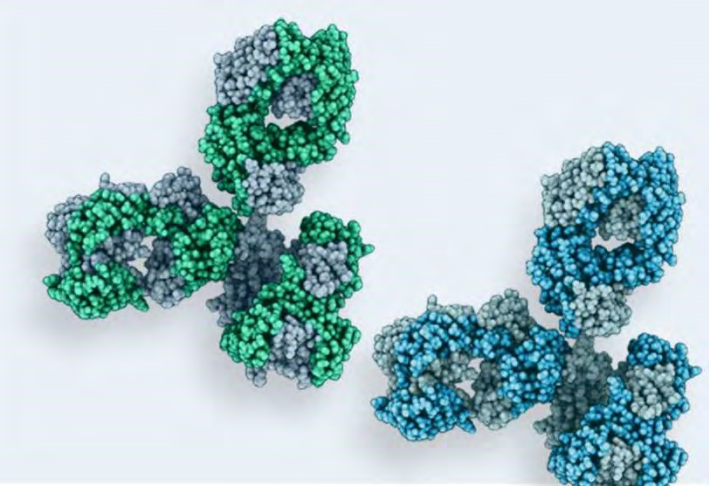
International Society of Nurses in Cancer Care

BIOsim

A train the trainer programme for nurses

Module 1



(Supported by an unrestricted grant from Pfizer)

Background to biosimilar development

- Objectives of the session

- At the end of this session the nurse will be able to
  - Understand the background to the development of biosimilars
  - Have an appreciation of process of biologic growth
  - Understand the terms extrapolation and immunogenicity as applied to biosimilars
  - Understand the benefit to patients and health systems

Q. What do we mean by biologics?

A biologic is

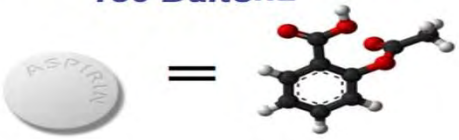
- A substance that is made from a living organism or its products and is used in the prevention, diagnosis, or treatment of cancer and other diseases. Biological drugs include antibodies, interleukins, and vaccines. Also called biologic agent and biological agent.

- https://www.cancer.gov/publications/dictionaries/cancer-terms/def/biological-drugaccessed September 2018

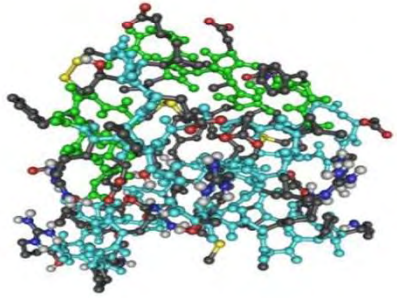
What are biologics?

- In contrast to most drugs that are chemically synthesised and whose structure is known, most biologics are complex mixtures that are not easily identified or characterised[1]

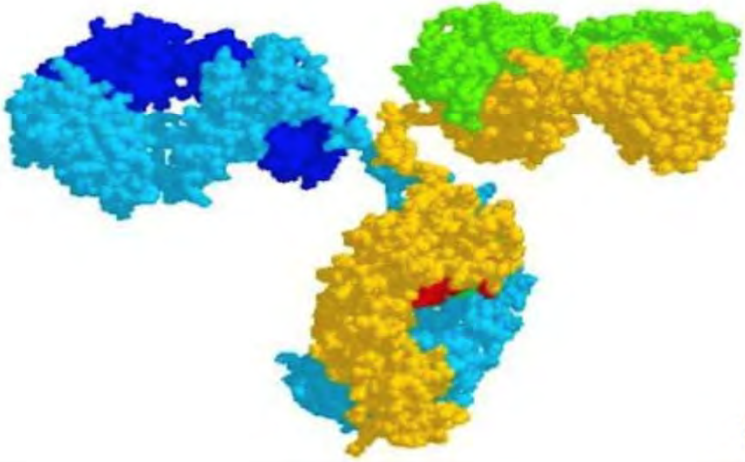
Aspirin
(Acetylsalicylic acid)
180 Daltons



Insulin
5,700 Daltons



mAb
150,000 Daltons



Not to scale

FDA. What are “Biologics” Questions and Answers. [Accessed September 2014]. http://www.fda.gov/AboutFDA/default.htm

