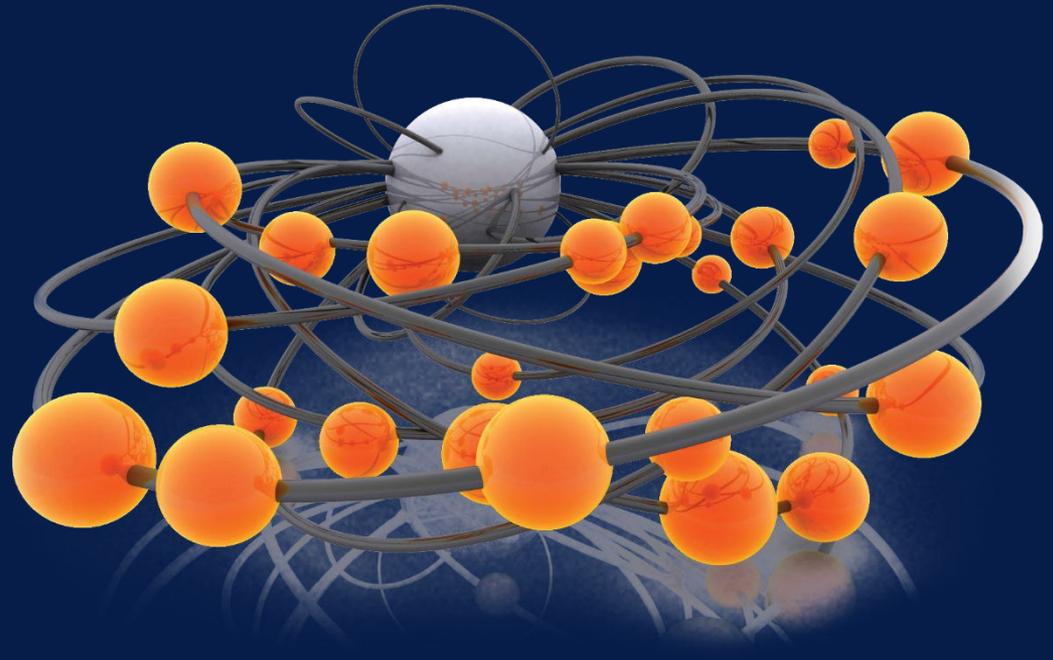


UNDERSTANDING THE SIMILARITIES AND DIFFERENCES BETWEEN THE INNOVATOR AND BIOSIMILAR COMPARABILITY EXERCISE

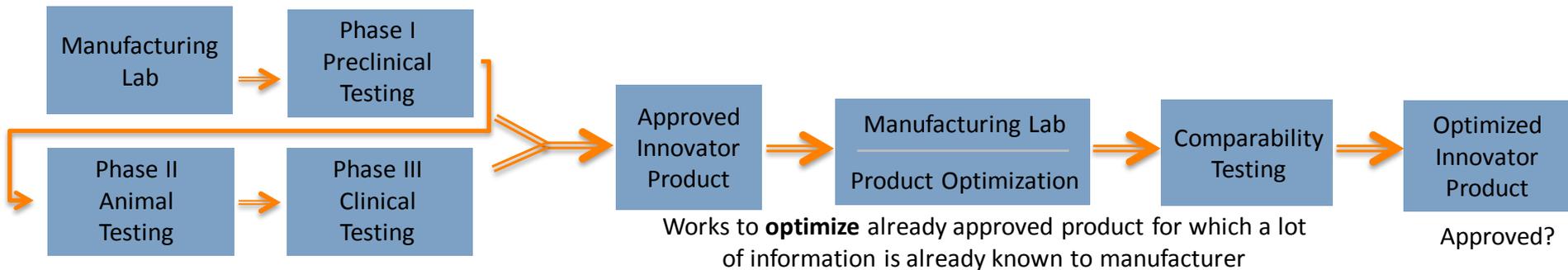
Karen Hauda
Sr. Director
May 8, 2013



Innovator Manufacturing Change vs. Biosimilar Product Development

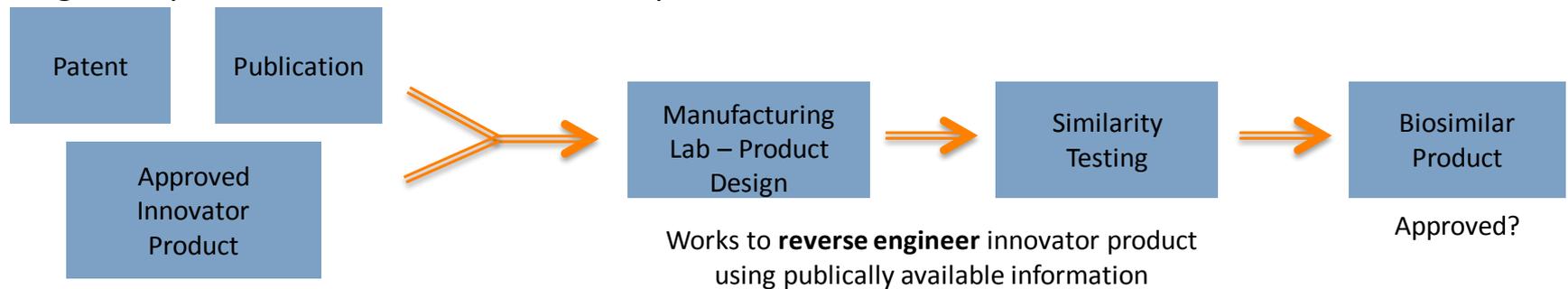
Innovator Manufacturing Change

Optimizing an approved process for a product that has undergone significant R&D and a full pre-clinical and clinical regulatory approval process



Biosimilar Product Development

Attempting to reverse engineer or recreate the innovator's product starting from published information and the product on the market



* While the technological processes for comparing products may be similar, a biosimilar manufacturer and innovator have very different knowledge and tools available to them

Clarifying Terminology:

Comparability is Often Used in Different Ways and for Different Purposes

Innovator Comparability

Innovator comparability testing measures quality attributes of a single product after a manufacturing process change

Also referred to as:

- Innovator product manufacturing change
- Manufacturing change comparability
- Manufacturing comparability

Biosimilar Comparability

Biosimilar testing involves the analytical, pre-clinical, and clinical comparison between two different, but related products

