An introduction to Biosimilars

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Cancer Vanguard Overview

- The Cancer Vanguard comprises
  - RM Partners
  - UCLH Cancer Collaboration
  - Greater Manchester Cancer Vanguard Innovation

- These three local delivery systems are transforming the clinical model of cancer care delivery by providing evidence based solutions that can be replicated nationally

Vanguard and Sandoz Joint Working

The Cancer Vanguard is about driving innovation

- One innovation coming to cancer treatment in the NHS is a group of medicines called biosimilars
- Sandoz, a Novartis Division, pioneered the science of biosimilars and its biosimilars have been used in the NHS for over ten years
- The Cancer Vanguard have partnered with Sandoz to develop a process for evaluating biosimilars through education and research

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Agenda

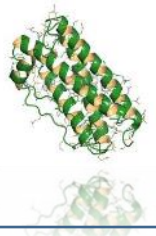
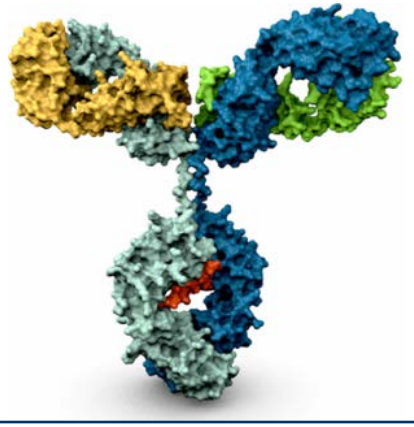
- What are biologics?

- What are biosimilars?

- How are biosimilars developed?

What are biologics?

What are biologics?

Paracetamol	Filgrastim (a growth factor)	Antibody (mAb)
Small molecule	Protein (without sugars)	Glycoprotein (with variable sugars)
		
▪ Chemical synthesis ▪ Single substance ▪ 151 Da ▪ MoA ambiguous	▪ Made using bacteria ▪ Single main substance ▪ One chain, 175 amino acids ▪ 18,803 Da ▪ Receptor binding only	▪ Made using mammalian cells ▪ Mixture of variants ▪ Four chains,1330 amino acids ▪ 144,000 Da ▪ Receptor binding, effector functions

Note: Illustrations not to scale.

Kozlowski S, et al. N Engl J Med 2011;365(5):385–8; Revers L & Furczon E. Canadian Pharmacists Journal 2010;143(3):134–9; Revers L & Furczon E. Canadian Pharmacists Journal 2010;143(4):184–91.

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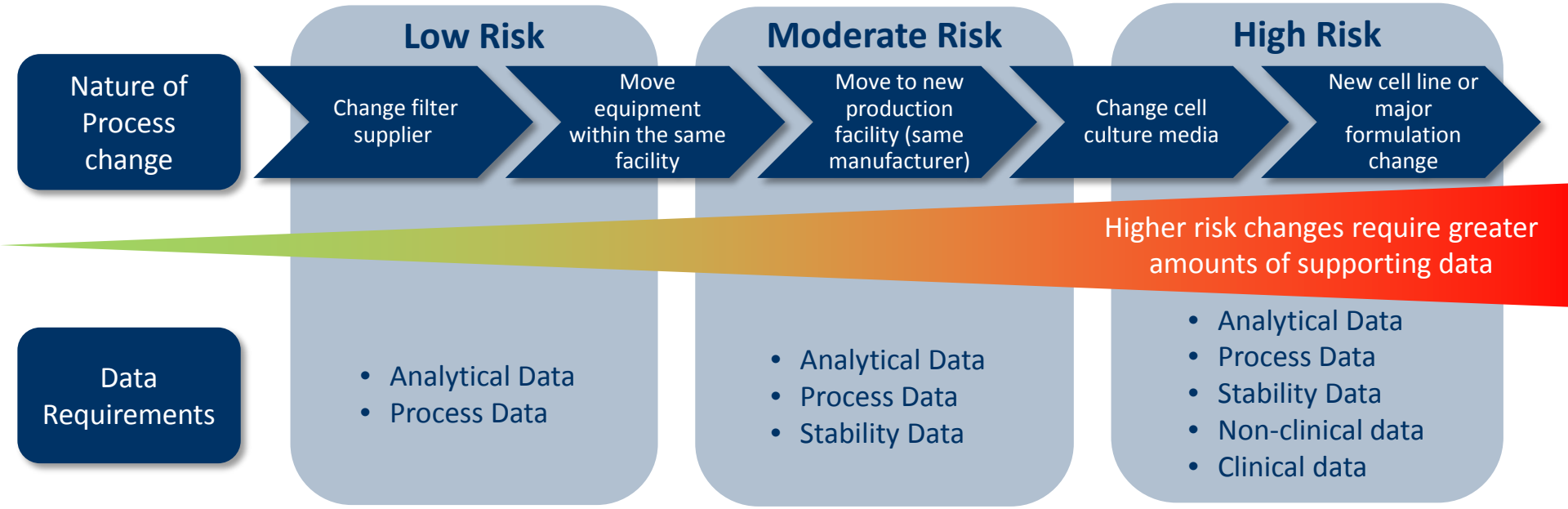
Biologic manufacture

