Important Considerations for the Introduction of Biosimilars in the U.S.

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Outline

Differences between biosimilars and generics

The complex nature of biologics

The role of interchangeability, substitution and pharmacovigilance in the introduction of biosimilarsf

Monoclonal Antibody Programs at Roche – Decades of Development

Monoclonal antibodies have been developed at Roche for a variety of indications including oncologic and non-oncologic indications

Examples of approved antibodies include:

- Bevacizumab for CRC, NSCLC, BC, RCC, GBM, OC
- Trastuzumab for Her2+ BC (metastatic and adjuvant) and GC
- T-DM1 for Her2+ metastatic breast CA (previously treated with trastuzumab)
- Pertuzumab for BC (Her2+ metastatic and neoadjuvant in combination with Herceptin)
- Rituximab for NHL, CLL, and RA
- Obinutuzumab for CLL
- Tolcilizumab for RA
- Omalizumab for allergy

Newer monoclonal antibody platforms being developed (ex., humanization, ADC, glycoengineering, single chain, bispecific antibodies)

Terminology: Intended Copies, Biosimilars, Biobetter

Intended Copies of biological products (ICBPs**)**

- Copies of already licensed biological products that have not met the regulatory criteria for biosimilars

Biosimilar (EMA / WHO definition**)**

- Generally applies to products that have been shown to be similar to the reference product in appropriate comparative, head to head quality, non-clinical and clinical studies.
- Sometimes also known as: Follow-on biologics or subsequent entry biologics

Biobetter

- Intended to be better or superior to the innovator product with marked differences in clinical efficacy, safety and/or convenience.
- Biobetters are NMEs and should go through the full development and approval process

Biosimilars | Biologics Manufacturing

The proprietary process is the product

Generics

Follow-on products of traditional chemical pharmaceuticals are exact chemical copies

Relatively easy to reproduce exactly

Biosimilars

Similarity has been shown in terms of quality, safety and efficacy to the originator

There are no ‘bio-generics’, there are only similar products

Manufacturing based on unique cell lines

Processes are very complex and difficult to reproduce

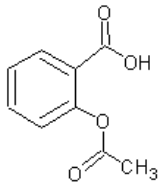
Changes may lead to different clinical **efficacy** and **safety**

Complexity of Biologics

Protein Complexity: Structure

Biopharmaceuticals are structurally diverse

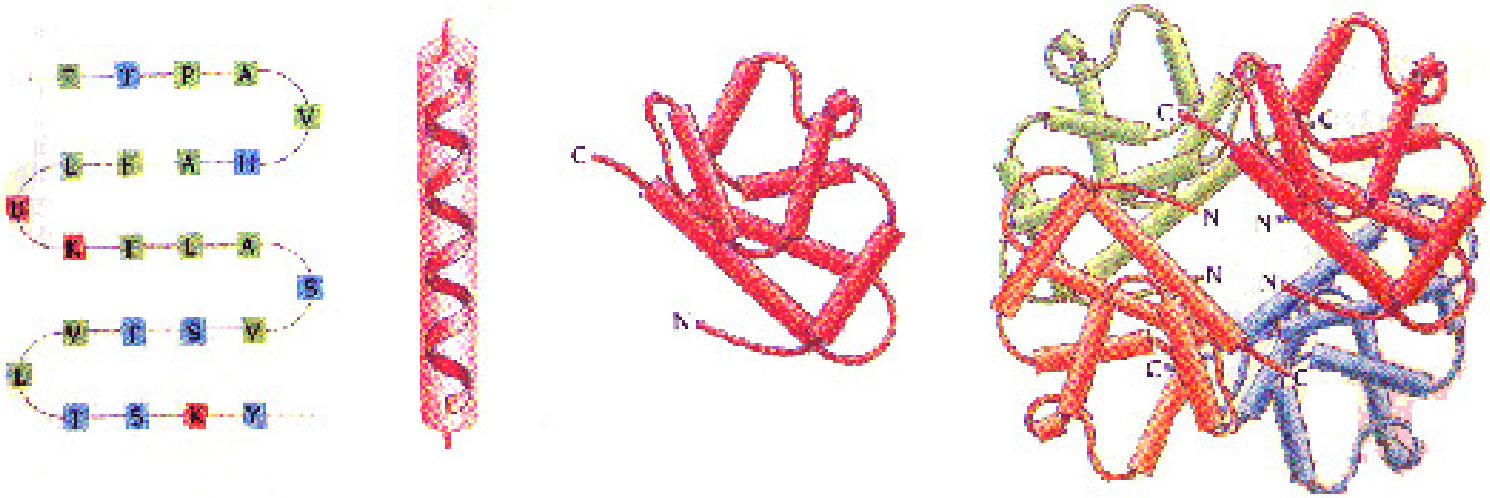
Chemical pharmaceutical:
Simple structure of elements