Biologic manufacture

- Biologics are produced from living organisms

Adapted from EGA Handbook on biosimilar medicines; available from http://www.egagenerics.com/index.php/publications

http://cancervanguard.nhs.uk/wp-content/uploads/2017/03/UK_MKT_SDZ_17_0027d-Vanguard-Introduction-Training-Slide-Set-for-website-FINALii-1.pdfaccessed September 2018

https://www.pfizerbiosimilars.com/manufacturing-biosimilars

Definitions

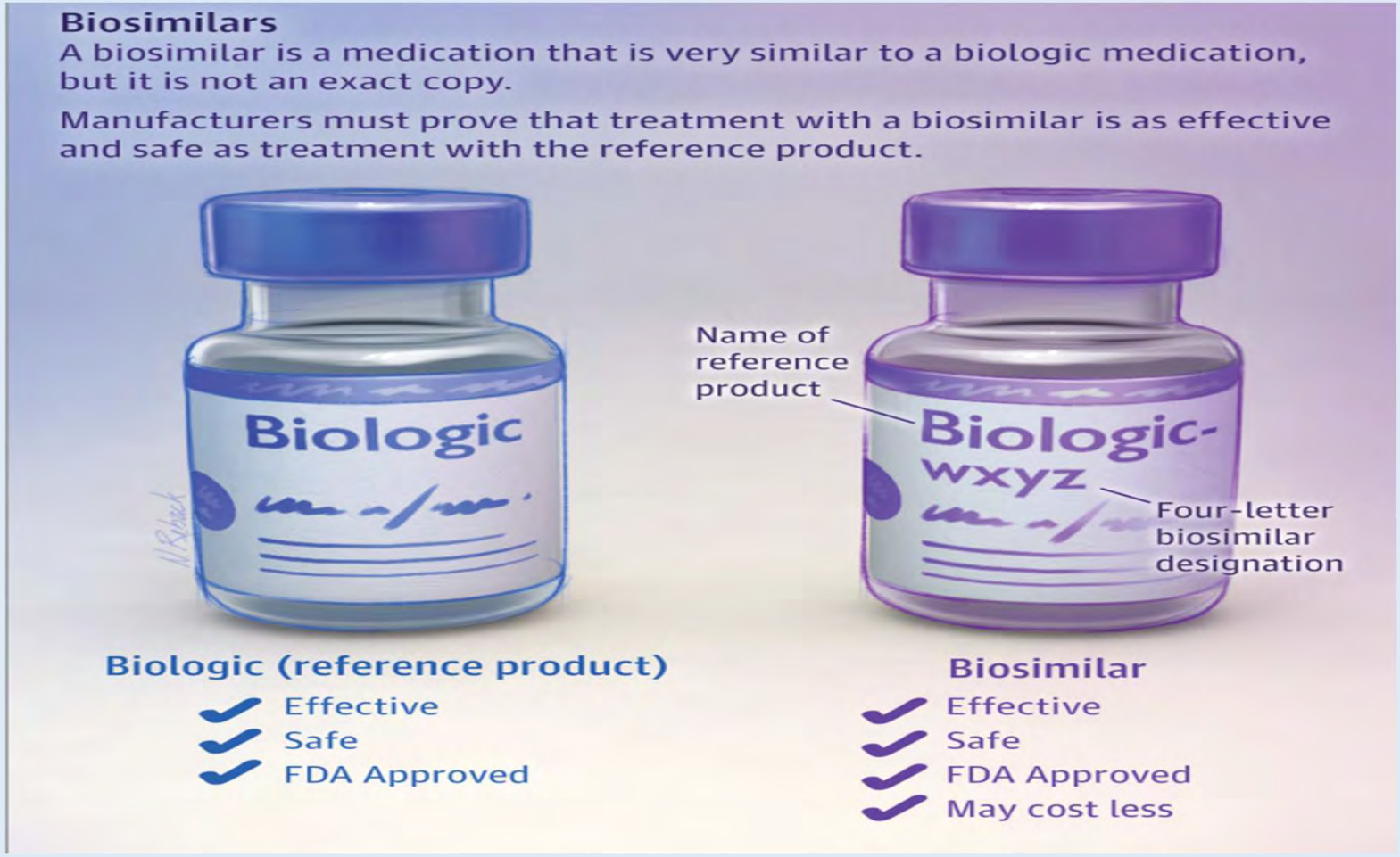
Reference product

- A reference product is a biological product approved by the FDA under the Public Health Service Act based on a full complement of product-specific data, including nonclinical and clinical data.