Also referred to as:

- Biosimilarity Exercise
- Comparability Exercise
- Biosimilarity Comparison
- Biosimilar Reference Product Comparison

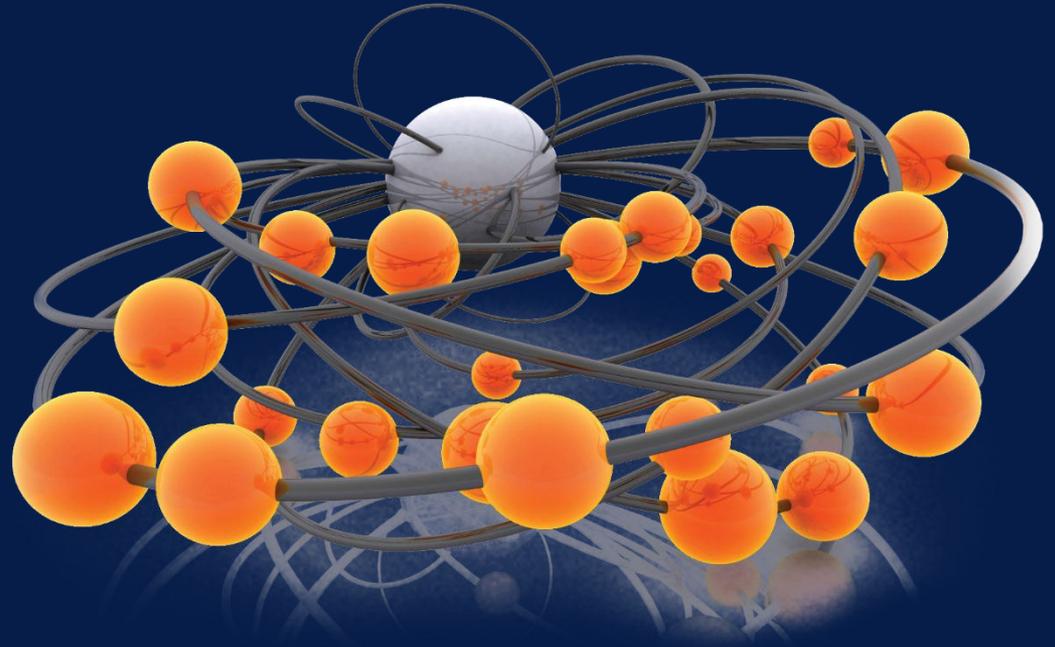


Post Manufacturing Change Assessment vs. Biosimilar Development

Key Considerations:

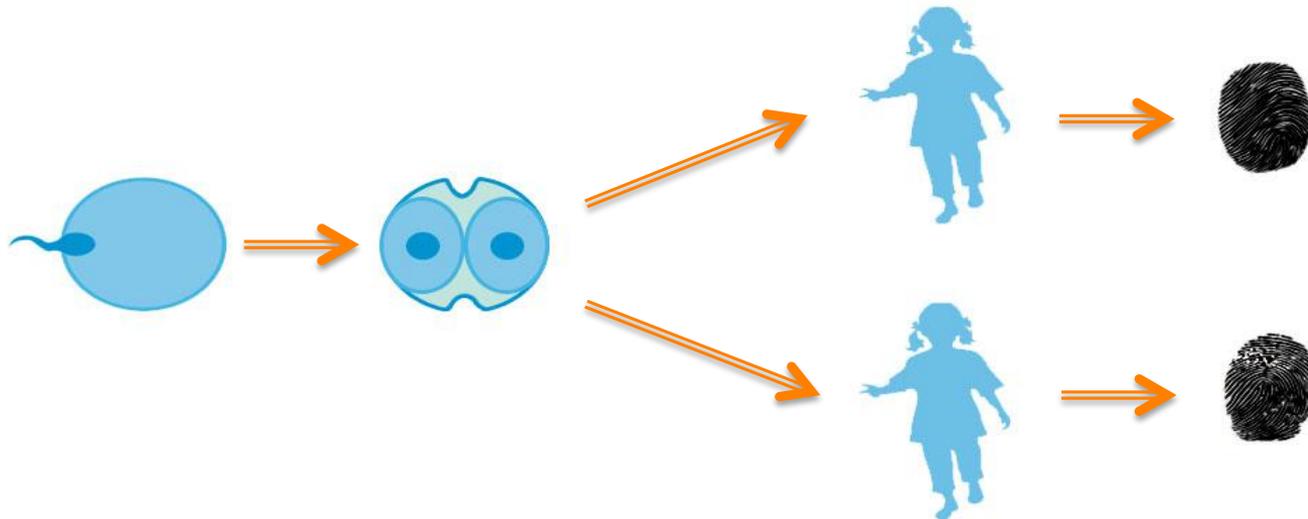
- ‘Similar’ does not equal ‘same’
- Small alterations can make a BIG difference
- US FDA and EMA clearly distinguish the requirements for manufacturing comparability vs. biosimilarity
- Knowledge produces consistency and confidence

'Similar' Does Not
Equal 'Same'