Aspirin = $C_9H_8O_4$

Biopharmaceutical:

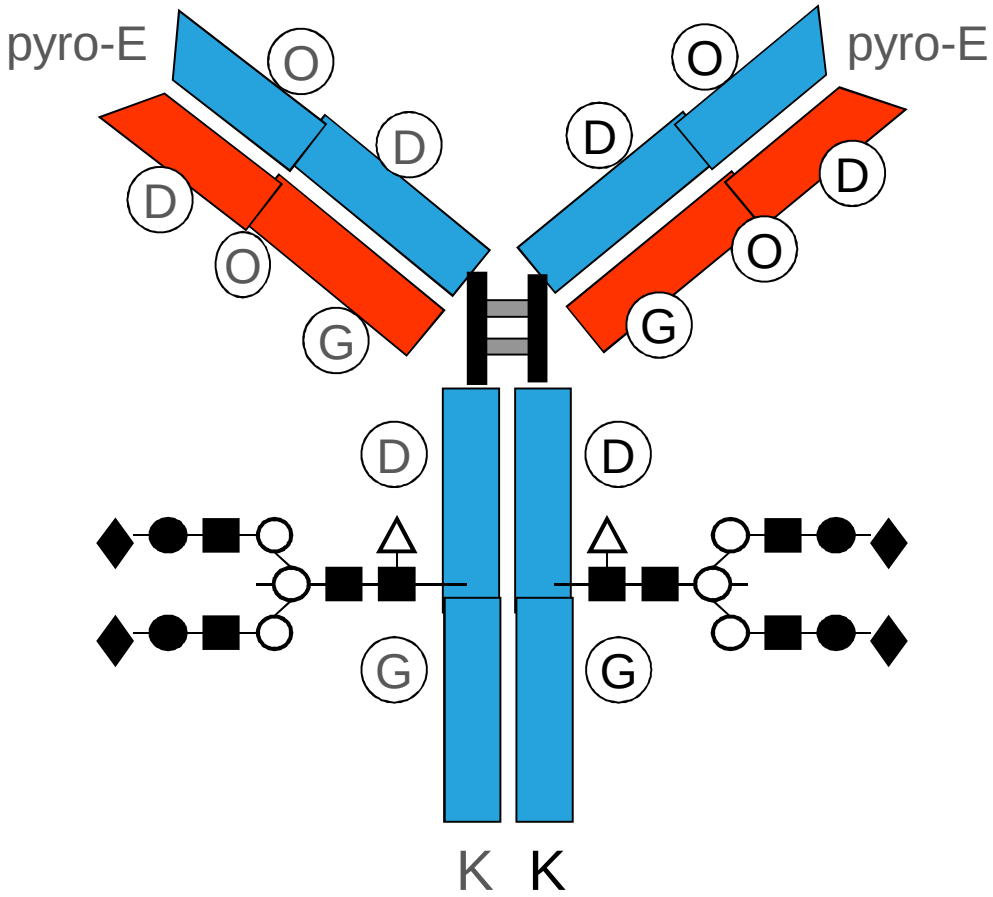
Multiple levels of structural complexity



Primary	**Secondary**	**Tertiary**	**Quaternary**
Amino acid sequence	***Alpha, beta sheets***	***Folding***	***Polypeptide arrangement***

Biological Product Complexity

Examples of modifications: inherent or due to the manufacturing process



- Pyroglutamyl peptides
- Deamidation
- Methionine oxidation
- Glycation
- High mannose, G0, G1, G1, G2
- Sialylation
  - C-terminal Lysine