- Biologics are produced from living organisms

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

Impact of manufacturing changes

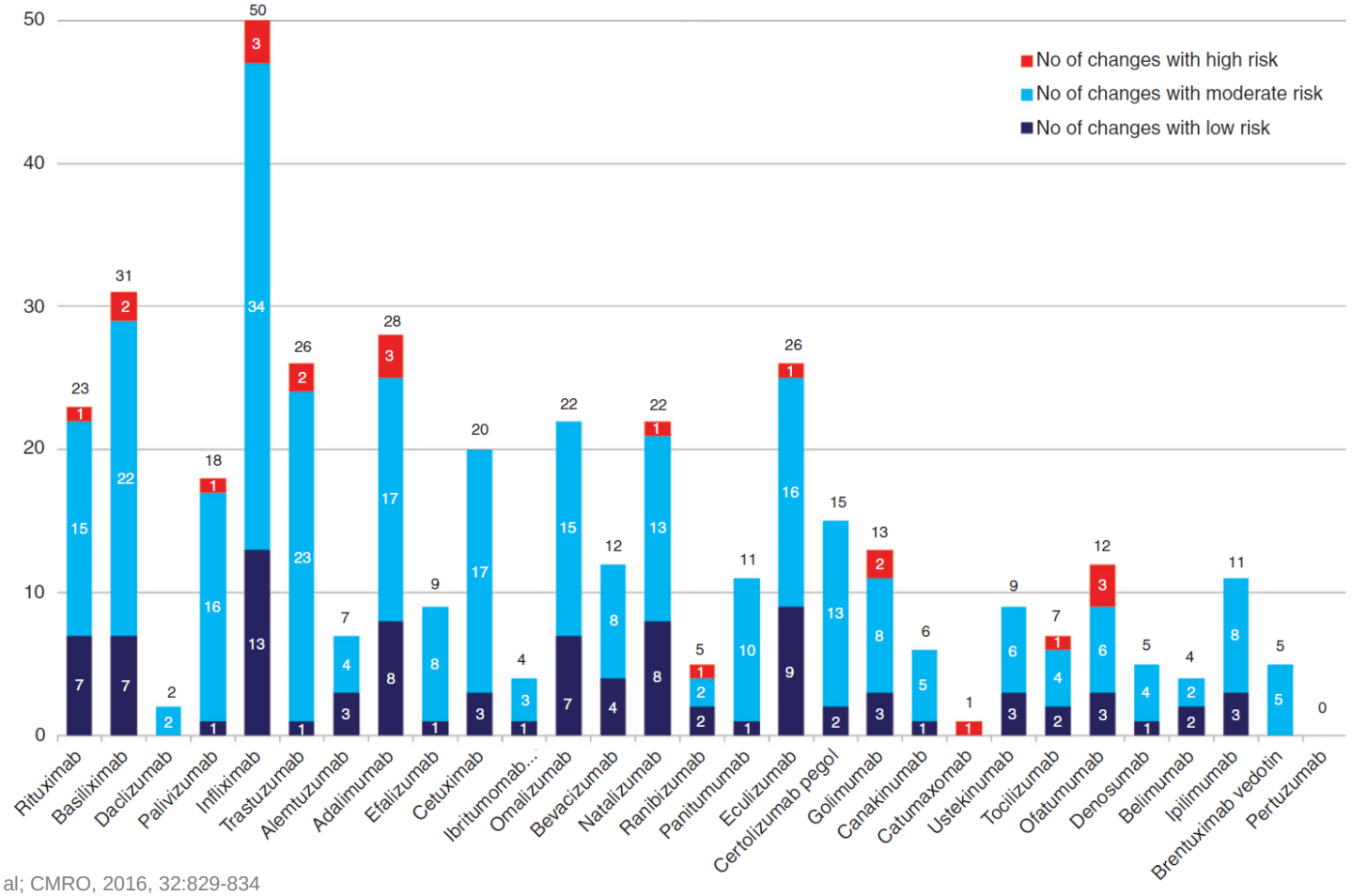
- Manufacturing changes can create variability in the biologic molecule