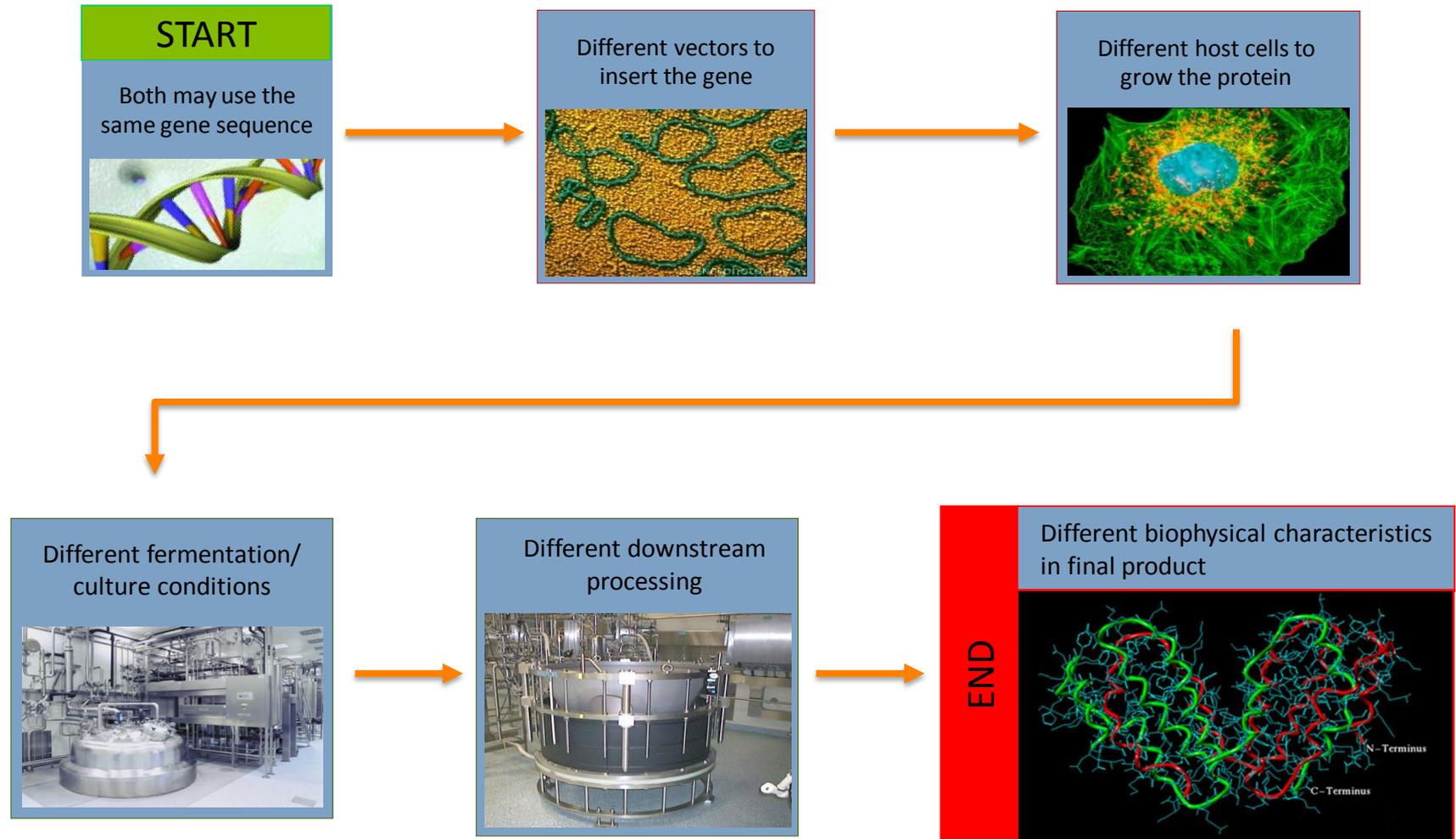


Biosimilars and Twins: Identical DNA, Minor differences in Features

- The active ingredient of a biosimilar can at best only **resemble** that of the innovator product
- How an innovator makes its biologic can **never be duplicated** down to the last detail; a biosimilar is made using cells, materials and processes that differ from the innovator product
- This is true even if a biologic and its biosimilar start from the same **genetic blueprint**, in much the same way as **identical twins**, despite the same genes, have **different fingerprints**

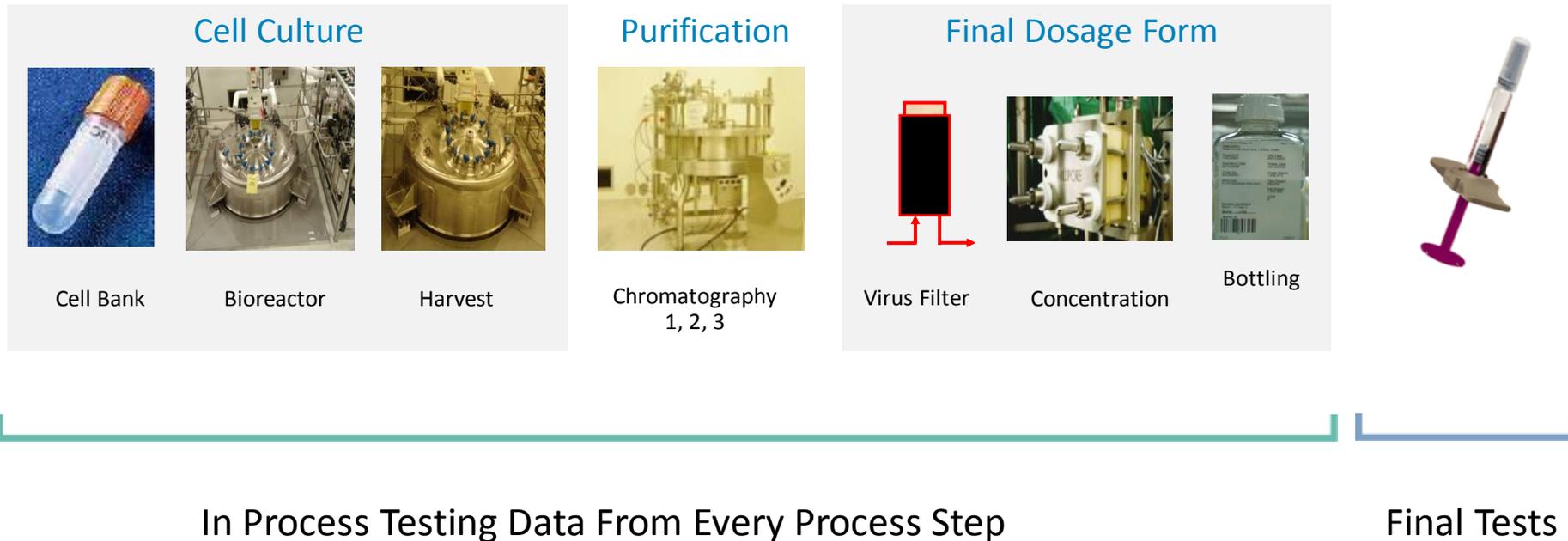


Two Different Processes Create Two Non-Identical Biologic Products



Biologics Manufacturing Control at Every Step

For comparability, the innovator has a rich testing database from every in process step of every batch, the biosimilar only has access to the final product



Accumulated Experience and Knowledge Generates Sustainable Quality and Predictability

