

# Biosimilar Adoption Process Timeline

Pharmacy-Led

Horizon Scanning

Quantify Opportunity

Evaluate Service Impact

Agree Adoption Process

Optimise Reference Biologic

Complete Preparation

Introduce Biosimilar

Calculate Actual Budget Impact

Review Monitoring Data

-6

-3

-0

3

Month

Form MDT Steering Group

Engage Patients and Patient Groups

Obtain DTC Approval

Monitoring

Review Resource Impact

Commence Staff Education

Review Biosimilar Data

Trust Level

Click on each task for further details and materials

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## Horizon Scanning

Regularly scanning for biosimilar launches ensures that institutions are informed in sufficient time to have smooth biosimilar adoption.

Scanning will also show if other biosimilars in the same therapy area are expected around the same time. This will prevent duplication and enable planning in case of competition between molecules.

There are a variety of resources available. Check with your procurement pharmacist for ones used within your institution, or alternatively click on the links below.

[Click here](#) for link to UK Medicines Information (UKMi) Prescribing Outlook resource and enter “Prescribing Outlook” in the search box (registration to Specialist Pharmacy Service required for access).

[Click here](#) to read latest insights into oncology product launches in the British Oncology Pharmacy Association (BOPA) newsletter.

**Timeframe:** Ongoing

**Task:** Watch the market for upcoming biosimilar launches

**Lead:** Pharmacy

**Involved:** Pharmacy  
Procurement, Area Specialists  
and Commissioning Pharmacists

**Resource:** UKMi website and  
BOPA newsletters

## Quantify Opportunity

Prior to commencing any biosimilar adoption process, it is critical to consider what is to be gained and what challenges are to be anticipated.

### Checklist:

- ✓ Quantify current usage of biologic under consideration across all indications and treatment pathways in terms of number of patients, quantity of drug (in both mg and dose units) and current spend on different presentations
- ✓ Review current biological medicines guidance, including cost-effectiveness guidance from NICE, adoption toolkits, Key Therapeutic Topic (KTT) and case studies which may impact future usage of the biologic/biosimilar
- ✓ Consider formulations used in current practice and their likely biosimilar availability (timing of product launches, compounding, dose banding, presentation sizes, delivery devices and stability data)
- ✓ Assess the risk of introduction, for example consider:
  - Is the data package supported by clinicians?
  - Is the supply chain history good?
- ✓ Evaluate costs of implementation, capacity of clinical teams and how it will be funded (see service impact study for details). Account for patient support services currently available
- ✓ Take account of system incentives including Specialised Commissionings for Quality and Innovation (CQUINs), gain share possibilities and NHS England or Clinical Commissioning Group (CCG) direction. Evaluate how savings made can be reinvested to improve clinical service. Model return on investment and timeline for anticipated savings
- ✓ Establish if data collection, reporting or monitoring of patient outcomes will be required as part of biosimilar introduction
- ✓ Consider contracting opportunities for wider improvements to biological medicines such as: standard terms, service development and improvement plans (SDIP) and data quality improvement programmes (DQIP)

**Timeframe:** Around 6 months prior to availability

**Task:** Assess viability and impact of adopting a biosimilar

**Lead:** Pharmacy

**Involved:** Specialist Pharmacists, Clinical Leads

**Resource:** Checklist, Service Impact Study

Service Impact Study



## Form MDT Steering Group

Biosimilar adoption works best when everyone who is affected by it is informed early and given the opportunity to get involved. This prevents any stakeholder anxiety and allows time for an institution to make decisions on usage before commissioning pressures are imposed. Defining everyone's role and establishing regular communication will help the adoption process run smoothly.

### Checklist:

- ✓ Involve at least one lead clinician and identify lead to drive adoption
- ✓ Seek members from across all departments where reference biologic under consideration is currently used
- ✓ Agree roles in steering group
- ✓ Ensure commissioning and clinician collaboration
- ✓ Appoint biological (oncology) pharmacist to project manage
- ✓ Consider additional clinical and pharmacy specialists and administrative support
- ✓ Identify key stakeholders to engage with (stakeholder plan for internal and external stakeholders including clinicians, pharmacists, nurses, patient and professional groups and wider NHS)
- ✓ Use regional pathways to facilitate clinician trust

**Timeframe:** Around 5 months prior to availability

**Task:** Identify and engage key stakeholders early

**Lead:** Trust level

**Involved:** multidisciplinary team (MDT) in affected therapy area

**Resource:** Checklist

## Evaluate Service Impact

While the financial savings opportunity offered by a biosimilar is relatively easy to determine, it is critical to evaluate the wider impact of the biosimilar on the whole Trust.

### Checklist:

- ✓ Ensure implementation is feasible from a work resource perspective, i.e. can it be done within existing resources?
- ✓ Evaluate predicted savings
- ✓ Predict the resource required so that it can offset potential savings on drug acquisition to reveal the true cost of the drug
- ✓ Identify areas in need of additional preparation (i.e. coding for reimbursement, clinical trials, cold storage capacity, IT requirements etc.)
- ✓ Collect data on current service and develop process to implement service impact study

The Vanguard has developed a study template for determining and evaluating this impact. Please click on the Service Impact Study link below to view.