Biosimilar product

- A biosimilar product is a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and has no clinically meaningful differences in terms of safety, purity and potency (safety and effectiveness) from the reference product.

What is a biosimilar ?



JAMA Oncol. 2018;4(7):1023. doi:10.1001/jamaoncol.2018.0999

What is the difference between a generic drug and a biosimilar drug?

How Are Biosimilars Different From Generics?

Generic medicines are an exact copy of a brand-name medication. Manufacturers are able to make identical versions of a medication when the ingredients are simple chemicals. However, the ingredients in some medicines, such as vaccines, growth factors, or monoclonal antibodies used in cancer, are made from living cells and are too complicated to make into a generic version. These complex medications are referred to as biologics. Biosimilars are medicines that are very similar to these biologics but are not exact copies. The biologic medication that the biosimilar is based on is called the *reference product*.

Why ‘biosimilar’ not ‘bioidentical’?

- **Microheterogeneity**
  - An effect of the inherent variability of the biological system used for manufacture
  - Resulting product is a mixture of different forms of the same protein

- **Post-translational modifications**

  Glycosylation, methylation, oxidation, deamination
  - May occur after a change in cell line or manufacturing process
  - Resulting product is highly similar, but not identical to the originator
  - Make complex molecules, such as mAbs and –cept fusion proteins, particularly difficult to replicate

But...originator products are also subject to variability

(Weise M, et al. Nat Biotechnol 2011;29:690-3, European Commission. What you need to know about biosimilar medicinal products. A consensus information document. [Accessed September 2014]. http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf
Dörner T, et al. Ann Rheum Dis 2013;72:322-8. 4. Schneider CK. Ann Rheum Dis 2013;72:315-8.)

Same ingredients, same recipe

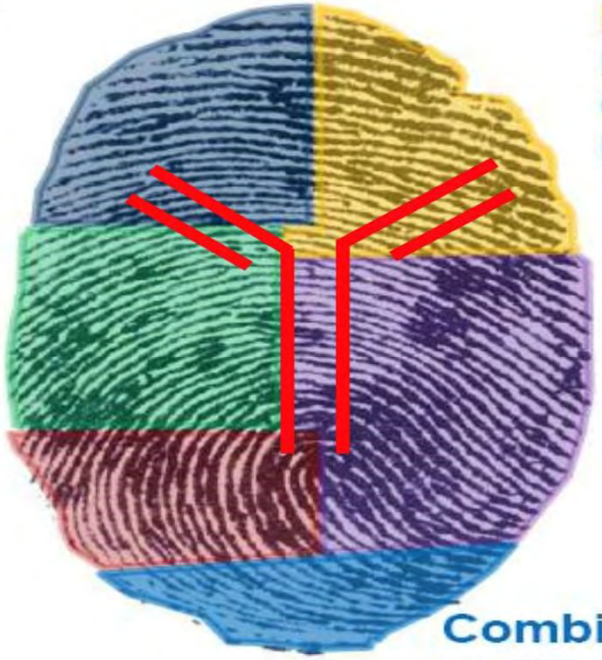
Both cake , both edible

Fingerprinting mAbs: Analytical/biologic methods to assess structure/function relationships

Primary structure e.g.:
LC-MS intact mass
LC-MS subunits
Peptide mapping

Impurities e.g.:
CEX, cIEF acidic and basic variants
LC glycation
Peptide mapping deamidation, oxidation, mutation, glycation
SEC/FFF/AUC aggregation

Biological activity e.g.:
Binding assay
ADCC assay
CDC assay



Higher order structure e.g.:
NMR
CD spectroscopy
FT-IR

PTMs e.g.:
NP-HPLC-(MS) N-glycans
AEX N-glycans
MALDI-TOF N-glycans
HPAEC-PAD N-glycans
MALDI-TOF O-glycans
HPAEC-PAD sialic acids
RP-HPLC sialic acids

Combination of attributes e.g.:
MVDA, mathematical algorithms

A comprehensive set and combination of orthogonal analytical methods revealing structure-function relationships, delivering in depth comparability information and allowing extrapolation towards non-measured attributes

FDA Guidance downloads: Biosiimilars – An Update. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM315764.pdf

CRITICAL QUALITY ATTRIBUTES

Batch variability of critical quality attributes must be assessed and controlled to ensure consistent product quality