YEAR	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Innovator Development	Discovery and Target Validation			Cell Line, Process Development				Process Characterization, Validation						Process monitoring, Scale and Site changes, Comparability Protocols, Process consistency Assurance											
				Characterization of Molecule, Structure /Function Studies, Justify and Establish Specifications					Deep understanding of Product Properties, Comparability Protocols to assure consistent product																
				Non-clinical Studies																					
				Ph 1 clinicals	Phase 2 Clinicals	Phase 3 Clinicals			BLA/MAA	Clinical Studies for additional Indications															
				Pre-Approval Safety Database					Post-Approval Safety Database, Post-Approval Pharmacovigilance, Post-Marketing Observational Studies, Post-Marketing Safety Studies																

YEAR						1	2	3	4	5
Biosimilar Development						Cell Line, Process Development, Characterization				
						Analytical Characterization, Establish Specifications				
						Non-Clinical Studies				
						Clinical studies			BLA/MAA	
						Pre-Approval Safety Database				

CASE STUDIES:

EMA Biosimilar Applications Rejections and Withdrawals

Biosimilar vs. Innovator	Year	Differences	Consequence
Alpheon (<i>interferon alpha 2a</i>) vs. Roferon-A [®]	2006	<ul style="list-style-type: none"> Differences identified between the two medicines (such as impurities) Non-validated finished product evaluation process Lack of stability data Rates of return of disease after treatment discontinuation, and more side effects¹ 	<ul style="list-style-type: none"> CHMP recommended that Alpheon be refused marketing authorization No new trials being conducted for Alpheon
Human Rapid Marvel, Human Long Marvel and Human 30/70 Insulins vs. Humulin [®] S, I and M3 Insulins, respectively	Feb 2008	<ul style="list-style-type: none"> Clinical differences in rates of lowering blood sugar levels² <ul style="list-style-type: none"> - “Trend in favor of Humulin” Inadequate submission of active or finished product process Non-validated manufacturing process 	<ul style="list-style-type: none"> Marvel withdrew its applications for marketing authorizations
Solumarv, Isomarv and Combimarv vs. Humulin [®] S	Nov 2012	<ul style="list-style-type: none"> New bioequivalence data needed to be in line with new requirements in the EMA biosimilar insulin guideline (currently being revised) Questions raised on clinical study size and patient population as well as the sensitivity of the clamp study 	<ul style="list-style-type: none"> Marvel withdrew its applications for marketing authorization Intends to repeat and submit new bioequivalence on each PK/PD data clamp study

Humulin and Referon-A are trademarks of Eli Lilly, and Roche respectively

(1) Questions and Answers on Recommendation for Refusal of Marketing Application for Alpheon. 2006 Doc. Ref. EMEA/190896/2006.

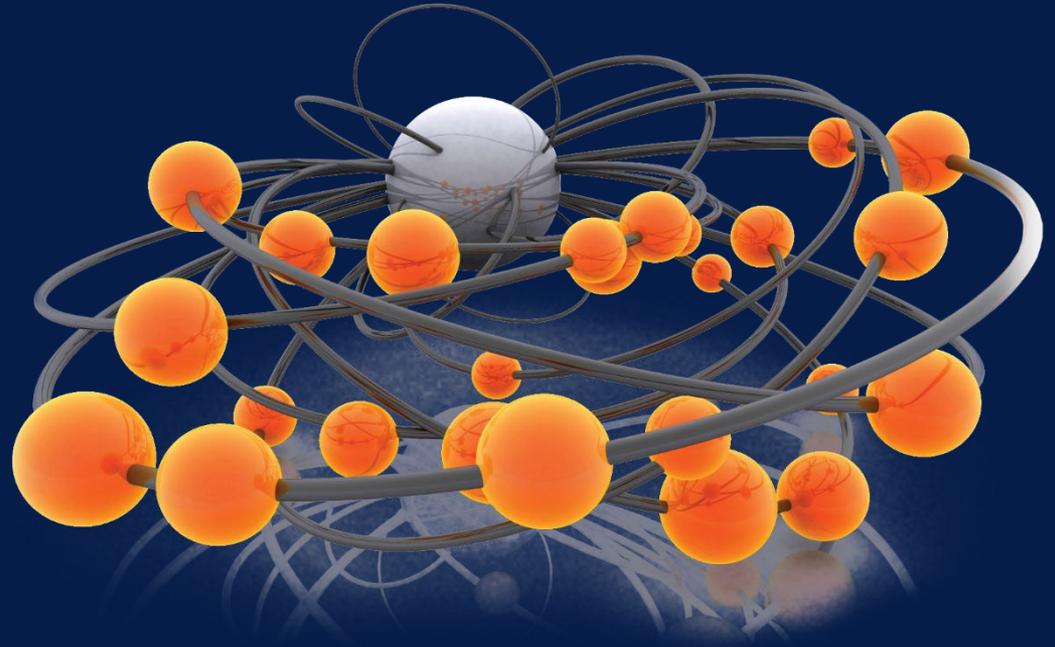
(2) Questions and Answers on Recommendation for Refusal of Marketing Application for insulin Human Marvel 2008 I Doc. Ref. EMEA/4193/2008.

(3) Press Release. Marvel LifeSciences Ltd withdraws its marketing authorization application for Solumarv, Isomarv and Combimarv (human insulin). 2012 Doc. Ref. EMA/747975/2012.