**Timeframe:** Around 4 months prior to availability

**Task:** Assess viability and impact of adopting a biosimilar

**Lead:** Pharmacy

**Involved:** Finance and Information departments

**Resource:** Checklist, Service Impact Study

[Service Impact Study](#)



## Agree Adoption Process

Once the opportunity and impact to service have been evaluated, based on this information the next step is to agree the process for adopting the biosimilar into use in the Trust as a whole. Thorough understanding of how the reference medicine is used within the Trust is critical to identify and engage with every event, from vial to patient. Some specialities or individuals may be reluctant to use a biosimilar and the Trust must decide how to address and manage this.

For further pharmacy-focused activities, please refer to the BOPA guidance on biosimilar adoption.

### Checklist:

- ✓ Agree which patients will be eligible for the new biosimilar: in-treatment patients, patients between reference biologic and biosimilar, and patients between biosimilars? For all indications or specific indications?
- ✓ Agree what monitoring, in line with reference biologic monitoring, will be conducted
- ✓ Conduct risk assessment and evaluate medicines governance implications
- ✓ Prescribing policy – consider electronic prescribing/supply implications and chemotherapy regimens
- ✓ Biosimilars are prescribed by brand name; ensure that systems can accommodate brand name prescribing
- ✓ Pharmacovigilance considerations/traceability as per reference biologic
- ✓ Registry participation – in house or external
- ✓ Role of clinician choice in consultation with the patient
- ✓ Agree timeline to adoption
- ✓ Chair capacity

**Timeframe:** Around 4 months prior to availability

**Task:** Set up adoption process for this biosimilar

**Lead:** Pharmacy

**Involved:** Drugs and Therapeutics Committee (DTC), MDT

**Resource:** Checklist, BOPA, European Society for Medical Oncology (ESMO) and NICE Guidance

### Resources:

[BOPA Position Statement](#)

[NICE Advice on Biosimilars](#)

[ESMO Biosimilar Position Paper](#)

## Engage Patients And Patient Groups

As biosimilars are a relatively new technology, patients and patient groups may not be familiar with them. The patient voice must be included when making the decision to use a biosimilar. A patient panel or patient advocate should be engaged. There are examples of where this has been highly beneficial to biosimilar implementation and resulted in almost complete biosimilar usage. [Click here](#) for link to the University Hospital of Southampton experience as an example.

### Checklist:

- ✓ Set up a meeting to engage with patients or patient forum. If a patient forum doesn't exist within the Trust, discuss obtaining equivalent input with the Patient Advice and Liaison Service (PALS) within the Trust
  - The meeting should be led by a Senior Clinician/CNS/Senior Pharmacist in consultation with the PALS
  - Present details of biosimilar concepts, ensure reasonable level of biosimilar understanding
  - Present details of planned introduction including the opinions of leading clinicians within the Trust and expected impact to patients, the Trust and the NHS
  - Listen for areas of concern or knowledge gaps. Where possible, use these as themes for the patient information leaflet or frequently asked questions. Address queries in the meeting, checking suitability of answer and impact of response to patient confidence

**Timeframe:** Around 3 months prior to availability

**Task:** Understand patient perspective

**Lead:** Trust level

**Involved:** Service lead

**Resource:** Statements for professional bodies and patient groups, i.e. British Society of Gastroenterology and National Rheumatoid Arthritis Society

### Resources:

[Lymphoma Association: Biosimilars for lymphoma](#)

[British Society of Gastroenterology position statement](#)

[National Rheumatoid Arthritis Society position statement](#)

Patient Information Leaflet: General Biosimilar Patient Information Template for NHS Trust Use →

## Commence Staff Education

Robust staff education on biosimilar principles improves the confidence of both staff and patients. Careful consideration should be given to the needs of each professional group to ensure training is as relevant and accessible to them as possible. The Vanguard has produced, piloted and validated an educational presentation. See below for link to this Biosimilar Principles educational presentation.

### Checklist:

- ✓ Seek support for training from Trust management
- ✓ Identify key groups most likely to be involved in usage of this biosimilar
- ✓ Assess current level of biosimilar knowledge and preferred means of receiving training
- ✓ Where possible, conduct small group training on biosimilar principles. Consider feedback forms that allow staff to identify remaining knowledge gaps. Molecule-specific information should follow discussions on biosimilar principles
- ✓ Consider constant information updates through newsletters or questions of the week on intranet, etc.
- ✓ Ensure the way staff can get further information is clearly identified on all material
- ✓ Consider running workshops within the institution, inviting others from nearby centres with experience to contribute to programme

**Timeframe:** Around 3 months prior to availability

**Task:** Foster confidence in biosimilar concepts

**Lead:** Trust level

**Involved:** Biosimilar champions, education and training leads

**Resource:** Checklist, Biosimilars Educational Slide Deck, Education Impact Assessment Questionnaire, Biosimilar FAQs

[Education Impact Assessment Questionnaire](#)



[Biosimilars Educational Slide Deck](#)



[Biosimilar FAQs](#)





## Review Biosimilar Data

Due to the stringent EMA regulation of biosimilar development, data associated with biosimilars is different from that of the reference molecule. In particular, not every indication of the reference molecule needs to be studied. Prior to considering a biosimilar, a DTC should review all available data and timing of future publications for the biosimilar under review (see next page).