Adapted from: ***Steven Kozlowski; FDA***

Modifications may result in approximately 10^8 potential variants

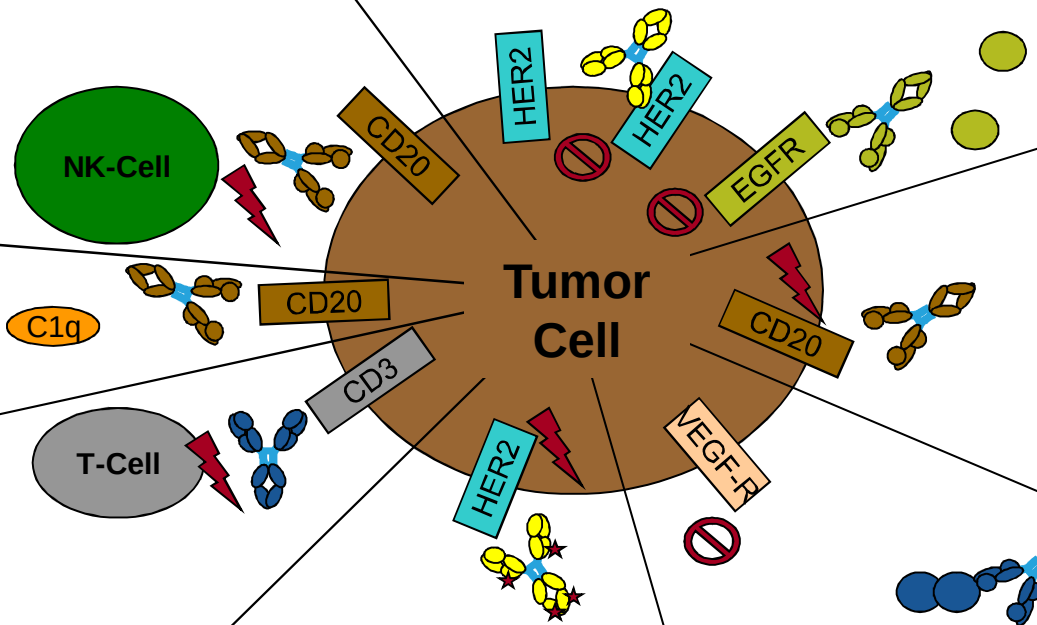
The Mode of Action of mAbs is Complex and May Involve Contributions from Multiple Mechanisms

Inhibition of Signal Transduction or Receptor Activation
- Inhibition of Ligand Binding (Example: Cetuximab)
- Induction of Receptor Internalization (Example: IGF-1R-Abs)
- Inhibition of Receptor Dimerization (Example: Pertuzumab)
- Inhibition of Receptor Shedding (Example: Trastuzumab)

Activation of Effector Mechanisms

Antibody-dependent cellular Cytotoxicity (ADCC)

(Examples: Rituximab, Trastuzumab)



Complement Activation (CDC)

(Example: Rituximab)

Induction of Apoptosis

(Example: Rituximab)

Activation of T-Cells

(Example: Catumaxomab)

Targeting of Toxins

(Example: T-DM1)

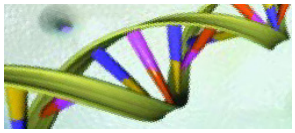
Blocking Ligand Binding

(Example: Bevacizumab)

The *in-vivo* mode(s) of action are often incompletely understood and may differ between indications