Acceptable variation	• Some degree of variation is acceptable as long as intended use is unaffected
Variability controls	• Tightly controlled by understanding controlling and validating the manufacturing process assessed with each batch release
Specification defined	• Defined as a list of test references to analyse process and appropriate frame of reference ie range or limit
Specification criteria	• A list of criteria to which the drug should conform to at any stage of the manufacture process
Batch release specification	• Quality standards proposed and justified by FDA to ensure safe and effective over shelf life

Changes to the process

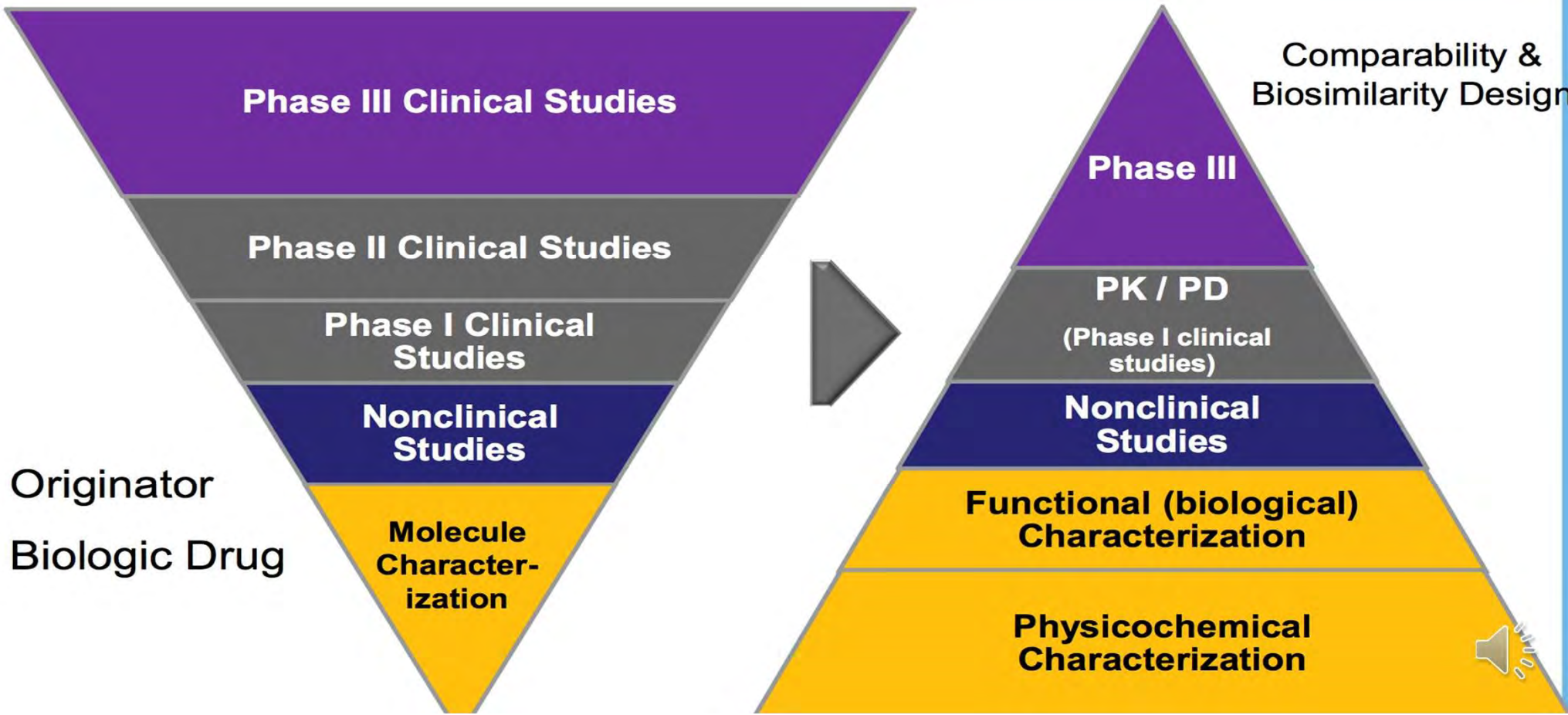
- Most biological product manufacturers need to make changes to their manufacturing systems at some point – such as changing the supplier of raw materials, or replacing a piece of equipment.
- Measures such as batch release specifications and comparability analyses before and after manufacturing changes are necessary checks to ensure that the variability of the biological product is within acceptable limits.
- Therefore, even though there is inherent batch-to-batch and lot-to-lot variability in biological products, the differences can be assessed and managed effectively.