Adapted from Lee J, Litten J and Grampp G, CMRO, 2012; 28:1053-1058

Variability is in the nature of biologics

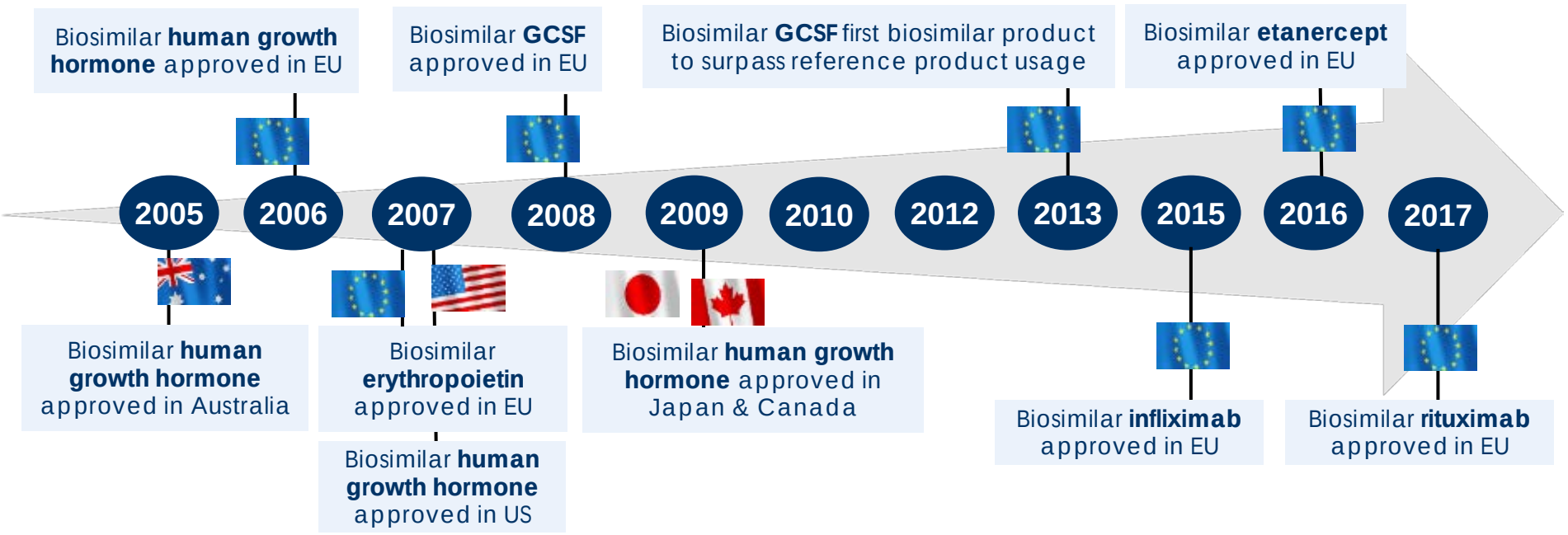
- Manufacturing changes are tightly regulated



Vezér B, Zrubka Z et al; CMRO, 2016, 32:829-834

What are biosimilars?

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

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Biosimilar-a regulatory term

- A biosimilar is “essentially the same” as the reference biologic medicine with some natural variability

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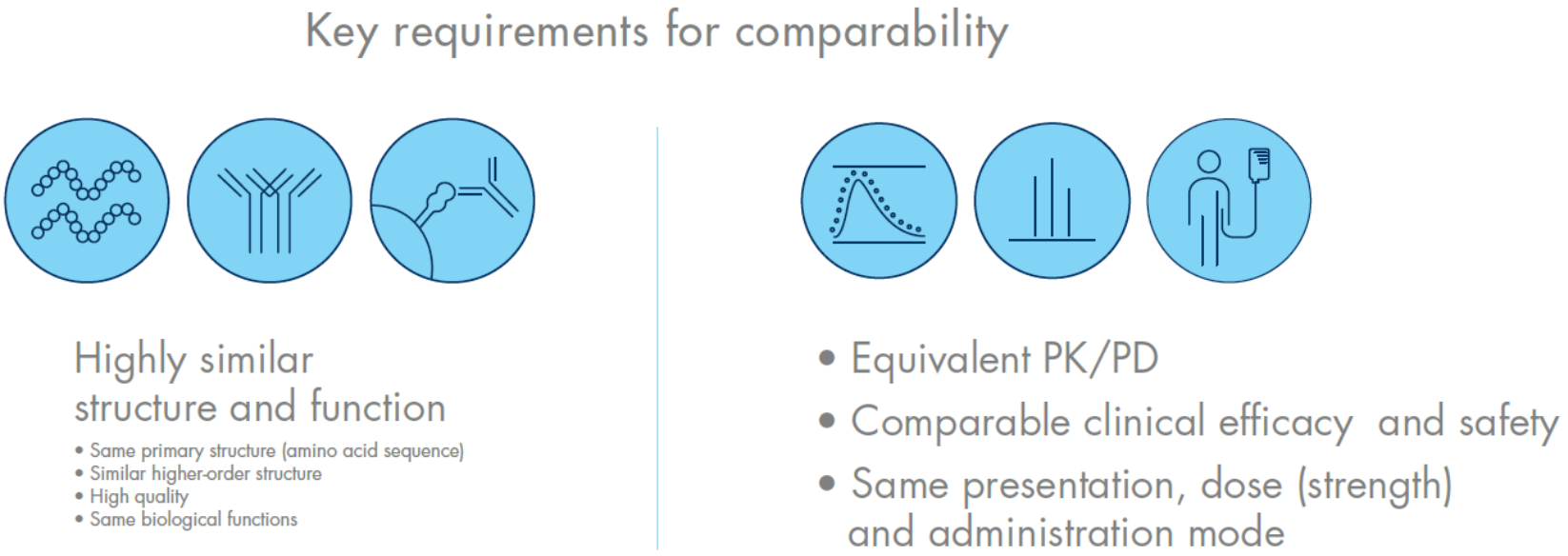
*“The **active substance** of a biosimilar and its reference medicine is **essentially the same** biological substance, though there may be minor differences due to their complex nature and production methods. **Like the reference medicine, the biosimilar has a degree of natural variability.** When approved, its variability and any differences between it and its reference medicine **will have been shown not to affect safety or effectiveness**.”*

Source: Questions and answers on biosimilar medicines (similar biological medicinal products). European Medicines Agency. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf last accessed March 2017

How are biosimilars developed?