Modified from: Hasmann, M. et al. (2009) ChiuZ, in press

The Manufacturing Process for Biologics is Also Highly Complex



Establishment of genetically engineered cells that produce the desired product

Scale-up and production of large quantities

Downstream processing and purification

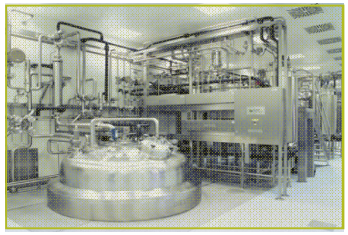
Human gene

DNA vector

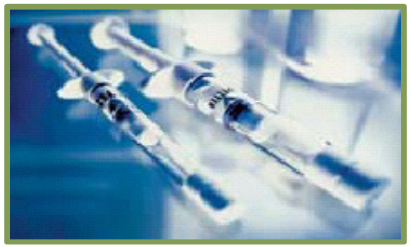
Cloning into DNA vector

Transfer into host cell

Bacterial or mammalian cell produces protein



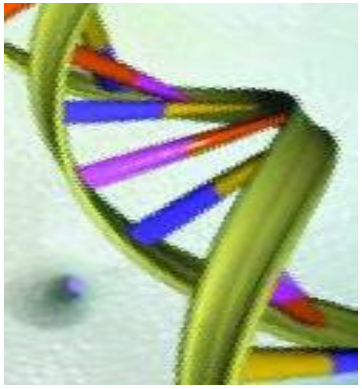
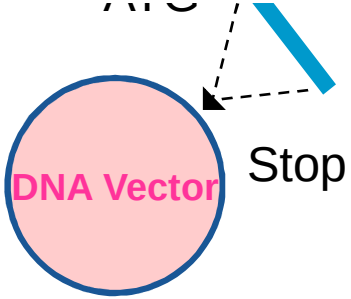
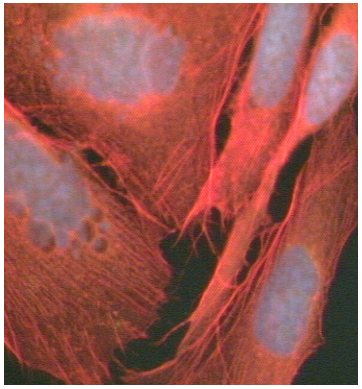
Fermentation



Formulation

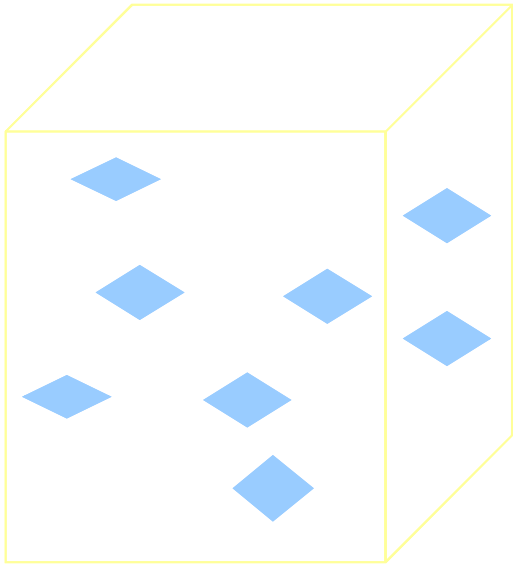
Each stage of the complex manufacturing process confers unique properties on the resulting biologic product

The Manufacturing of Biosimilars will be Inherently Different from the Original Biologic

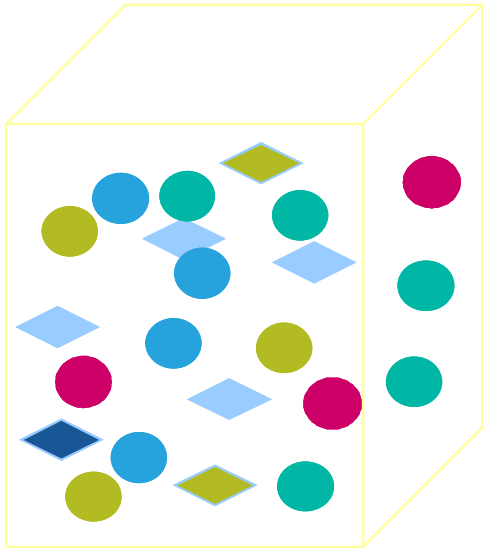
Human Gene Sequence	DNA Vector	Host Cell Expression	Ferment ation	Purificat ion
				
Maybe the same gene sequence	Probably a different DNA vector	A different recombinant production cell	A different fermentation process	A different downstreaming protocol

Immunogenicity of Biologics

Protein Microheterogeneity



Small Molecule Drug



Protein Drug

Key Concern: Immunogenicity

Neutralizing antibodies → impact on therapeutic effect

- coagulation factor concentrates (eg, Factor VIII and Factor IX),
- enzyme replacement therapies (eg, acid-α-glucosidase and glucocerebrosidase),
- hormones (eg, GH)
- cytokines (eg, GM-CSF and IFNβ)

