling

Immunogenicity

- Immunogenicity is primarily affected by the use of concomitant medications across different indications, rather than patient populations.
- As a result, meeting similarity criteria for immunogenicity in a sensitive population (with concomitant methotrexate in RA patients, and as monotherapy in AS patients) was felt to be sufficient extrapolate that immunogenicity is not expected to be different in IBD patients.

Toxicity

- Across multiple indications, the common and rare but serious adverse events are noted to be similar.
- Major toxicities such as serious infections and malignancies are similar across disease populations.
- As a result, there was no reason to expect a different safety profile in IBD patients treated with CT-P13, compared to the reference product

Extrapolation Summary

- In summary, the applicant addressed the mechanism(s) of action, PK, Immunogenicity and Safety across multiple indications
- The Agency determined that the scientific justification was sufficient to extrapolate the approval of the Biosimilar to all of the eligible indications held by the reference product.

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Impact of Immunogenicity

Clinical Concern	Clinical Outcome
Safety	<ul style="list-style-type: none"> • Neutralize activity of endogenous counterpart with unique function causing deficiency syndrome • Hypersensitivity reactions • Infusion Reaction
Efficacy	<ul style="list-style-type: none"> • Enhancing or decreasing efficacy by: <ul style="list-style-type: none"> - changing half life. - changing biodistribution.
Pharmacokinetics	<ul style="list-style-type: none"> • Changing half life
None	<ul style="list-style-type: none"> • No discernable impact from Ab

Interchangeability: Definition

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*

Conclusions

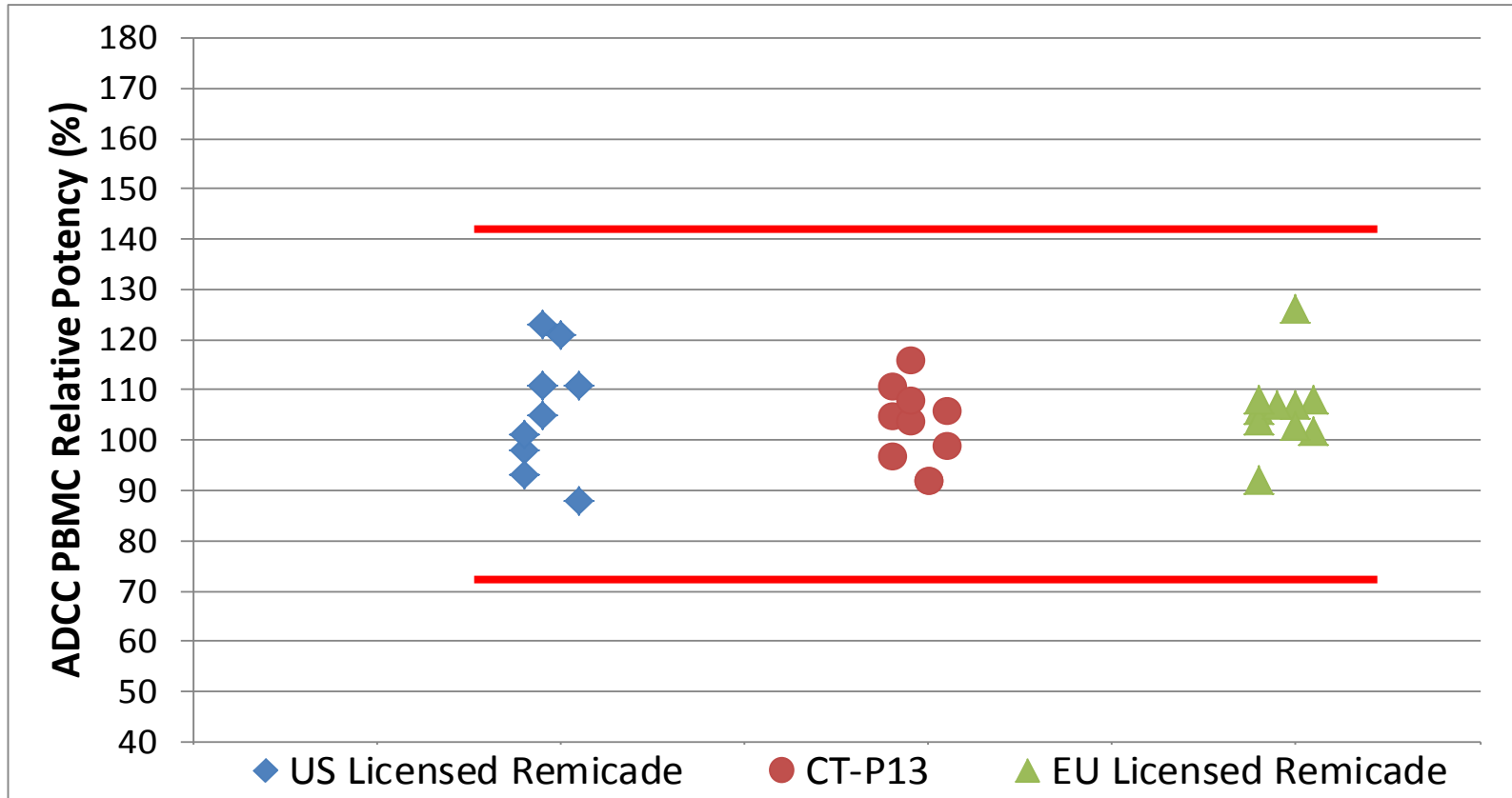
- A biosimilar is highly similar to the reference product, and has no clinically meaningful differences from the reference product.
- Biosimilars are evaluated very stringently to ensure that they are highly similar.
- Despite not necessarily being studied in IBD, GI providers should feel confident that the biosimilar has met a strict bar for similarity, and IBD indications were granted because there is no scientific basis to expect differences in clinical outcomes for IBD patients, compared to the reference product based on totality of the evidence, where clinical studies are a small piece of the overall data package.
- Currently FDA has not approved any biosimilar as “interchangeable.”