### Checklist:

- ✓ Review available published clinical data
- ✓ Understand and analyse the biosimilar data package, relevance of the endpoints etc.
- ✓ Consider the patient number, duration of follow-up and applicability of endpoints assess likely involvement in professional registries (i.e. British Society for Rheumatology–Biologics Register (BSRBR))
- ✓ Scan for future, pending data releases and ongoing studies. The manufacturer's medical information service can provide this information

**Timeframe:** Around 2 months prior to availability

**Task:** Check biosimilar data is understood

**Lead:** Trust level

**Involved:** Lead only

**Resource:** Checklist, Service Impact Study, Biosimilars Trust Policy – Template

[Biosimilars Trust Policy – Template](#)



[Service Impact Study](#)



## Obtain DTC Approval

DTC approval processes will vary from Trust to Trust. If not present on the DTC, ensure lead clinician affected by the biosimilar introduction is significantly involved in preparing application and that they endorse its use.

### Checklist:

- ✓ Follow biosimilar policy guidance on DTC approval process
- ✓ Complete implementation checklist as part of DTC application
- ✓ Agree groups of patients eligible for biosimilar use across indications and the whole Trust
- ✓ Agree process for the coordinated and timely introduction of the biosimilar
- ✓ Agree review date for biosimilar usage
- ✓ Agree required monitoring parameters

**Timeframe:** Around 2 months prior to availability

**Task:** Obtain formulary approval

**Lead:** Trust level

**Involved:** DTC, Clinical Unit Leads, Specialist Pharmacist

**Resource:** Checklist, Biosimilars Trust Policy – Template

Biosimilars Trust Policy –  
Template



## Optimise Reference Biologic

Prior to introducing a biosimilar, it is good practice to ensure the reference molecule is being used as optimally as possible. This provides the best possible platform for the biosimilar to be introduced and evaluated.

### Checklist:

- ✓ Where possible, collect and analyse relevant pharmacokinetics (PK) and pharmacodynamics (PD) markers (e.g. ATA, serum concentrations, markers of disease activity) – requirement will be dependent on indication
- ✓ Where appropriate, alter dose or frequency of reference molecule to ensure optimal treatment in line with established guidelines

**Timeframe:** Around 3 months prior to availability

**Task:** Assess viability and impact of adopting a biosimilar

**Lead:** Pharmacy

**Involved:** Clinician Lead

**Resource:** Checklist, The Pharmaceutical Journal article from Southampton: Biosimilars and inflammatory bowel disease: a switch programme using CT-P13

Resources:

[The Pharmaceutical Journal article from Southampton](#)

## Complete Preparation

Biosimilar adoption will be more successful in environments that have planned well, and completed their preparations sufficiently in advance of usage to minimise stakeholder anxiety. Early preparation also allows for time to address any late-rising educational needs.

### Checklist:

- ✓ Set up product in dispensing software
- ✓ Prepare changes to product in prescribing software in test environment where possible
- ✓ Order stock of biosimilar in all preparations expected to be used. Confirm delivery date and quarantine on receipt. Ensure capacity in pharmacy and wards/units for biosimilar storage
- ✓ Follow local standard operating procedures (SOPs) for switch/change process of medicinal product (e.g. reduce stock/minimum levels)
- ✓ Risk assess if reference and biosimilar are both to be used in the hospital, and take appropriate steps to minimise risk at both pharmacy and ward level
- ✓ Advertise the information in relation to the switch/change in all affected clinical areas of impending change of molecule, highlighting same/similar name risk (including photos of product if available)
- ✓ Complete patient information

**Timeframe:** Around 2 weeks prior to availability

**Task:** Finish preparations in advance of biosimilar use

**Lead:** Pharmacy

**Involved:** IT Leads, Pharmacy Procurement

**Resource:** Checklist, Service Impact Study

Service Impact Study



## Introduce Biosimilar

This is the agreed, pre-determined day of first administration of the biosimilar. This day should be in line with the locally agreed implementation plan in the adoption process of the individual biosimilar.

If all preparations have gone well, this day should go smoothly.