Hypersensitivity reactions

Cross-reactivity with an endogenous protein that has a vital, non-redundant biological function

- PEGylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF),
- PRCA with epoetin alfa

Wadhwa, Idrugs, 2009

Factors Influencing Unwanted Immunogenicity

Product characteristics, molecular structure, variation in amino acid sequence (relative to native protein), novel epitopes, aggregates, degradation products, oxidation and deamidation

Process related, such as host cell proteins, other contaminants and process change

Formulation

Biological properties such as immunostimulatory or immunosuppressive, use as replacement therapy or only therapy

Dosing: single or multiple injections, high or low dose, short or long period

Route of administration

Genetic factors (HLA class II and gene deficiences)

Immune status: competent or immunocompromised

Patient age

Any concomitant medication

Disease state: acute or chronic, inflammatory or oncology

Target: endogenous counterpart, redundant or unique

Interchangeability, Substitution and Pharmacovigilance

A Regulatory Pathway for Biosimilars

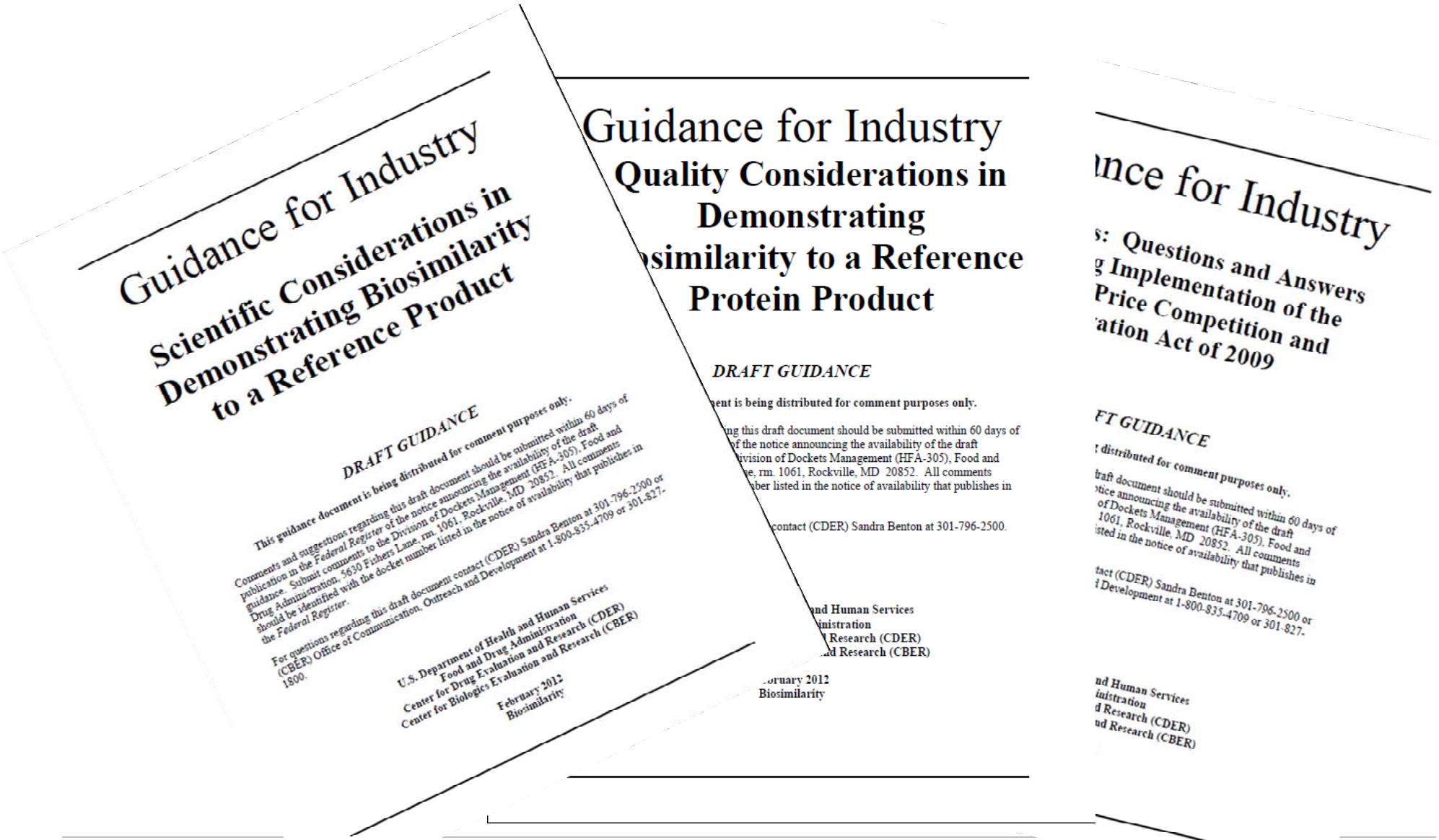
The Affordable Care Act passed in 2010 established a regulatory pathway for biosimilars in the U.S. via the 351(k) pathway

