An introduction to Biosimilars
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
• What are biologics?

• What are biosimilars?

• How are biosimilars developed?
What are biologics?
What are biologics?

Paracetamol: Small molecule
- Chemical synthesis
- Single substance
  - 151 Da
- MoA ambiguous

Filgrastim: Protein (a growth factor)
- Made using bacteria
  - Single main substance
  - One chain, 175 amino acids
    - 18,803 Da
  - Receptor binding only

Antibody (mAb): Glycoprotein (with variable sugars)
- Made using mammalian cells
  - Mixture of variants
  - Four chains, 1330 amino acids
    - 144,000 Da
  - Receptor binding, effector functions

Note: Illustrations not to scale.


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Biologic manufacture

- Biologics are produced from living organisms

Modify host cells (e.g. bacteria, yeast, mammalian) to produce recombinant proteins

Grow cells under controlled conditions (fermentation, upstream process)

Extract, refold, purify to generate drug substance (downstream process)

Formulate to stable finished drug product (vial, syringe, cartridge)

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

- **Low Risk**
  - Change filter supplier
  - Move equipment within the same facility
  - Analytical Data
  - Process Data

- **Moderate Risk**
  - Move to new production facility (same manufacturer)
  - Analytical Data
  - Process Data
  - Stability Data

- **High Risk**
  - Change cell culture media
  - New cell line or major formulation change
  - Analytical Data
  - Process Data
  - Stability Data
  - Non-clinical data
  - Clinical data

Higher risk changes require greater amounts of supporting data

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?
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 class1,2,3

Biosimilars are now in routine use in the NHS, particularly in rheumatology and gastroenterology

3. For full adverse event profiles, please refer to Zarzio and Omnitrope SPCs available at: www.medicines.org.uk/emc
Biosimilar—a regulatory term

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

“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.”

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

Key requirements for comparability

- Highly similar structure and function
  - Same primary structure (amino acid sequence)
  - Similar higher-order structure
  - High quality
  - Same biological functions

- Equivalent PK/PD
- Comparable clinical efficacy and safety
- Same presentation, dose (strength) and administration mode

Biosimilars are made to match

- Biosimilars are systematically developed to match the reference product

Differences in development

Originator

- Clinical
- PK/PD
- Non-clinical
- Analytical

Major goal is to determine the clinical effect

Biosimilar

- Clinical
- PK/PD
- Non-clinical
- Analytical

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:
## Cancer Vanguard

### Development approach for biosimilars is closer to originators than to generics

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

• Focus of biosimilar development is to establish similarity to the reference 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

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

3. PHASE IV | REGISTRIES
   • Additional data following the product long-term

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)

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

**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

**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

**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)


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**Totality of the evidence**

- Biosimilars must be highly similar at all levels

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**1. STRUCTURE**

**2. FUNCTION**

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

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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:

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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


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Extrapolation of indication

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

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<tr>
<th>Structural attributes</th>
<th>Reference</th>
<th>Biosimilar</th>
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'SIMILARITY SPACE'

Cancer Vanguard

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

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

Questions?