Biosimilars are highly similar to reference biologic

- Biosimilars are approved biologics that have been demonstrated to be highly similar to a reference product



European Medicines Agency (EMA). Guideline on similar biological medicinal products. CHMP/437/04 Rev 1/2014 [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf [Accessed 2016 March 18];
US Food and Drug Administration. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product 2015 [online] Available from URL: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf [Accessed 2016 March 18].

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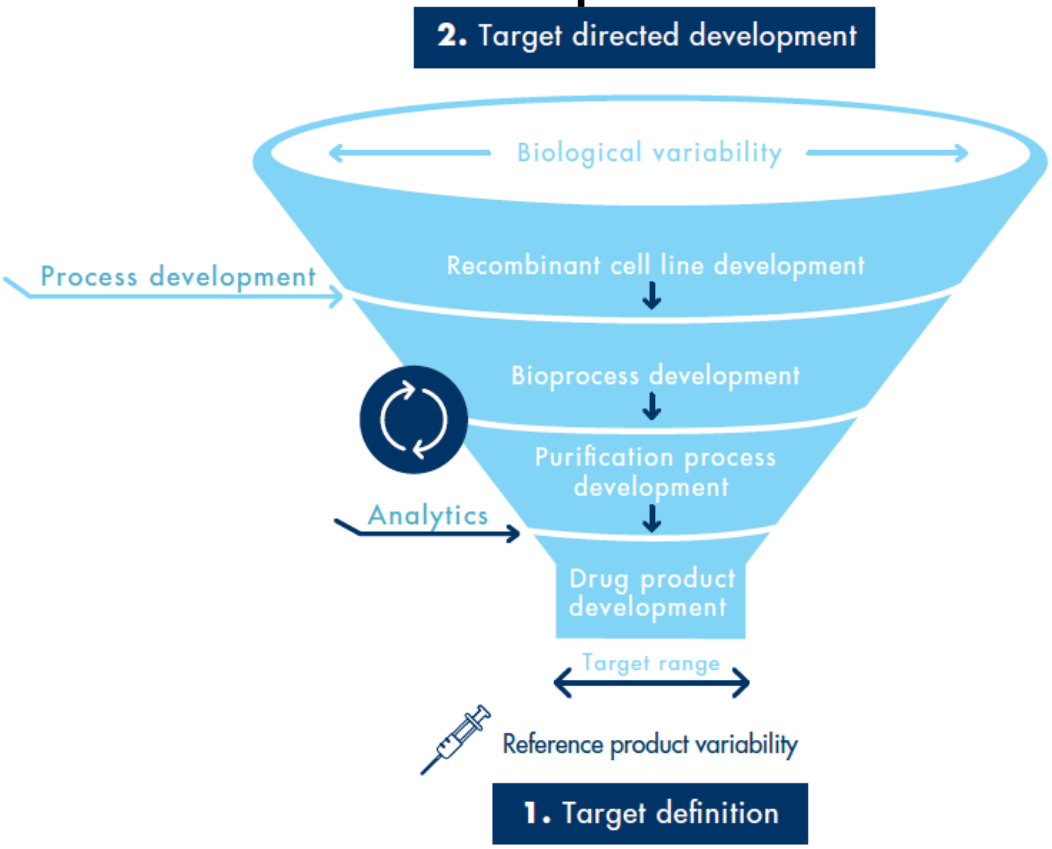
Biosimilars are made to match

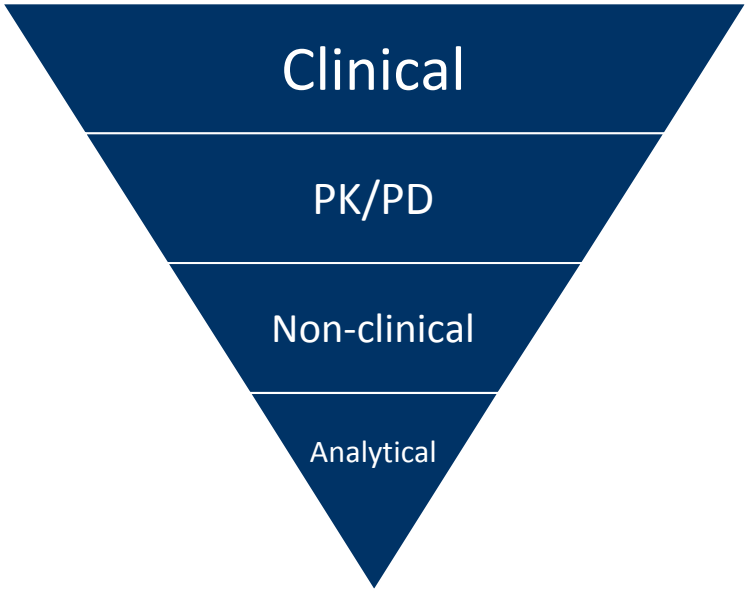
- Biosimilars are systematically developed to match the reference product



Adapted from McCamish M & Woollett G 2011. MAbs;3(2): 209–17.

