Biosimilars: A Small yet Reliable Step Towards Affordable Healthcare

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Disclaimer

The opinions expressed in this presentation are those of the presenter and do not necessarily reflect official support or endorsement by the FDA.

Overview

- **Benefits from Biologics**
- **Why Biosimilars**
- **Foundation of Biosimilars - Analytical Similarity**
- **Constructing a Comprehensive Analytical Similarity Assessment Program**
- **When to initiate Clinical Programs to confirm similarity and to address residual uncertainty**

Biologics: Pros & Cons

Pros: Well defined therapeutic efficacy by introducing specific exogenous factors targeting specific pathway:

- **Hormones:** insulin
- **Cytokines:** G-CSF
- **Enzymes:** rhGAA – "Extreme Measures"
- **Monoclonal antibodies:** "Jimmy Carter's Doctors Find No Evidence of Cancer After Breakthrough Treatment" – anti-PD1

Cons: Cost

- **Insulin: 15 – 20 Tons/24B**
- **Enzymes: ~200K/yr/patient**
- **mAbs: up to 9K/shot, ~3000 times the cost of gold**

Patient JL, 15 pounds December 15, 1922

Patient JL, 29 pounds February 15, 1923

Top Commercially Performing Biologics

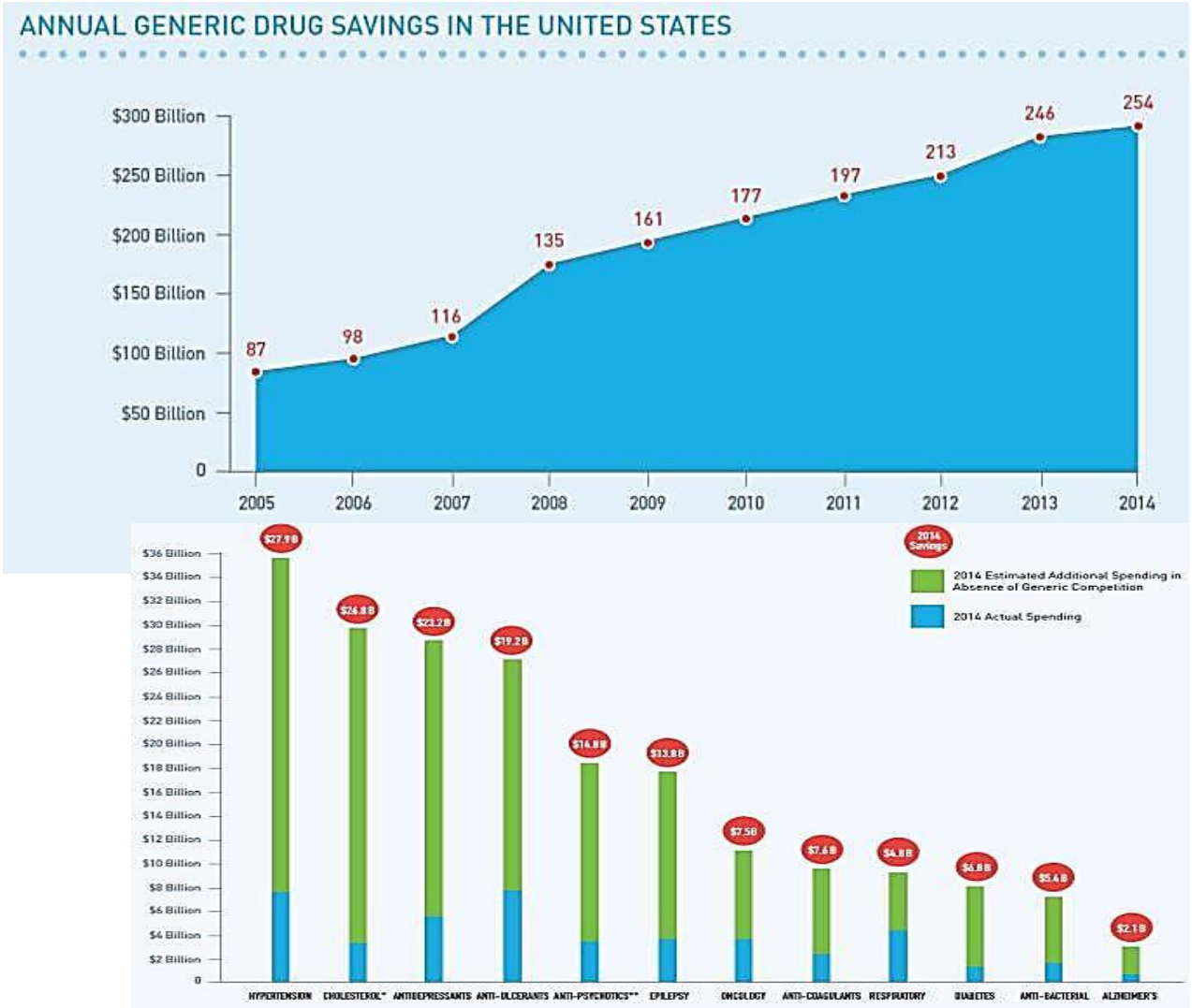
Brand Name	Sales (Mil)	Indication
Humira (1)	13021	autoimmune
Remicade (3)	10151	autoimmune
Enbrel (4)	9120	autoimmune
Lantus (5)	8152	diabetes
Rituxan (6)	7356	oncology
Avastin (7)	6841	oncology
Herceptin (9)	6690	oncology
Neulasta	4596	neutropenia
Lucentis	4254	AMD
Avonex	3013	MS
NovoRapid	3012	diabetes
Humalog	2785	diabetes
Stelara	2474	autoimmune