Resources:

- **FDA Guidance on Biosimilars:**
 - <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf>
- **FDA Draft Guidance on Interchangeability:**
 - <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf>
- **FDA Information of Biosimilars:**
 - <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm>

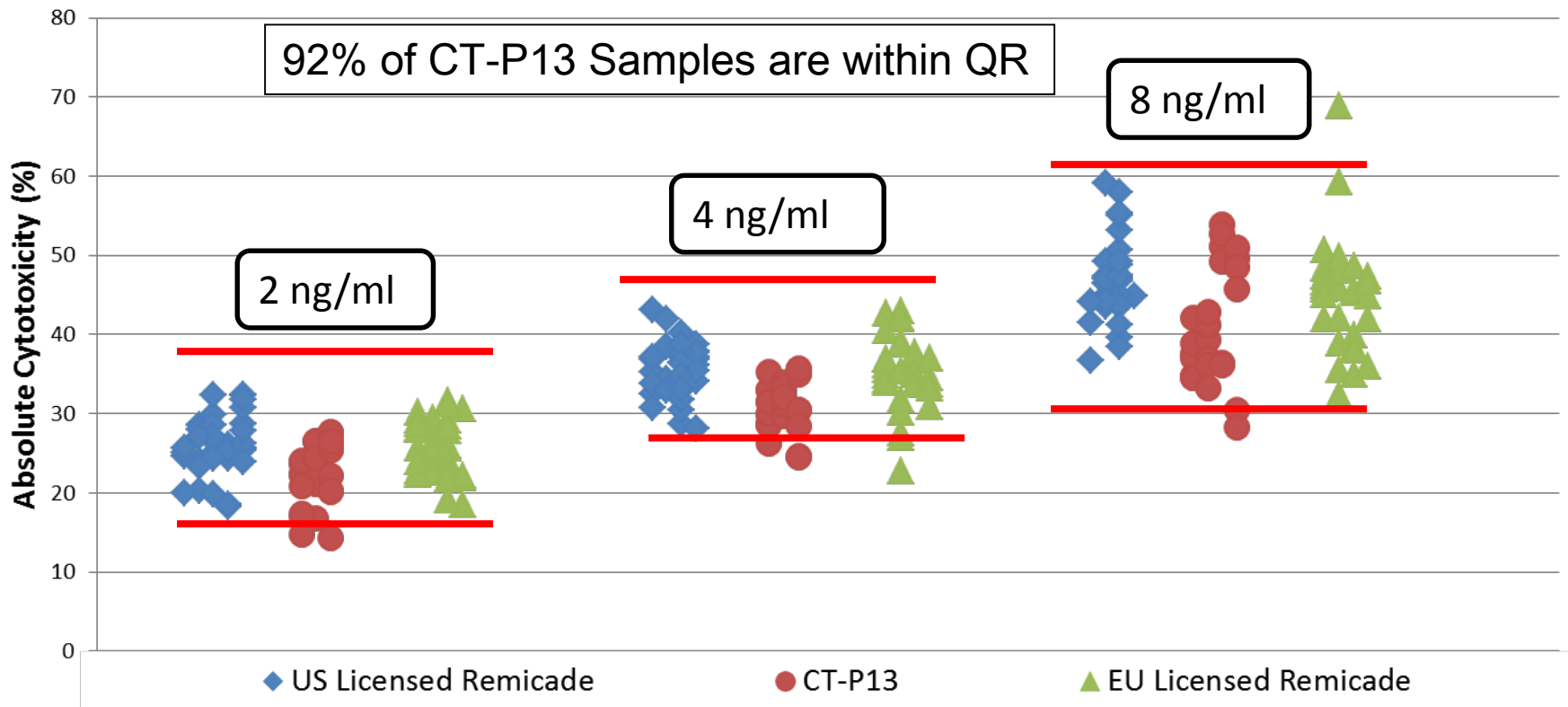
Additional Slides

QR Analysis: PBMC ADCC



- ADCC assay uses
 - Transfected transmembrane TNF- α Jurkat cells as target cells
 - PBMC from healthy donor as effector cells

QR Analysis: NK-ADCC Cytotoxicity



- NK-ADCC assay:
 - Transfected transmembrane TNF- α Jurkat cells used as target cells
 - NK cells purified from peripheral blood used as effector cells