Regulatory processes for biosimilars are different but no less rigorous

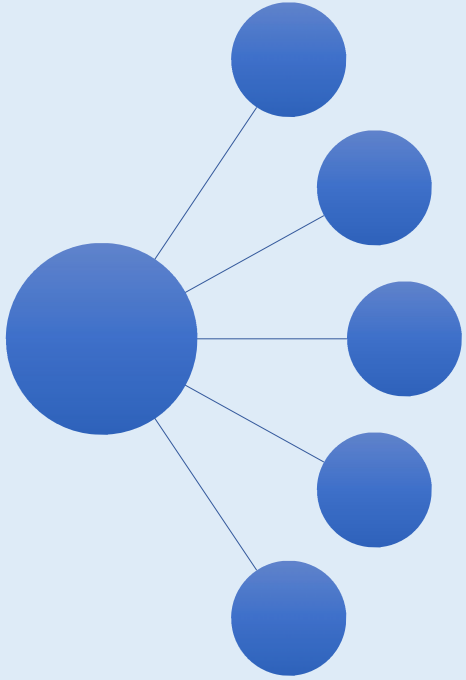
But what about evidence?

- Do we need large clinical trials to demonstrate same efficacy?

Scientific evidence to characterise the biologic biosimilar antibody



So…. If biosimilar drug has been tested for safety in a small appropriate population the drug can be extrapolated to other (bigger) populations



Extrapolation

- Extrapolation is a scientific and regulatory principle that refers to the approval of a biosimilar for use in an indication held by the reference product but not directly studied in a comparative clinical trial with a biosimilar.
- Extrapolation of efficacy and safety data from one indication to another may be considered if biosimilarity to the reference product has been shown by a comprehensive comparability programme, including safety, efficacy, and immunogenicity in a key indication that is suitable to detect potentially clinically relevant differences, and there is sufficient scientific justification for extrapolation.
- Extrapolation of data is an established scientific and regulatory principle that has been exercised for many years.

- If the biosimilar has been tested in one population AND the manufacturer can demonstrate safety in a smaller population AND a rigourous manufacturing process, evidence can be *applied* to other populations.

- Therefore no need for further phase 3 studies

Indication extrapolation in practice

iIFX indication	CT-P13 indication
Ankylosing spondylitis (AS)	Phase I, randomised, double-blind trial in 250 patients. Pharmacokinetic, safety and efficacy profiles all comparable to iIFX
Rheumatoid arthritis (RA)	Phase III, randomised, double-blind trial in 606 patients. Non-inferior efficacy, comparable immunogenicity and safety to iIFX
Psoriatic arthritis	
Psoriasis	
Crohn's disease	
Ulcerative colitis	

Further indications extrapolated on the basis of successful AS & RA data, detailed proof of **molecular similarity,** and recognition of the **conserved pathophysiology** across all current iIFX indications

Indications gained through traditional clinical trial programme - £££ and many years. Not feasible to repeat for a biosimilar medicine

Biologics: A Regulatory Perspective

Characteristic	351(a) Originator	351(k) Biosimilar	351(k)(4) Interchangeable Biosimilar	351(a) Non-originator Biologic	351(a) Next-generation "Biobetter"
Description	First-to market biologic molecule; will likely be the reference product	"Highly similar" to reference product; approved via biosimilars pathway	A biosimilar that can be substituted for the reference without permission from prescriber	It is "another brand name" of an already approved biologic	Biologic that has been altered to achieve improved clinical outcomes
Depth of data submitted to the FDA	"Standard" data package: efficacy and safety	Abbreviated data package for comparability	More extensive data package for comparability supporting that the interchangeable biosimilar anticipated to produce same clinical effects for all the reference product's licensed conditions	"Standard" data package: efficacy and safety	"Standard" data package: efficacy and safety
Compared to originator?	N/A	Yes	Yes	Yes or no	Likely (standard of care)

Lucio SD, et al. Am J Health Syst Pharm. 2013;70:2004-2017. FDA. Considerations in demonstrating interchangeability with a reference product: guidance for industry. January 2017.