### Checklist:

- ✓ Activate changes to prescribing and dispensing software in live environment
- ✓ Re-advertise the information in relation to the introduction in all affected clinical areas of impending change of molecule, highlighting same/similar name risk (including photos of product if available), including pharmacy contact details
- ✓ Ensure patient support materials are available. Click on links below for access to patient information leaflets
- ✓ Ensure dispensary and medicines information staff are fully briefed
- ✓ Consider allocating additional support, identified as a need, to units with e-prescribing systems to assist staff in affected clinical areas with any initial prescribing difficulties

**Timeframe:** At time of availability

**Task:** Initiate biosimilar usage

**Lead:** Pharmacy

**Involved:** Clinical Leads,  
Specialist Pharmacist, Pharmacy  
Technical Services (if applicable)

**Resource:** Checklist, Service  
Impact Study, Patient Information  
Leaflet, Biosimilar FAQs

### Resources:

[Lymphoma Association: Biosimilars for lymphoma](#)

[UK Medicines Information: Answers to commonly asked questions about biosimilar versions of rituximab](#)

Patient Information Leaflet:  
General Biosimilar Patient  
Information Template for  
NHS Trust Use →

Service Impact Study →

FAQs on Biosimilars  
for Clinicians →

## Monitoring

In common with reference biologics, collecting clinical data for patients on biosimilars for submission to central registries (e.g. BSR-BR or British Association of Dermatologists Biologics Intervention Register (BADBIR)) may be mandated under a pharmacovigilance condition of the drug's licence. Every effort should be made to comply with those obligations. For those who do not have this requirement, monitoring of patient data may be considered within the Trust and should be agreed as part of the formulary application, including identification of those who would be responsible for collecting and analysing the data, and timeframe over which the data should be collected.

### Checklist:

- ✓ Review agreed clinical outcomes:
  - Standard response criteria
  - Adverse event monitoring e.g. infusion related reactions (IRRs)
  - If sub-groups were selected for initial biosimilar use, does this data provide justification for expanding use to a wider population?
- ✓ Assess patient satisfaction
- ✓ Assess staff perceptions post training/launch
- ✓ Share learning

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)

**Timeframe:** At time of availability

**Task:** Set up for safe biosimilar use

**Lead:** Clinical Team

**Involved:** Locally dependent

**Resource:** Checklist, Service Impact Study

Service Impact Study



## Calculate Actual Budget Impact

Now the biosimilar is in use, it is important to check the impact on the budget is occurring as expected and to look for variation in practice of biosimilar adoption within the trust. While still early, this is a time to identify where concerns are and work to address them, e.g. ensuring patients are on the correct regimens prior to the switch.

### Checklist:

- ✓ Monitor expenditure and savings against projections
- ✓ Ensure biosimilar reimbursement is correct
- ✓ Review wastage
- ✓ Identify clinical areas with slow uptake
- ✓ Benchmark uptake against similar providers

**Timeframe:** Approximately 3 months after adoption

**Task:** Assess viability and impact of adopting a biosimilar

**Lead:** Pharmacy

**Involved:** Lead only

**Resource:** Checklist, Service Impact Study

Service Impact Study



## Review Monitoring Data

If it is agreed to collect data in the monitoring task, data must be reviewed periodically. It should be agreed at the commencement of the data collection who should review the data and how often. This task serves as a reminder that collected data must be reviewed, not only to ensure patient safety but also to check that biosimilar adoption is proceeding as anticipated.

### Checklist:

- ✓ Incorporate data collection requirements under CQUIN and other mandatory monitoring such as Medicines Optimisation dashboard metrics or bespoke gainshare data requirements, as made available
- ✓ Review agreed clinical outcomes
- ✓ Standard response criteria
- ✓ Adverse event monitoring e.g. IRRs
- ✓ If sub-groups were selected for initial biosimilar use, does this data provide justification for expanding use to a wider population?
- ✓ Assess patient satisfaction
- ✓ Assess staff perceptions post training/launch
- ✓ Share learning

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)

**Timeframe:** Approximately 3 months after adoption

**Task:** Monitor agreed clinical outcomes

**Lead:** Clinical Team

**Involved:** Locally dependent

**Resource:** Checklist, Service Impact Study

Service Impact Study





## Review Resource Impact

Once biosimilar use is underway, it is important to monitor the impact of their use and compare this against what was projected, not only financially, but also on the wider service resource. This is central to understanding the whole picture of biosimilar implementation and their value.

### Checklist:

- ✓ Quantify actual costs associated with switching:
  - Formulary application process
  - Update to pharmacy systems
    - Dispensing, prescribing, production unit
  - Staff education/training
  - Update local guidelines
  - Development of patient information
- ✓ Quantify ongoing change in resources post implementation:
  - Reconstitution, site of administration, chair time, monitoring
- ✓ Monitoring of financial targets
- ✓ Share learning

**Timeframe:** Approximately 3 months after adoption

**Task:** Monitor agreed clinical outcomes

**Lead:** Clinical Team

**Involved:** Locally dependent

**Resource:** Checklist, Service Impact Study

Service Impact Study



## Service Impact Research Study

### Background:

Biosimilars are approved by the EMA if they are shown to be equivalent to their reference molecule in terms of safety, efficacy and quality. Due to the differences in their development program, biosimilars are able to be marketed at a cost significantly less than their reference product. To understand the impact of the reduced drug acquisition cost on total expenditure for that given treatment, it is necessary to fully characterise the areas of expenditure from vial to patient both prior to and after a decision to use a biosimilar has been made. This must account for one-off costs associated with implementing biosimilar usage, such as additional patient counselling requirements and also evaluate the impact of this biosimilar implementation on outcome measures such as patient satisfaction.