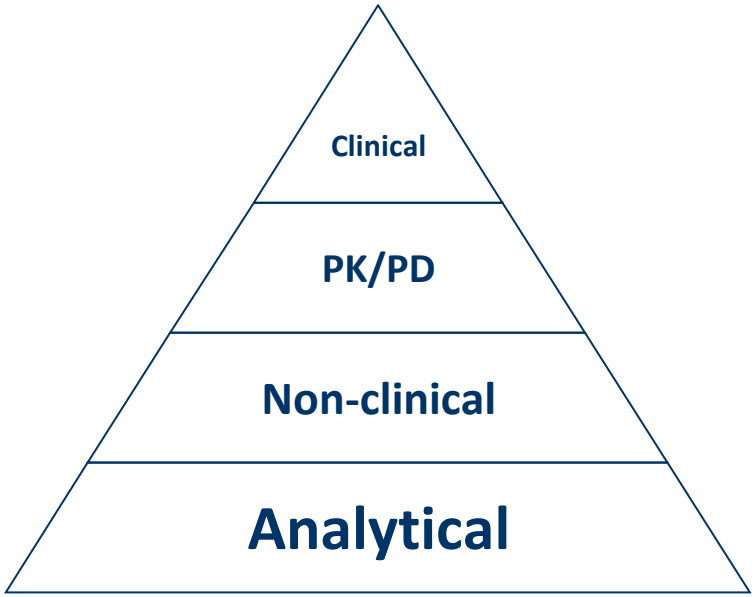
Differences in development

Originator



Major goal is to
determine the clinical effect

Biosimilar



Major goal is to determine similarity;

- Establishment of the scientific bridge to the clinical experience of the reference molecule
- Analytical methods provide the most sensitive tools to establish this scientific bridge

Adapted from:
McCamish M, et al. *Mabs*. 2011;3(2):209–17 and
McCamish M, Woollett G, Clin Pharmacol Ther. 2012;91(3):405-17

Development approach for biosimilars is closer to originators than to generics

	Generic	New biologic	Biosimilar
Time to market (years)	2–3	8–10	7–8
Clinical studies	Bioequivalence studies in healthy volunteers	Phase I, II, III efficacy and safety studies	Comparative phase I pharmacokinetic and Phase III study
Patients (n)	20–50	800–1000	~500
Post-approval activities	Pharmacovigilance, Risk Management Plan in special situations	Phase IV, Risk Management Plan including Pharmacovigilance	Phase IV, Risk Management Plan including Pharmacovigilance

Grande E & Carrato A. Cancer Chemother Rev 2011;6(3):23–30.

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Development process

- Focus of biosimilar development is to establish similarity to the reference product

Develop highly similar product 1

TECHNICAL DEVELOPMENT

- Fully characterise reference product
- Match molecule profile of biosimilar with reference product (structure & function/biological activity)
- Match final dosage form to reference product

Confirm biosimilarity 2

PRECLIN | PHASE I | PHASE III

- Demonstrate PK/PD equivalence
- Confirm efficacy and safety via tailored Phase III studies
- Support extrapolation to non-studied indications and interchangeability

Post-approval 3

PHASE IV | REGISTRIES

- Additional data following the product long-term

McCamish M & Woollett G. Clin Pharmacol Ther 20102;91(3):405–17;
Visser J, et al. BioDrugs 2013;27(5):495–507;
Weise M, et al. Blood 2012;120(26):5111–17.

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Understanding the molecule

- Integration of data from multiple analytical and biological tests provides complete understanding

- Combined data from **~45 different methods** provide **information on multiple attributes** (orthogonality)
- Every attribute is evaluated more than once (redundancy)

Berkowitz SA, et al. Nat Rev Drug Discov 2012;11(7):527–40.
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Understanding the molecule

- Integration of data from multiple analytical and biological tests provides complete understanding

PRIMARY STRUCTURE
- LC-MS intact mass
- Peptide mapping
- LC-MS subunits

IMPURITIES
- CEX, cIEF acidic/basic variants
- Peptide mapping, mutation, oxidation, deamidation, glycation
- SEC/FFF/AUC aggregation
- LC glycation

BIOLOGICAL ACTIVITY
- Binding assay
- ADCC assay
- CDC assay

HIGHER-ORDER STRUCTURE
- NMR
- CD spectroscopy
- FT-IR

POST TRANSLATIONAL MODIFICATIONS
- 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:
- MVDA, mathematical algorithms

- Combined data from **~45 different methods** provide **information on multiple attributes** (orthogonality)
- Every attribute is evaluated more than once (redundancy)