Interchangeability

- Drugs are often interchanged by doctors and pharmacists for different reasons
  - A cheaper brand is available
  - An unpleasant side effect
  - A procurement deal

- This common with generic drugs
- However interchangeability of biologics offers some concerns

Interchangeability

- Interchangeability is the use of a biosimilar without impacting on safety or efficacy if it is alternated or switching between the biosimilar and the innovator compared to the use of the innovator without alternation or switching
- Guidance has been issue by the FDA for the evaluation of interchangeability of a biosimilar and a reference product
  - There are no approved interchangeable biosimilars
- A drug must be designated to be interchangeable to permit drug substitution by a pharmacist without prescriber permission
  - Drug substitution rule and regulations are determined at the state level
  - Designation of a biosimilar as interchangeable does not automatically allow drug substitution

FDA. Considerations in demonstrating interchangeability with a reference product: guidance for industry. January 2017.
Barlas S. P T. 2017;42:509-512.
FDA. Prescribing biosimilar and interchangeable products. October 2017.

Finally what of the immune reaction to biosimilar drugs?

Immunogenicity

Ability of a substance to trigger an immune response or reaction

The immunogenicity of complex proteins such as mAbs is unpredictable; two similar, complex protein products may be immunogenic in different patients

KNOWN…

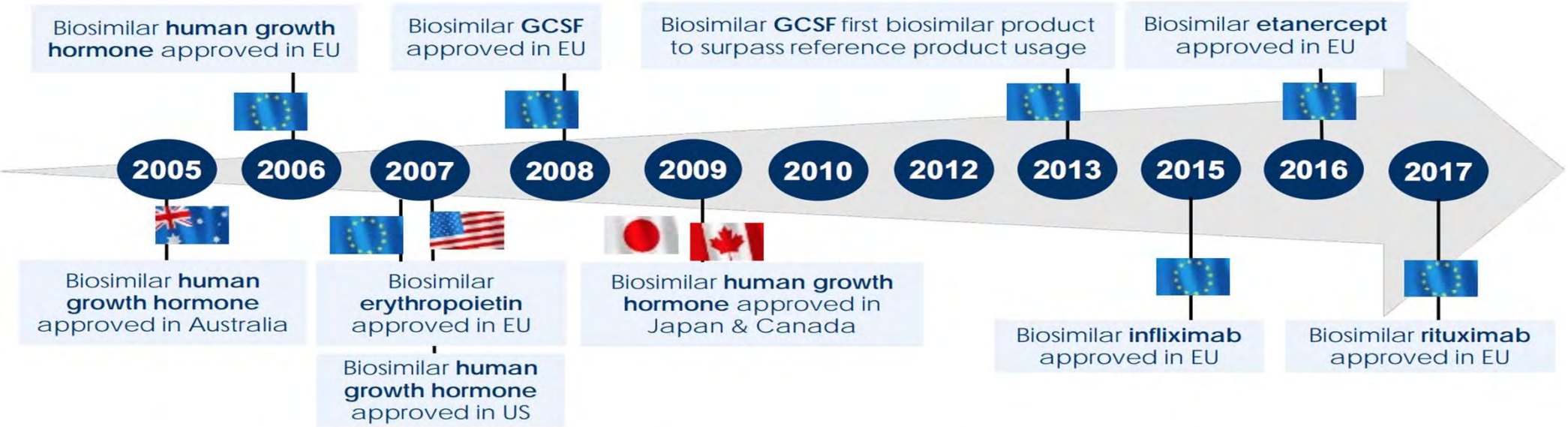
- All monoclonal antibody (mAb) therapies, including biosimilars, are subject to the development of antibodies
- Immunogenicity is influenced by many factors (nature of drug, impurities, excipients, stability, administration route, dosing regimen, patient characteristics, vials, stoppers)
- Patients who develop antibodies are more likely to have infusion reactions

UNKNOWN…

- What is the long-term adverse event profile for biosimilars?
- Will development of antibodies to biosimilars affect efficacy and safety?