### Hypothesis H<sub>A</sub>:

Biosimilar use has a net reduction on overall expenditure compared to their reference molecule and has no impact on patient satisfaction measures

### Aim:

To fully characterise total costs and services associated with delivery of a cancer treatment with a biosimilar equivalent and re-evaluate once a biosimilar is in use.

### Methods:

Assess associated costs in terms of the following factors as detailed below.

Items highlighted in green require prospective consideration and need input prior to the adoption of the biosimilar

	Evaluate before biosimilar introduction		Evaluate after biosimilar introduction	
	Task	Time frame	Task	Time frame
<b>1. Eligible patients</b>				
a. Total number of patients prescribed biologic under review	✓	For one month	✓	Monthly for first quarter, then quarterly for first year
i. Patients on IV and SC	✓		✓	
ii. Patients eligible for biosimilar usage according to Trust policy (all patients without indication protected by patent or research protocol)	✓		✓	
iii. Patients receiving biosimilar			✓	
b. Clinical trial patients on biologic under review				
i. Patients on commercial stock	✓		✓	
ii. Patients on sponsor funded trial stock	✓		✓	
iii. Patients receiving biosimilar			✓	
<b>2. Drug acquisition costs</b>				
a. Drug cost (actual spend- vial cost or mg costs)	✓	For one month	✓	Monthly for first quarter, then quarterly for first year
b. Service delivery model	✓		✓	
i. % (near patient vs. SC vs. compounder (3 <sup>rd</sup> party) vs. aseptic vs. at home)	Do you expect this model to change as a result of using a biosimilar?		Did this model change as a result of using a biosimilar?	
ii. Costs (near patient vs. compounder (3 <sup>rd</sup> party) vs. aseptic vs. at home)				

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c. Costs associated with additional stock storage and risk minimisation activities			✓	
d. Wastage (vial wastage, expired or unused infusions etc.)	✓ Do you perceive there being any wastage in your system?		✓	
e. Do you use dose banding?				
<b>3. Service costs</b>				
a. Counsel +/- consent patients	✓	Across 20 sequential patients	✓	Across 20 sequential patients in first and second month of use
b. Preparation of patient materials and education			✓	
c. Time associated with clerking patient	✓		✓	
d. Administration costs i. Chair time (Vs. total capacity) ii. Monitoring	✓ Is monitoring or chair time requirement expected to change?		✓ Did monitoring or chair time change?	
e. Resources associated with ensuring reimbursement from commissioners	✓ Do you anticipate use of biosimilars changing your reimbursement process?		✓	
f. Costs associated with prescribing or administration errors			✓	
<b>4. Costs associated with biosimilar introduction</b>				
a. Preparation and validation of aseptic worksheet		One-off measurement and calculation	✓	
b. Preparation for formulary application			✓	
c. Development/adaption of biosimilar policy and guidance			✓	
d. Development and delivery of patient focused and staff educational material			✓	
e. Costs of further education of staff (initial and ongoing)			✓	
f. Updating electronic prescribing and dispensing software			✓	
g. Costs due to lack of stability data/validated method			✓	
h. Costs associated with changes to prescribing activities and uncertainty			✓	
<b>5. Patient satisfaction survey</b>				
a. Costs to perform patient satisfaction survey	✓	100 patients in same month as 1 and 2	✓	100 patients in same month as 1 and 2
b. Assessment of patient global satisfaction with treatment	✓		✓	

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## Biosimilars Education Impact Assessment Questionnaire

### Before Training

#### What do you know about biosimilars?

Q1a. Before this training, had you heard the term “biosimilar/biosimilarity” in the last month?      No      Yes

Q1b. How well do you understand how biosimilar medicines are **developed**?

I know nothing I have extremely good knowledge  
 0    1    2    3    4    5    6    7    8    9    10

Q1c. How well do you understand how biosimilars are **licensed in the UK**?

I know nothing I have extremely good knowledge  
 0    1    2    3    4    5    6    7    8    9    10

Q1d. How well do you understand the concept of **extrapolation** in regards to biosimilars?

I know nothing I have extremely good knowledge  
 0    1    2    3    4    5    6    7    8    9    10

#### Biosimilars in your practice:

Q2a. How would you expect patients to respond **clinically** to biosimilars compared to the reference/original medicine?

Very much differently    Somewhat differently    Somewhat the same    Very much the same    Not Sure

Q2b. How confident would you be in using biosimilars in your patients?

Not at all confident Very confident  
 0    1    2    3    4    5    6    7    8    9    10

Q2c. How easy do you think it will be to introduce biosimilars into your department?

Impossible Straightforward  
 0    1    2    3    4    5    6    7    8    9    10

Q2d. What issues do you expect to arise if biosimilars are introduced into your department?

.....

**Talking about biosimilars:**

Have you ever had a discussion about biosimilars with:

Q3a. **Clinical colleagues:**      No      Yes

How confident were you at explaining what a biosimilar is:

Not at all confident Very confident

0      1      2      3      4      5      6      7      8      9      10

Q3b. **Patients:**      No      Yes

How confident were you at explaining what a biosimilar is:

Not at all confident Very confident

0      1      2      3      4      5      6      7      8      9      10

**Biosimilar training**

Q4a. Have you previously received any training on biosimilars?    No      Yes

Q4b. If yes, was it provided by:

Someone in your Trust      Professional Body      Pharmaceutical Industry      Other

Q4c. When did you have the training? Less than 1 month, 1-3 months ago, 3-6 months ago, more than 6 months

Q4d. How useful was it?