Berkowitz SA, et al. Nat Rev Drug Discov 2012;11(7):527–40.
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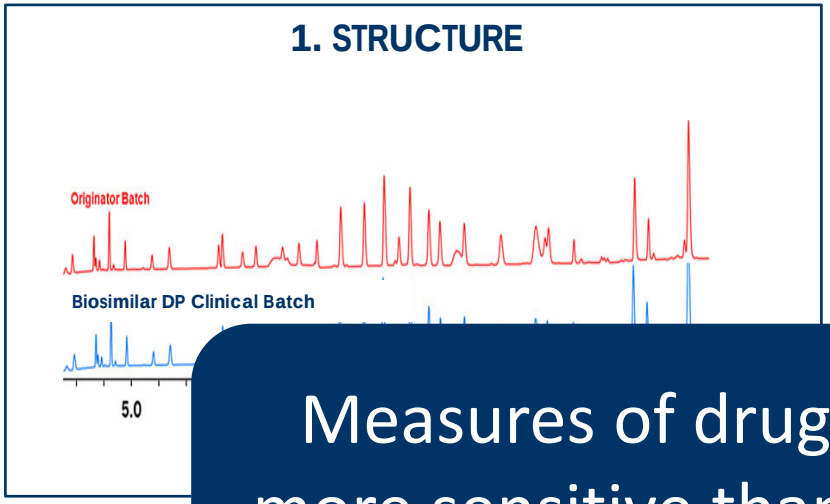
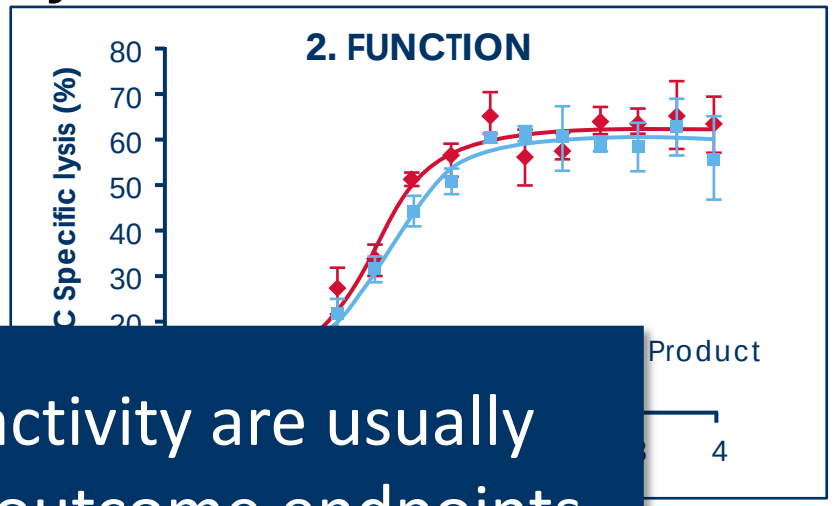
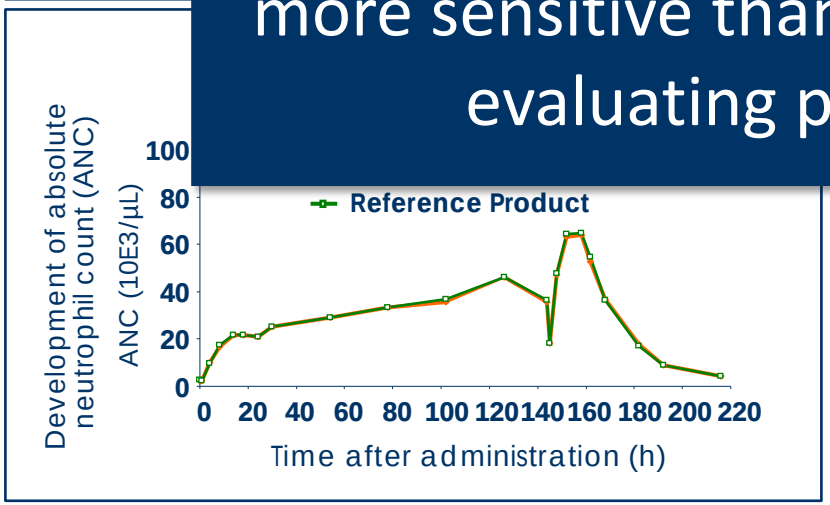
Totality of the evidence

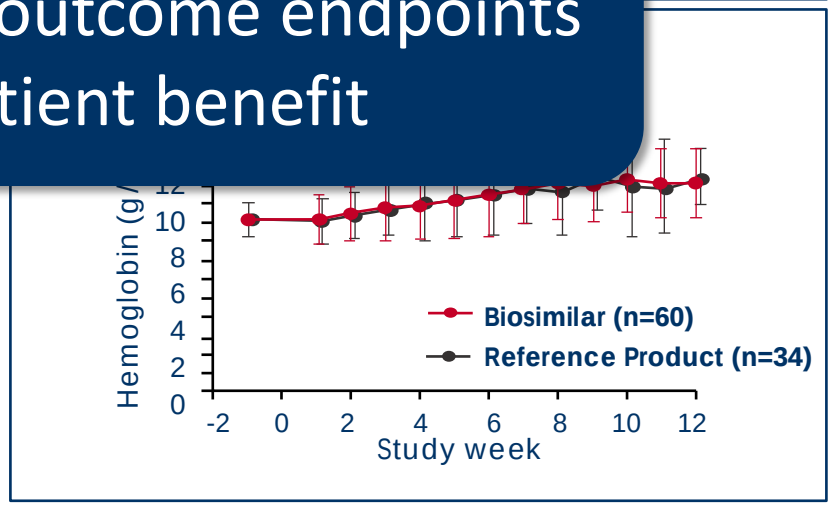
- Biosimilars must be highly similar at all levels