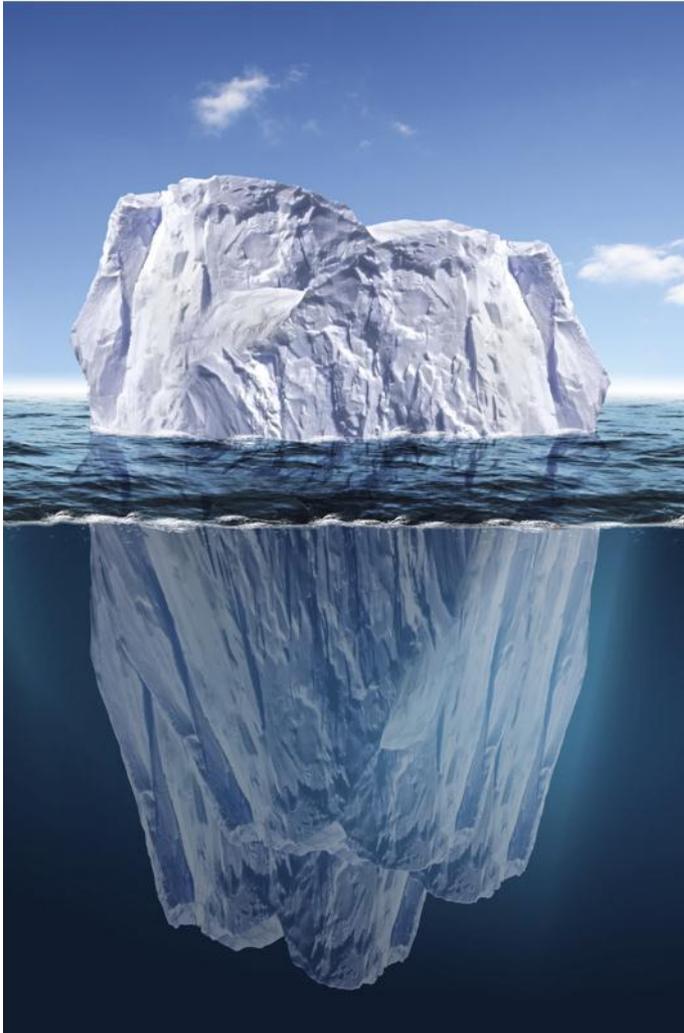
Biosimilars: 'Similar But Not the Same'

- Biosimilars manufactured by different manufacturers will differ from the innovative product and from each other
 - They are **not** generic biologics
 - They use a **different 'host cell'** to develop the biosimilar product
 - The active ingredient of a biosimilar can at best only resemble that of the original biologic
- How an innovator makes its biologic can never be copied down to the last detail; a biosimilar is made using different cells and different processes
- This is recognised in the Regulatory guidance: EMA Guideline On Similar Biological Medicinal Products *CHMP/437/04* (Effective Oct 2005)
 - “Due to the complexity of biological/biotechnology-derived products **the generic approach is scientifically not appropriate** for these products”

Small Alterations
Can Make a BIG
Difference



How Well Do We Understand Our Biologic?



GOAL: Consistent manufacturing yielding consistent product therefore producing consistent **SAFETY + EFFICACY**

Release Tests

- Certificate of Analysis

Characterization Tests

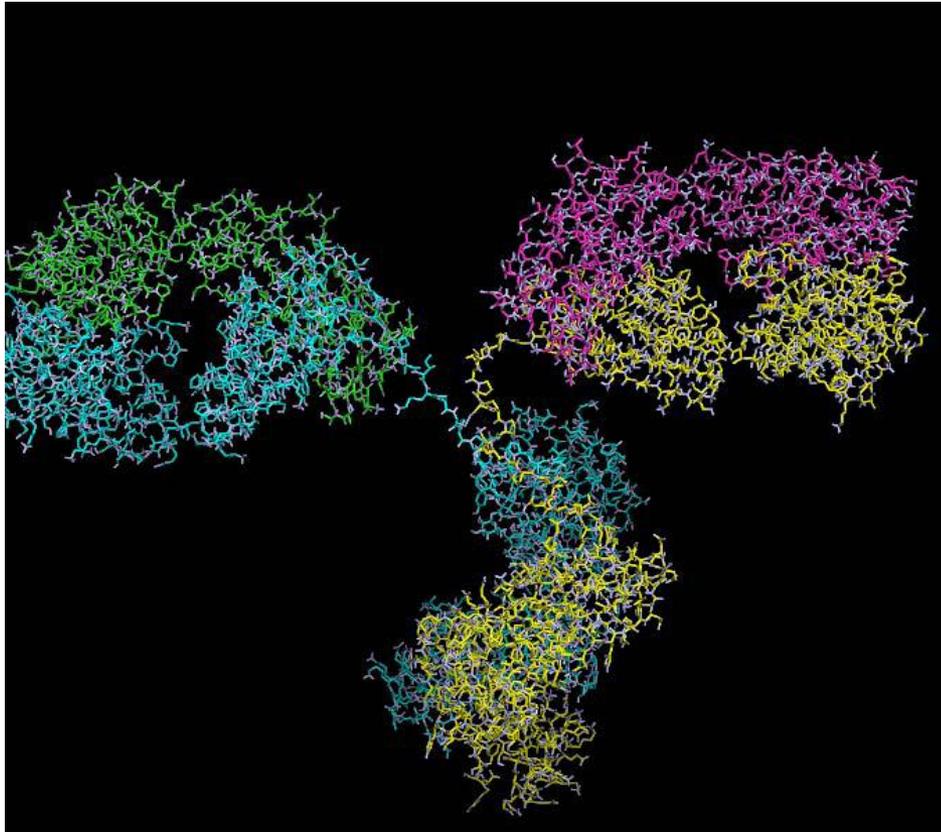
- Process characterization
- Extended product characterization and comparability

Process Control

- Process and product impurities
- Raw materials
- Process monitoring and in-process testing
- Controls, setpoints, ranges, hold times
- Process validation

Derived from: S. Kozlowski, P Swann/Advanced Drug Delivery Reviews 58 (2006).