NHS

Biosimilars are nothing new



- In 2006 the first biosimilar became available in the UK
- Since this time the safety profile of biosimilars has been consistent with the reference products and the product class[1,2,3]
- Biosimilars are now in routine use in the NHS, particularly in rheumatology and gastroenterology

1. Gascon P et al Support Care Cancer. 2013; 21(10): 2925–2932
2. Romer et al Horm Res 2009; 72(6): 359-369.
3. For full adverse event profiles, please refer to Zarzio and Omnitrope SPCs available at: www.medicines.org.uk/emc

An example from the UK

- Biosimilar rituximab

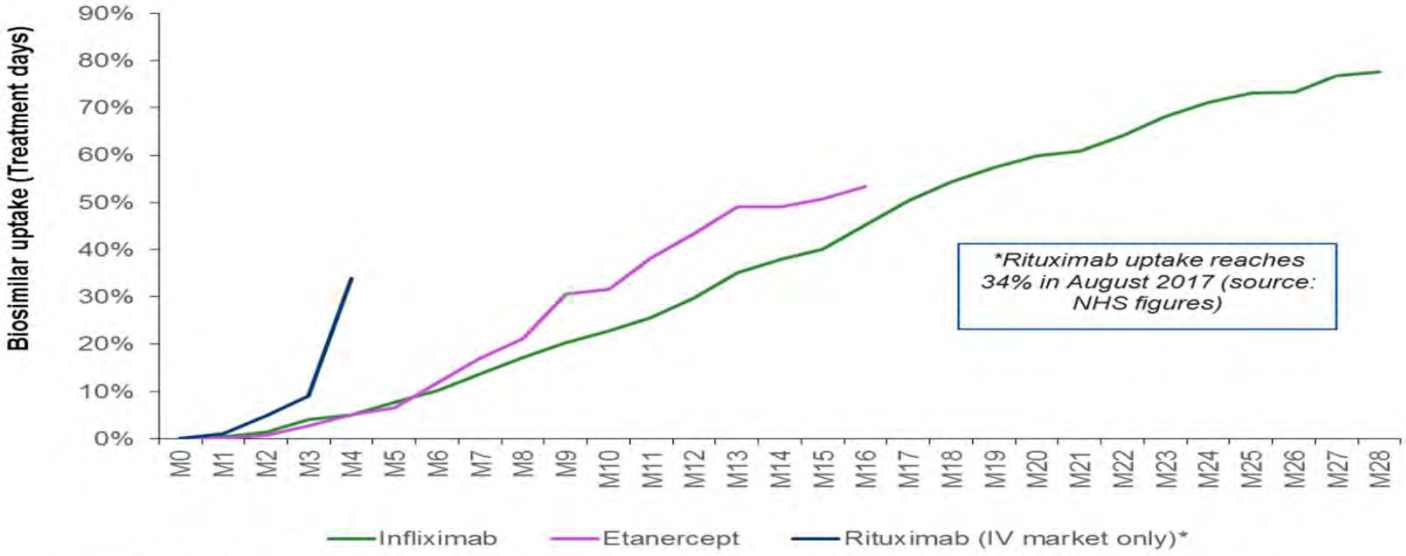
Early Experience from RMH and UCLH

- July 17 - complete switch to Biosimilar Rituximab all patients
- End of September 2017 in RMH and UCLH:
  - 317 patients treated with biosimilar Rituximab
  - 796 infusions
  - Mainly grade 1 and 2 reactions in line with originator
- No practical problems noticed