Brand Name	Sales (Mil)	Indication
Rebif	2364	MS
Erbitux	2257	oncology
Soliris	2234	PHN
Tysabri	1886	MS
Orencia	1885	autoimmune
Epogen	1865	Anemia
NovaMix	1675	diabetes
Perjeta	1503	oncology
Xolair	1333	asthma
Simponi	1328	autoimmune
Cimzia	1201	autoimmune
Tarceva	1228	oncology
Yervoy	1126	oncology
Total	103,350	

Biologics account for 26 out of the top 100 pharmaceutical products

Savings from Generics:

1.68 Trillion in 10 years (2005 -2014)



Generic Drug Savings in the U.S. Report, 2015

Savings from Biosimilars ?

	Originator ($)	Biosimilar ($)	saving
Remicade	1227	996	19%
Neupogen	340	283	17%
Humira	4500	?	

OUR UNIQUE CAPABILITIES POSITION US FOR LEADERSHIP IN BIOSIMILARS

	Status	Originator Worldwide 2015 Sales*
ABP 501	Global regulatory reviews	HUMIRA® ~ $14B
ABP 980	Phase 3 breast cancer	Herceptin® ~ $7B
ABP 215	Phase 3 complete (NSCLC)	Avastin® ~ $7B
ABP 710	Phase 1	REMICADE® ~ $8B
ABP 798	Clinical ready	RITUXAN® ~ $7B
ABP 494	Process development	ERBITUX® ~ $2B
Molecules #7–#9	Process development	~ $9B
Total		~ $54B

NSCLC = non-small-cell lung cancer
*Per EvaluatePharma (December 7, 2015); numbers may not add due to rounding
Provided January 12, 2016, as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update.

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https://www.fool.com/investing/general/2016/01/13/5-slides-that-tell-you-everything-you-need-to-know.aspx

Biosimilars: Biologics Version of Generics ?