6,440 Carbon Atoms Are a Lot to Track



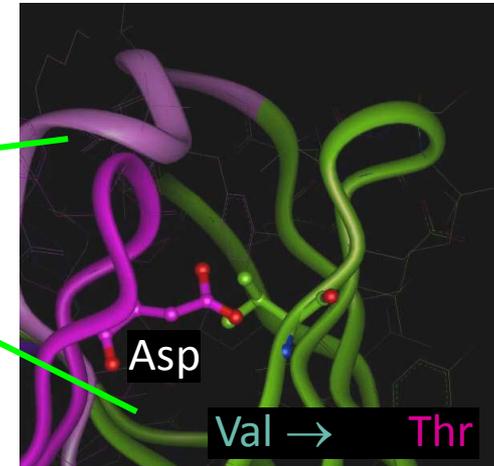
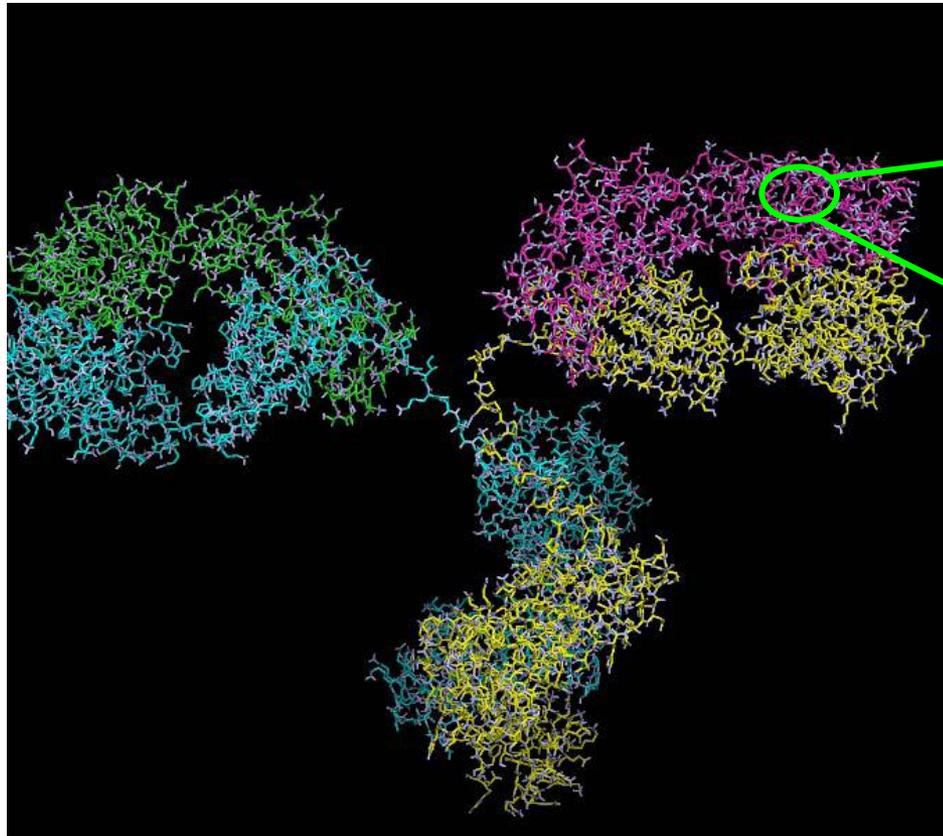
Molecular Weight: 148,683.5 [g/mol] Molecular Formula: C_{6,440}H_{9,928}
N_{1,704}O_{2,011}S₅₆ (Anti-canine lymphoma monoclonal antibody "MAb 231")

- Few intact antibody structures have been solved
- Rarely is detailed structural information available to help guide process development
- Differences frequently occur in a subpopulation of molecules further complicating analytical studies

What is important functionally?

Which Changes Matter? Which Don't?

We don't know unless identified and clinically tested!



Charlie Hutchens – Abbott Labs

A single additional H-bond increases thermodynamic stability and could change the aggregation.

Does this impact safety/efficacy?

Case Studies: “Not so Comparable” Manufacturing Changes

Innovator process changes resulting in significant clinical impact

Product	Change	Impact
Myozyme/Lumizyme ¹ (glucosidase alpha)	160 to 2,000 liter scale produced glycosylation differences	New clinical trial, biologics regulatory submission, and name change from myozyme to lumizyme
Eprex (epoetin alpha) ²⁻⁴	Replaced HSA with sorbitol-80 stabilizer using un-coated stoppers in PFS	Increased incidence of neutralizing antibodies and PRCA

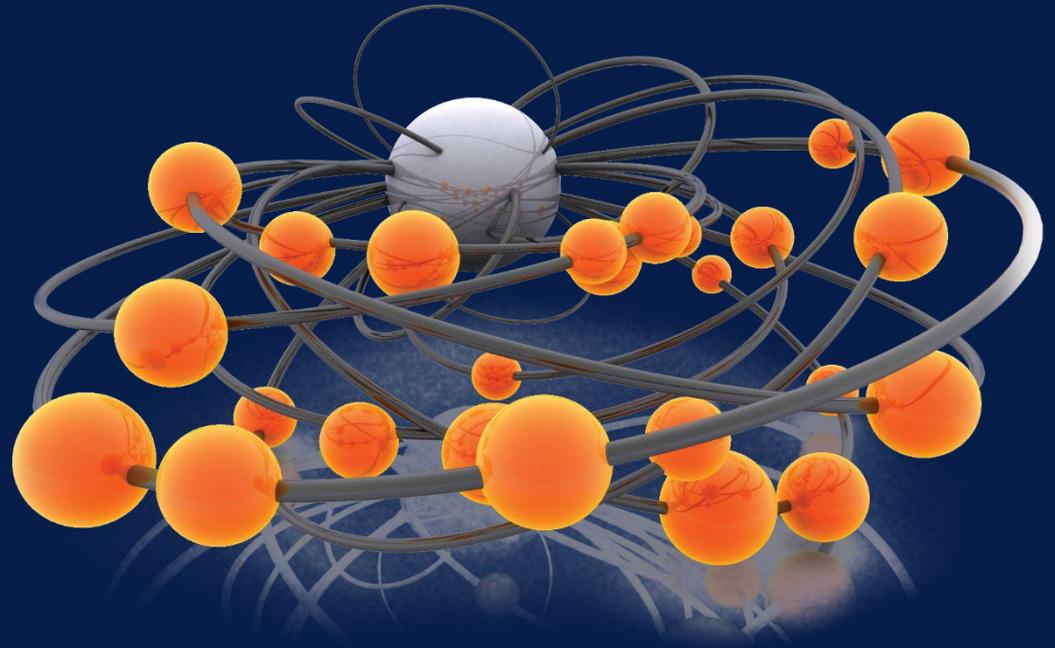
PRCA: pure red cell aplasia. HSA: human serum albumin. PFS: pre-filled syringe

1. <http://www.in-pharmatechnologist.com/Ingredients/Myozyme-becomes-Lumizyme-after-biologics-scale-up>.

2. Kuhlmann M. et al. 2010 10: 90 *British Journal of Diabetes & Vascular Disease*. Lessons learned from biosimilar epoetins and insulins.

3. Schellekens, H. *Nature Biotechnology* 2006;24(6): 613-14. (4) Bennett C. et.al. *N Engl J Med*. 2004 Sep 30;351(14):1403-8.