Not at all useful Very useful

0      1      2      3      4      5      6      7      8      9      10

Q4e. If less than 10, why?

Too brief      Not enough detail      Too detailed      Not relevant to my role      Too biased

Other:.....

**About you**

Q5a    Role:    Nurse      Doctor      Pharmacist      Other (please state) \_\_\_\_\_

Q5b    Therapy Area:

Q5c    Year of registration as a healthcare professional:

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## About the way you learn

Q6a. How do you prefer to learn new information?

Please select 3 in order of preference where 1=first, 2=second and 3=third

Learning format	Rank
Presentation/Lecture	
Online training	
Ward-based teaching	
Self-directed reading/training	
Attending meetings/congresses	
Webinar	
Interactive training session	
Other (please describe)	

Q6b. On average, how much time do you spend in total on role specific learning **each week**? Please circle most appropriate.

Less than 15min      30min   1hr      2hrs      3hrs      4hrs      5hrs      6hrs      1day

Please note that the following pages are to be used after completion of the training to measure success against the baseline measurements in pages 1, 2 and 3.

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## Biosimilars Education Impact Assessment Post-Training Questionnaire

### After Training

#### What do you know about biosimilars *now*?

Q7a. How well do you understand how biosimilar medicines are **developed**?

I know nothing I have extremely good knowledge  
 0    1    2    3    4    5    6    7    8    9    10

Q7b. How well do you understand how biosimilars are **licensed in the UK**?

I know nothing I have extremely good knowledge  
 0    1    2    3    4    5    6    7    8    9    10

Q7c. How well do you understand the concept of **extrapolation** in regards to biosimilars?

I know nothing I have extremely good knowledge  
 0    1    2    3    4    5    6    7    8    9    10

#### Biosimilars in your practice:

Q8a. How would you expect patients to respond **clinically** to biosimilars compared to the reference/original medicine?

Very much differently    Somewhat differently    Somewhat the same    Very much the same    Not Sure

Q8b. How confident would you be in using biosimilars in your patients?

Not at all confident Very confident  
 0    1    2    3    4    5    6    7    8    9    10

Q8c. How easy do you think it will be to introduce biosimilars into your practice?

Impossible Straightforward  
 0    1    2    3    4    5    6    7    8    9    10



## Talking about biosimilars:

How confident do you feel now at explaining what a biosimilar is to...

### Q9a. Clinical colleagues:

Not at all confident Very confident

0    1    2    3    4    5    6    7    8    9    10

### Q9b. Patients:

Not at all confident Very confident

0    1    2    3    4    5    6    7    8    9    10

For your role, please list the three biosimilars topics you would like to learn more about?

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_

# An Introduction to Biosimilars

The following slide set is available from the [Resource Gallery](#)

An audio version of the slide presentation can be found [here](#)

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# 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

# Agenda



- What are biologics?



- What are biosimilars?


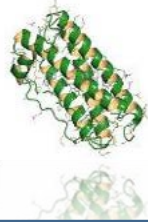



- How are biosimilars developed?

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# What are biologics?

# What are biologics?

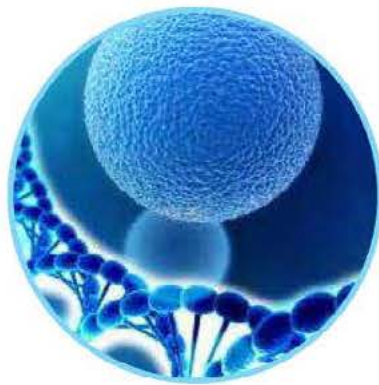
Paracetamol	Filgrastim (a growth factor)	Antibody (mAb)
<p>Small molecule</p> 	<p>Protein (without sugars)</p> 	<p>Glycoprotein (with variable sugars)</p> 
<ul style="list-style-type: none"> <li>▪ Chemical synthesis</li> <li>▪ Single substance                             <ul style="list-style-type: none"> <li>▪ 151 Da</li> </ul> </li> <li>▪ MoA ambiguous</li> </ul>	<ul style="list-style-type: none"> <li>▪ Made using bacteria</li> <li>▪ Single main substance</li> <li>▪ One chain, 175 amino acids                             <ul style="list-style-type: none"> <li>▪ 18,803 Da</li> </ul> </li> <li>▪ Receptor binding only</li> </ul>	<ul style="list-style-type: none"> <li>▪ Made using mammalian cells                             <ul style="list-style-type: none"> <li>▪ Mixture of variants</li> </ul> </li> <li>▪ Four chains, 1330 amino acids                             <ul style="list-style-type: none"> <li>▪ 144,000 Da</li> </ul> </li> <li>▪ Receptor binding, effector functions</li> </ul>

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.