Ayes:

- **Over 12 years of safety and efficacy profile of the originator product**
- **Extensive knowledge of attributes related to purity and potency of the originator molecule**
- **Extensive understanding of the mechanisms through which the molecule works**

Nays:

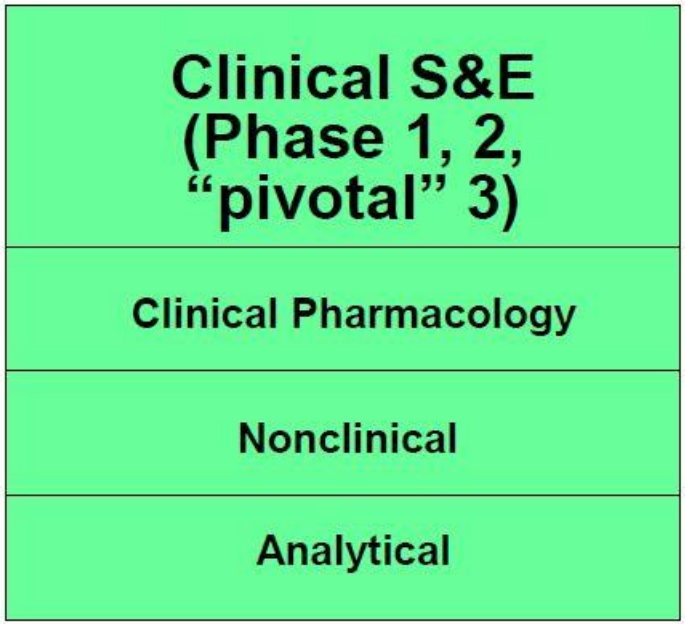
- **Characterization of biologics can be challenging!**

PROPERTIES	GENERICS	BIOSIMILARS
SIZE	Small	Large
MOLECULAR WEIGHT	~150 Daltons	~150,000 Daltons
STRUCTURE	Simple and well-defined	Complex with potential structural variations
MANUFACTURING	Predictable chemical process to make identical copy	Specialized biological process to make similar copy
COMPLEXITY	Easy to fully characterize	Difficult to characterize
STABILITY	Relatively stable	Sensitive to storage and handling conditions
ADVERSE IMMUNE REACTION	Lower potential	Higher potential
MANUFACTURING QUALITY TESTS	≤ 50	≥ 250
APPROVAL REQUIREMENTS	Small clinical trials in healthy volunteers	Large clinical trials in patients

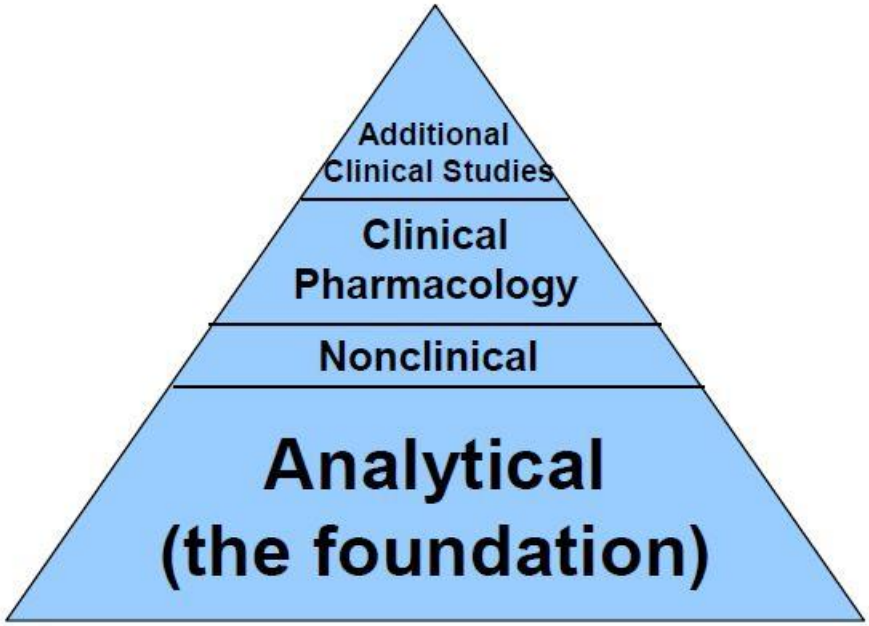
http://www.amgenbiosimilars.com/the-basics/biosimilars-versus-generics/

Key Concept: The Goals of Stand-alone and Biosimilar Development are Different

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



"Abbreviated" Development Program, 351(k)
Goal: To demonstrate biosimilarity



Parallel Development of clinical and analytics

Analytics Driven

John Jenkins, DIA 2016

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Challenges in Demonstrating Analytical Similarity