US FDA and EMA
Clearly Distinguish
the Requirements
for Manufacturing
Comparability vs.
Biosimilarity



Regulatory Perspective of Manufacturing “Comparability”

- Manufacturers make changes when:
 - Maintaining state of the art manufacturing process
 - Increasing scale
 - Improving product stability
 - Complying with changes in regulatory requirements
- Relevant quality attributes are evaluated
 - Manufacturers evaluate potential impact of process modifications on clinical safety and efficacy of the drug
- Such an evaluation should indicate whether or not confirmatory nonclinical or clinical studies are appropriate¹
 - This is known as the comparability exercise
- **How does this differ from the development of a biosimilar?**

1. ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.

Distinction of Comparability Exercises by US FDA

*“Demonstrating that a proposed product is biosimilar to a reference product typically **will be more complex** than assessing the comparability of a product before and after manufacturing changes made by the same manufacturer.”*

*“This is because a manufacturer who modifies its own manufacturing process has **extensive knowledge** and information about the product and the existing process, including established controls and acceptance parameters.”*

Distinction of Comparability Exercises by EU EMA

This guideline does not address the comparability exercise for changes introduced in the manufacturing process of a given product (i.e., changes during development and post-authorization), as addressed by ICH Q5E

“The comparability exercise for a similar biological medicinal product versus the reference medicinal product is an additional element to the normal requirements of the quality dossier and should be dealt with separately when presenting the data.”

Why Manufacturing Comparability is Not Biosimilarity

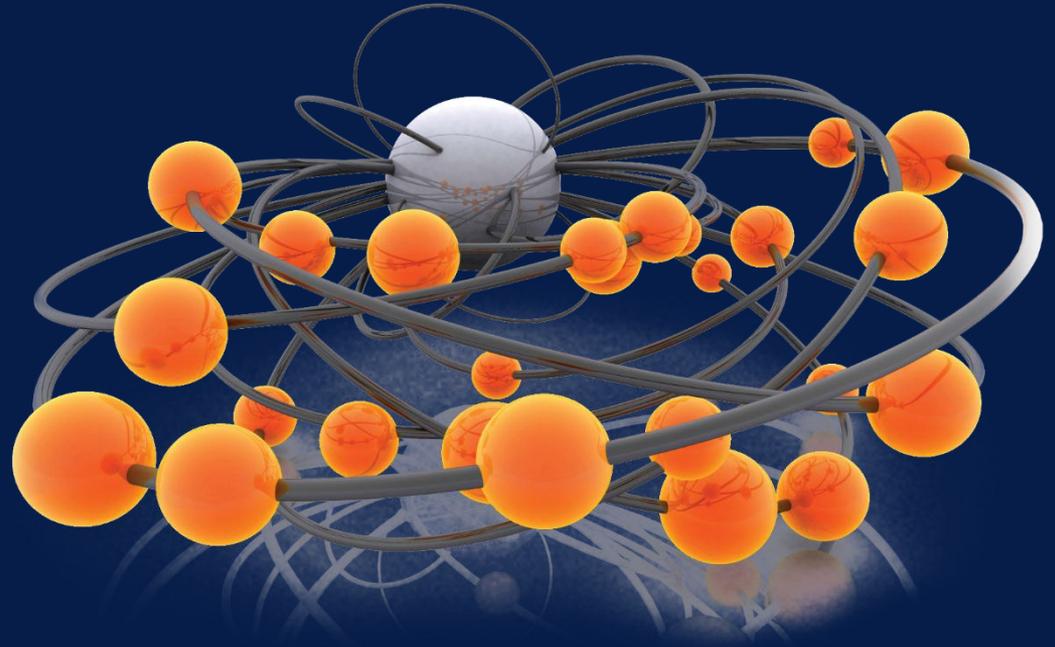
The manufacturer of a proposed product will likely have a different manufacturing process e.g., different:

- Cell line
- Raw materials
- Equipment
- Processes
- Process controls
- Acceptance criteria

From that of the reference product and no direct knowledge of the manufacturing process for the reference product

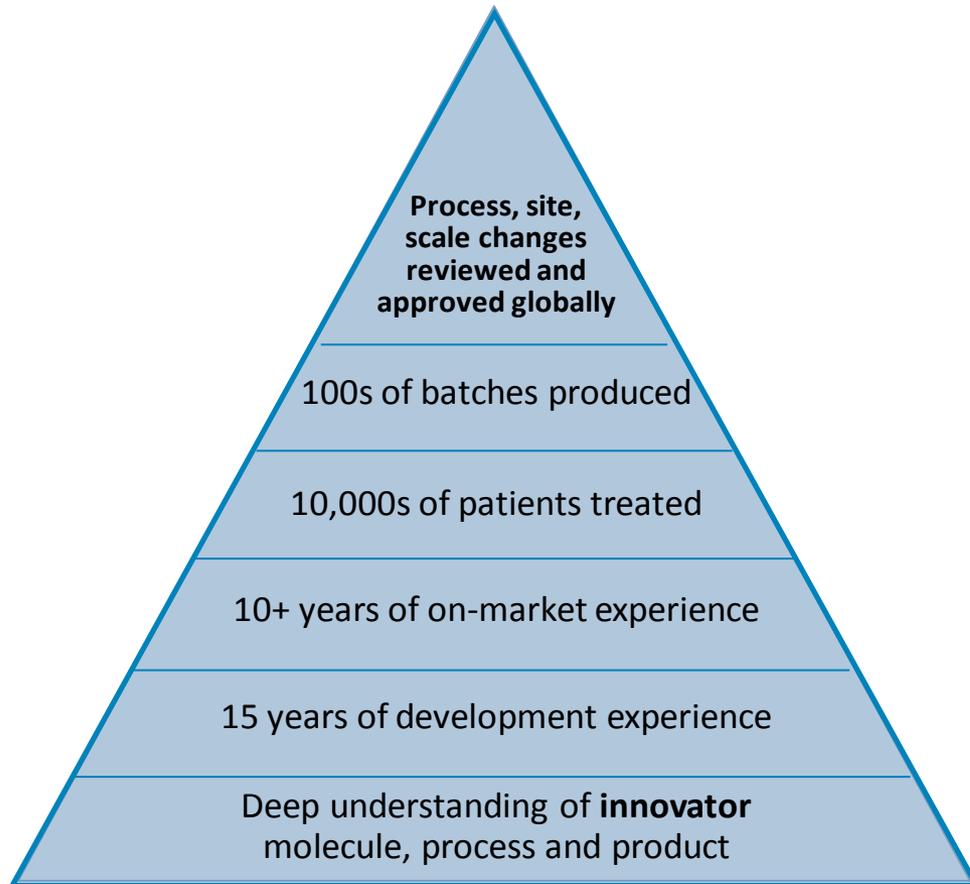
*“Therefore, even though some of the scientific principles described in ICH Q5E may also apply in the demonstration of biosimilarity, in general, **more data and information will be needed to establish biosimilarity** than would be needed to establish that a manufacturer’s post-manufacturing change product is comparable to the pre-manufacturing change product.”*