Measures of drug activity are usually more sensitive than outcome endpoints evaluating patient benefit





McCamish et al, ClinPharmacol & Ther 2012, Visser et al, BioDrugs 2013, Gascon P et al. Ann Oncol 2010, Weigang-Köhler et al. Onkologie 2009, da Silva et al. Leuk Lymphoma 2014

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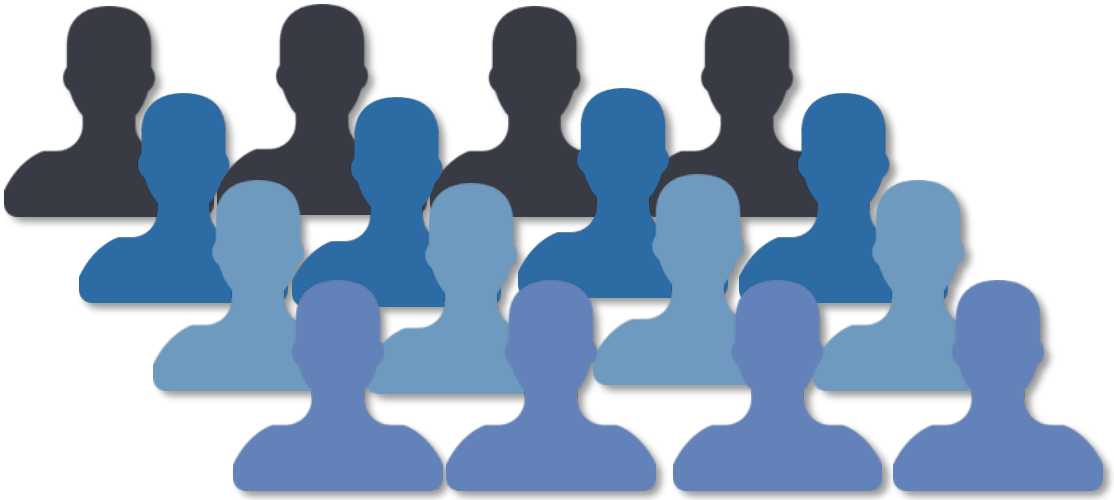
Patient populations

- Choosing the right indication for the clinical data is a critical part of biosimilar development and is done in conjunction with the EMA
- The aim of the biosimilar regulatory study may be different to that of the originator biologic



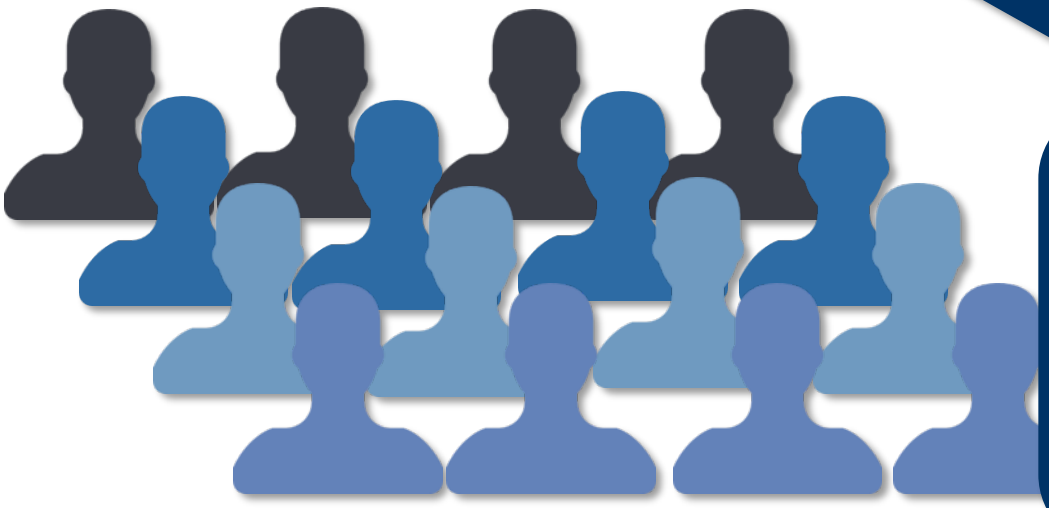
EBG's perspective on draft guidance on clinical/non-clinical issues. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500154186.pdf access March 2017

Patient populations

- Trial populations must be:
  - Sensitive
  - Homogenous

Sensitive populations have:
- Active disease
- Large effect size (drug effect)
- Immunocompetence