- **Biologics are heterogeneous! Different form can't be isolated**
- **Safety and Efficacy profile is the collective contribution of all forms of the molecule**
- **Different forms may contribute differently to different indications**

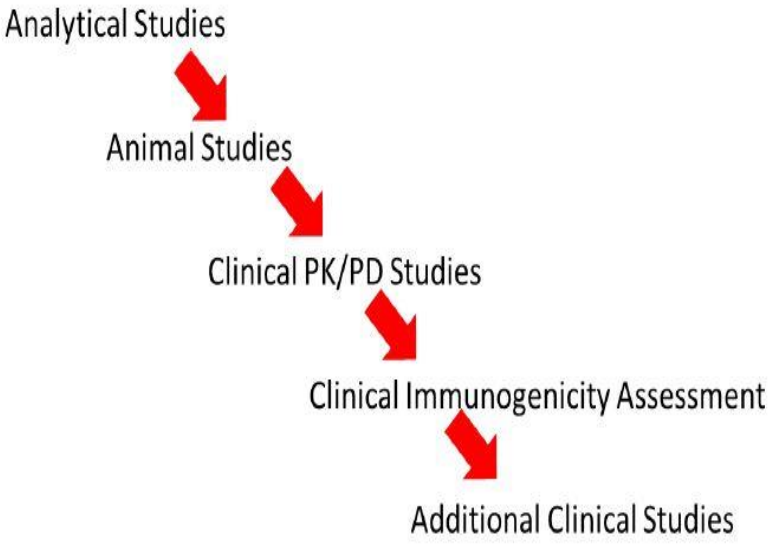
Humira: a TNF inhibitor is approved for:

RA, PsA, Ps, JIA, AS, CD, UC

- **TNF Binding to reduce cell killing – all indications**
- **ADCC/CDC: all but may be more prominent in treating IBDs**
- **Similarity should be demonstrated for attributes essential for all indications**

Analytical Similarity: The Foundation to Demonstrating Biosimilarity

- The stepwise approach starting with extensive structural and functional characterization
- Allows a thorough evaluation of the analytical differences and resulting residual uncertainty
- Identify next steps to address that uncertainty
  - Orthogonal methods to further evaluate impact on function
  - Control strategies to minimize the differences
  - Clinical
- Clinical studies:
  - Nature of trials
  - Extrapolation to all indications



Analytical Similarity Assessment Programs for Biosimilars

Understand your molecules:

- Primary mode of action
- Other biological activities for each sought indication
- Attributes collectively contribute to each biological activity
- General properties of a molecule

Understand your assay capability:

- Qualify your assays with adequate precision
- Capture the targeted range of high risk attributes of the Reference Product
- Capture the variation of your own manufacturing process
- Chase product quality variations, not assay variation

Apply Appropriate Statistical Analysis Based on Attribute Risk Ranking

Demonstration of statistical equivalence:

The highest risk ranking attributes evaluate clinically relevant mechanism of action for each sought indication

- **sufficient number of RP and biosimilar lots for equivalence testing**

Meeting the quality range of the reference product:

For attributes that are not directly linked to clinical performance but collectively contribute to overall efficacy and safety profile

- **sufficient number of RP lots to define a range for each attribute**
- **Demonstrate biosimilar product lots fall within the range**

Direct comparison of attributes not amenable to statistical analysis

- **amino acid sequence**
- **Results from semi-quantitative assays**

Biosimilar Product Development

- **Build the foundation – a robust analytical similarity assessment program**
  - **Establishes an analytical target profile**
  - **Assists to refine manufacturing process to ensure the ranges of critical attributes are maintained**
  - **Built in sufficient assays to interrogate attributes from different angles**
  - **Identifies, confirms differences, and provides a basis to implement a control strategy to minimize uncertainty – highly similar, not identical**
- **Do not rush your product to the clinics until your are confident that you can demonstrated analytical similarity. You may ended up with an expansive failure!**

Thank You !