# 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)



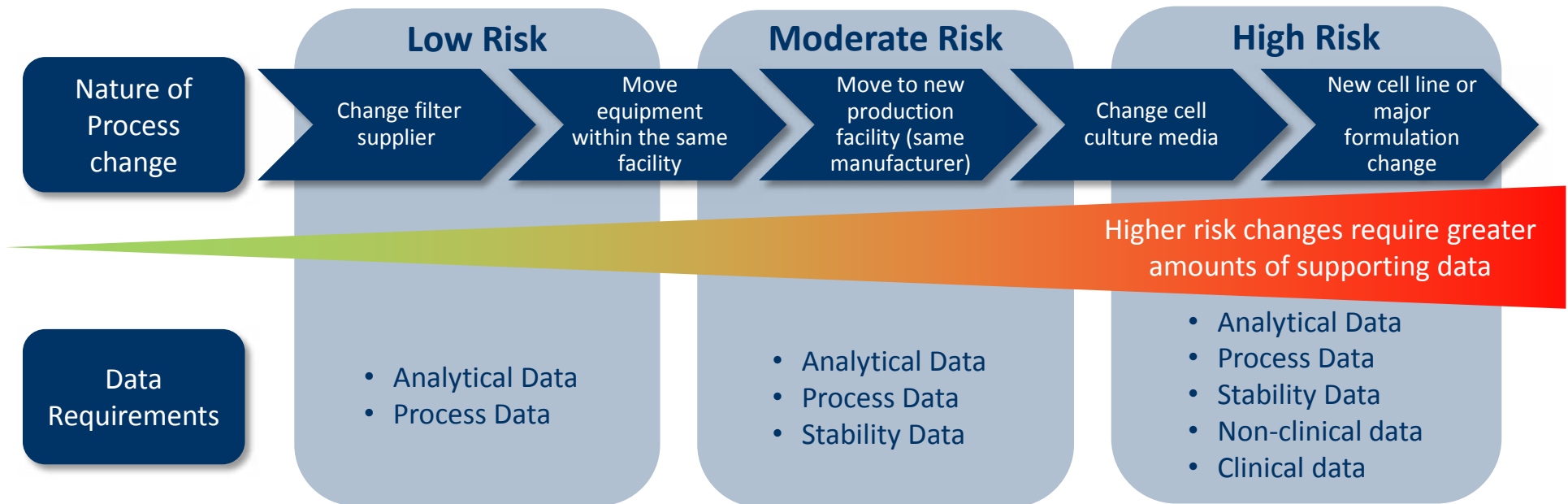
**Formulate to stable finished drug product**  
Vial, syringe, cartridge

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

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# Impact of manufacturing changes