This makes it easier to determine the effect of the drug



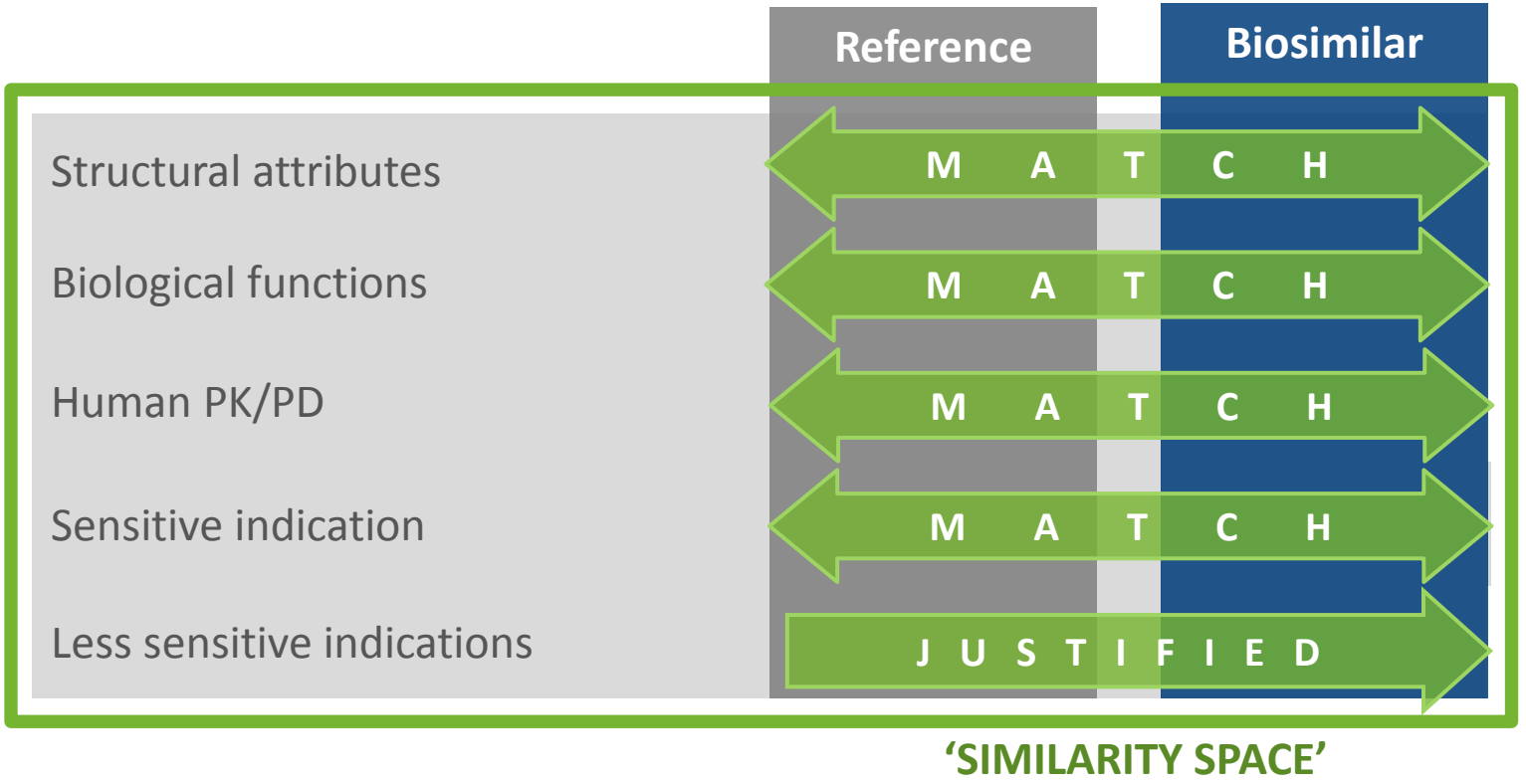
Homogenous populations have:
- Fairly consistent disease activity
- Less disease/patient confounders
- Minimal interpatient variability

This means smaller sample sizes can be used

EBG's perspective on draft guidance on clinical/non-clinical issues. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500154186.pdf Accessed March 2017

Extrapolation of indication

- Extrapolation is based on the entire similarity exercise, including clinical experience with the reference product



Ebbers HC. J Crohns Colitis 2014;8(5):431–5; Kurki P, et al. J Crohns Colitis 2014;8(3):258; Weise M, et al. Blood 2014;124(22):3191-6; Weise M, et al. Blood 2012;120(26):5111–17; SDZ-generated/owned figure (November 18 2014).

Post-authorisation activities

- As for any biopharmaceutical, the clinical safety of biosimilars must be monitored through continued pharmacovigilance

- A pharmacovigilance plan must be adopted
  - Involves collection and assessment of AE data, post-approval studies and registries

- The need for risk minimisation strategies must be evaluated
  - Assesses whether strategies are needed beyond the pharmacovigilance plan

- A risk management plan must be submitted
  - Typically includes the same obligations and activities as for the reference medicine

European Medicines Agency (EMA). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005 Rev. 1. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf) [Accessed 2016 March 23].
Zuñiga L, Calvo B. Pharmacoepidemiol Drug Saf 2010;19:661–9. Choy et al. Semin Oncol 2014;41:S3–S14

Summary

Biosimilars: Summary

- Biologics can be thoroughly analysed and characterised
- Biosimilars are systematically developed to be highly similar to their reference biologic
- Clinical studies aim to confirm the characterisation work
- Extrapolation builds on the entire similarity exercise
- Post authorisation studies continue safety monitoring
- Biosimilars must meet the same quality standards as originator products
- Biosimilars may increase patient access to biologic medicines and contribute to savings for healthcare systems[1]

1. Eleryan MG et al. Biosimilars: potential implications for clinicians, Clin Cosmet Investig Dermatol, 2016;17:135-42

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Questions?