FDA implements the law through a series of regulations

- FDA has issued draft guidances
- Final guidance around biosimilarity and interchangeability is pending

States will set rules around substitution of interchangeable biosimilars by amending their Pharmacy Practice Acts, which currently cover generic substitution only

FDA:
Biosimilar Draft Guidelines



What is the Main Difference Between Innovator and Biosimilar Development Programs?

The goals of the programs differ

Biosimilar		Innovator
Sensitive and homogeneous (patients are *models*)	Patient population	Any
Comparative versus innovator, normally equivalence	Clinical design	Superiority vs standard of care (SoC*)
Sensitive Clinically validated PD markers	Study endpoints	Clinical outcomes data or accepted/ established surrogates (e.g. OS and PFS)
Similar safety profile to innovator; no new findings	Safety	Acceptable benefit/risk profile versus SoC*
Similar immunogenicity profile to innovator	Immunogenicity	Acceptable risk/benefit profile versus SoC*
Possible if justified	Extrapolation	Not allowed

* In some cases SoC may not exist

FDA View on Interchangeability from Draft Guidance on Biosimilars (Feb 2012)

An interchangeable product must be shown to be biosimilar to the reference product and meet the other standards described in section 351(k)(4) of the PHS Act.

At this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment.

FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product

Substitution of Interchangeable Biosimilars in the Pharmacy Setting

Changes to state pharmacy laws are needed to conform with the Affordable Care Act as biosimilars are expected to enter the U.S. market as early as next year.

Substitution will allow greater patient access to biosimilar medicines dispensed in the pharmacy setting

Due to the complexity and sensitivity of biologic drugs, it is important that patients' records show which biologic/biosimilar was dispensed.

BIO Principles for Substitution of Interchangeable Biosimilars for Innovator Biologic Products

Substitution should occur only when the FDA has designated a biologic product as interchangeable

The prescribing physician should be able to prevent substitution, i.e. DAW

The patient should, at a minimum, be notified of the substitution

The prescribing physician should be notified of the substitution

A record of the substitution must be kept by the pharmacy and the physician for a set period of time

US and European Status on Substitution of Interchangeable Biosimilars

More than a dozen U.S. states have introduced legislation allowing pharmacist substitution of interchangeable biosimilars while including important patient safety parameters

- Bills signed into law: Oregon, North Dakota, Florida, Virginia, Utah
- Bills still being debated: Delaware, Illinois, Massachusetts, Pennsylvania

Fifteen countries across Europe have brought in new rules to require physician authorization before substitution of biological medicines by biosimilars (***Source: APM Health Europe, 21 February 2008***).

The Role of Pharmacovigilance (PV) for Biosimilars

Safety in the post-authorization setting must be investigated =>may exceed routine PV (eg. participation in registries)

Biosimilar antibody products should have unique identity or name and prescriptions be made by brand name, allowing traceability to the patient level

Labeling for biosimilar antibodies must clearly identify the sources of the specific clinical safety and efficacy data obtained during its development (e.g. extrapolation, originator's data, data of the biosimilar)

Summary

Biosimilars are not generics

Biologics are complex and require highly specialized manufacturing

Biosimilars are likely to enter the U.S. market in 2014

Regulations are important to ensure safety of patients

Interchangeable biosimilars will meet a higher standard for approval by the FDA

Substitution of interchangeable biosimilars must be done in a responsible, transparent manner