Cancer Vanguard

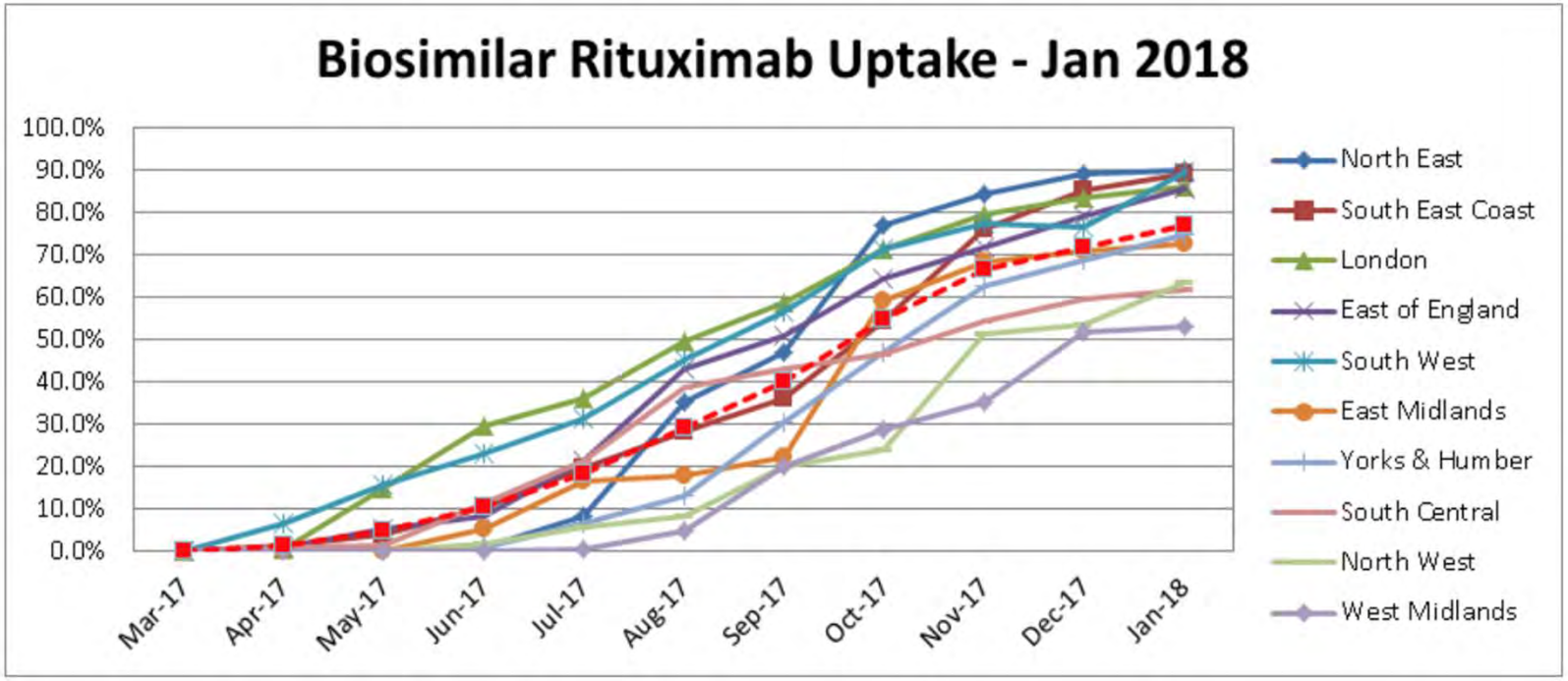
NHS

Impact of this change versus Infliximab and Etanercept



Source: QI MIDAS Restricted MTH Jun 2017; Each product treatment day share calculated with respect to the individual, relevant accessible market

The Cancer Vanguard is a partnership between
Greater Manchester Cancer Vanguard Innovation, RM Partners and UCLH Cancer Collaborative



Full year savings at 80% = £80m

BIOSIMILARS MAY OFFER A NUMBER OF POTENTIAL BENEFITS TO VARIOUS STAKEHOLDERS

Potential of biosimilars for patients, payers, and providers

Increased use of biologics

Additional treatment choices at lower cost to the health care system

Improved access and outcomes

Increase access to biologics, which may lead to improved health outcomes overall

Health care system efficiency

Possible savings and efficiencies to the health care system

Expanded options for patients

Offer a variety of therapeutic options

https://www.pfizerbiosimilars.com/health-care-system-benefitsaccessed july2018s

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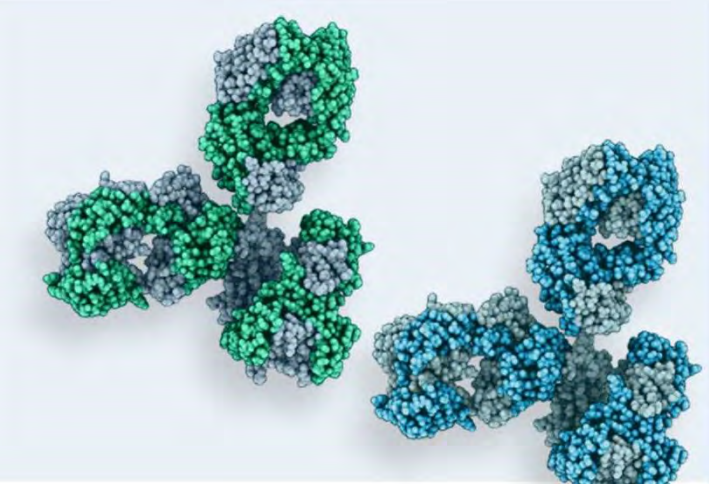
Questions ?