Knowledge
Produces
Consistency and
Confidence

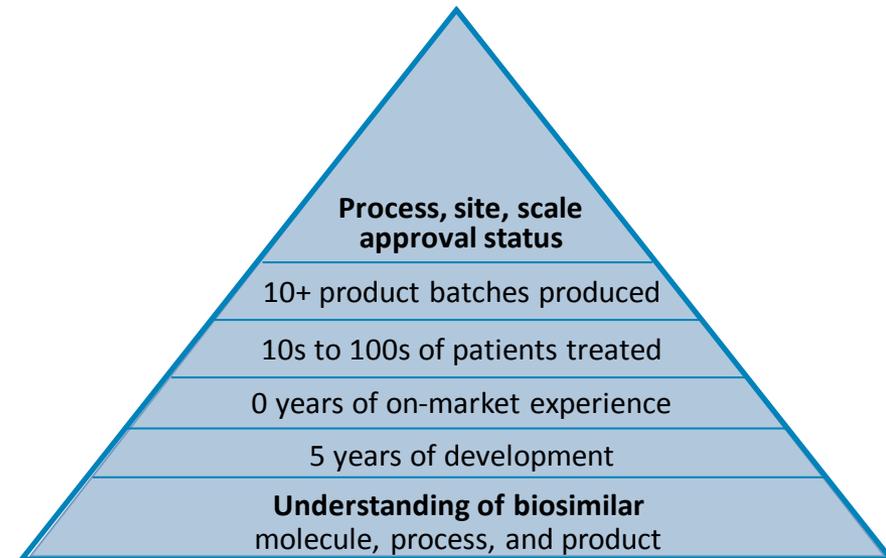


Experience Brings Confidence

Innovator Biologic Justification for Changes



Biosimilar Biologic Basis for Approval



The numbers and years shown for innovators and biosimilars are estimates, based upon time of biosimilar approval, and may differ in some cases.

HUMIRA as an Example:

Innovators Have Singular Knowledge of Their Controls, Compound, Process, and Product

Incremental Capacity added to Assure Supply while maintaining high quality

- 16 years of approved scale, equipment, yield, raw material changes
- Tight trends controlled through process knowledge, controls and specifications
- >500 batches of interchangeable product
- Patient confidence continuously assured
- Over 23,000 Patients Enrolled in HUMIRA Randomized Clinical Trials

1996 1998 2000 2002 2004 2006 2008 2010 2012

Developed and launched at one site with multiple scales

Scale-up

Scale-up

Scale-up



What About Drift?



Drift ≠ Manufacturing Change

Drift is **unintended** change over time in some characteristic(s) of bioengineered products if not controlled within regulatory limits

- All biologics, whether innovator products or biosimilars, can drift if not adequately controlled
- Regulators require and manufacturers need to apply appropriate quality controls and specifications to control against the potential for drift
- Products not meeting these requirements will not be released for use by patients.

Manufacturing Change and Drift are Very Different Concepts

Conclusions

1. Demonstrating biosimilarity to a reference product differs from assessing the manufacturing comparability of a product before and after manufacturing changes made by the same manufacturer¹⁻³
2. EMA/FDA recognize differences between manufacturing comparability vs establishing biosimilarity because:
 - Similar does not equal same
 - Small alterations can make a BIG difference
 - Innovator's exclusive knowledge produces consistency and confidence following a manufacturing change
 - Drift is not the same as a manufacturing change

1. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. US FDA Feb. 2012.

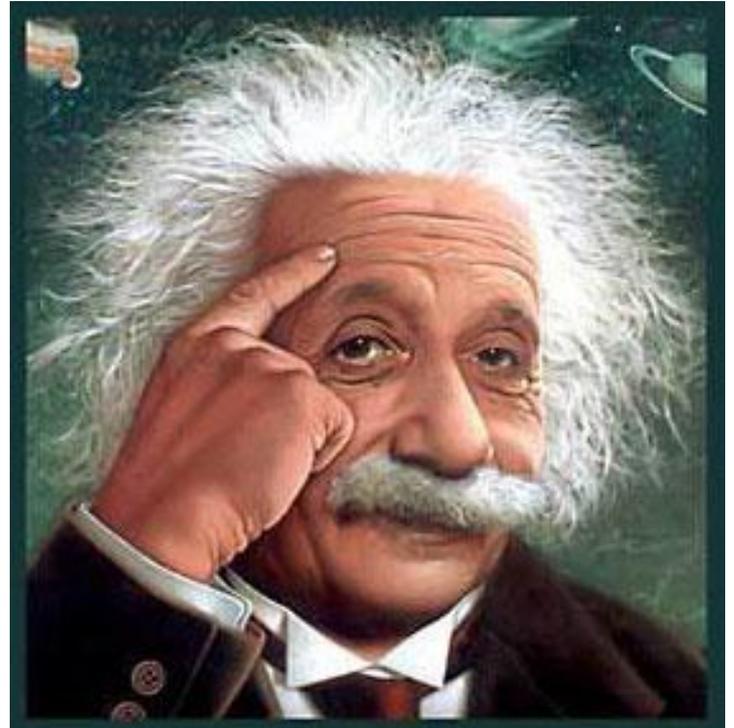
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

2. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality Issues. EMEA/CHMP/BWP/49348/2005.

3. ICH Q5E Comparability of biotechnological/biological products subject to changes in their manufacturing process.

“The only source
of knowledge
is experience.”

- Albert Einstein



abbvie