- Manufacturing changes can create variability in the biologic molecule

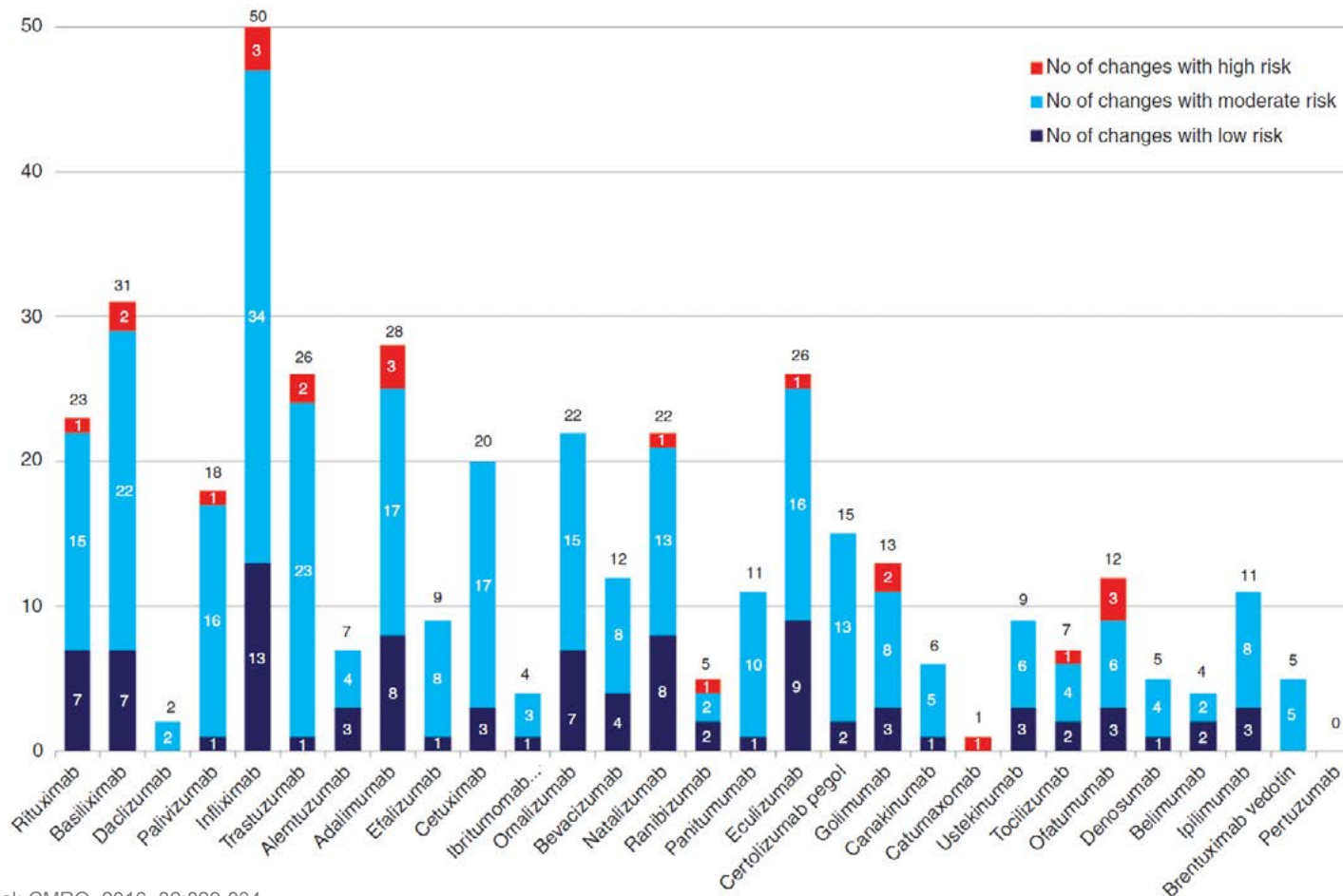


Adapted from Lee J, Litten J and Grampp G, CMRO, 2012; 28:1053-1058

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# Variability is in the nature of biologics

- Manufacturing changes are tightly regulated

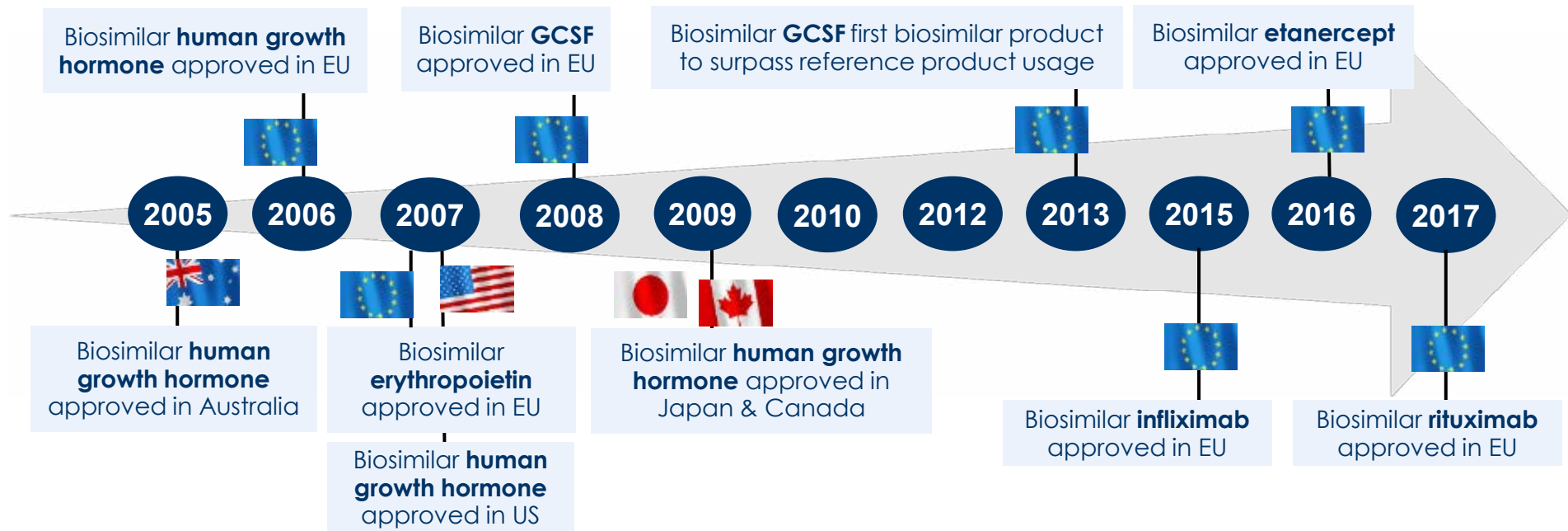


Vezér B, Zrubka Z et al; CMRO, 2016, 32:829-834  
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# What are biosimilars?

# 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<sup>1,2,3</sup>
- 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](http://www.medicines.org.uk/emc)

## Biosimilar-a regulatory term

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



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

*“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](http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf) last accessed March 2017

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# How are biosimilars developed?

## Biosimilars are highly similar to reference biologic

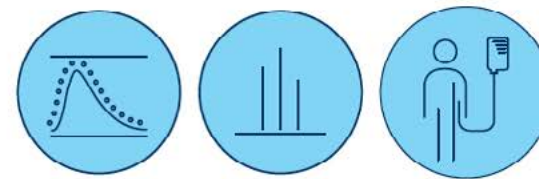
- Biosimilars are approved biologics that have been demonstrated to be highly similar to a reference product

### 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

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](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf) [Accessed 2016 March 18];

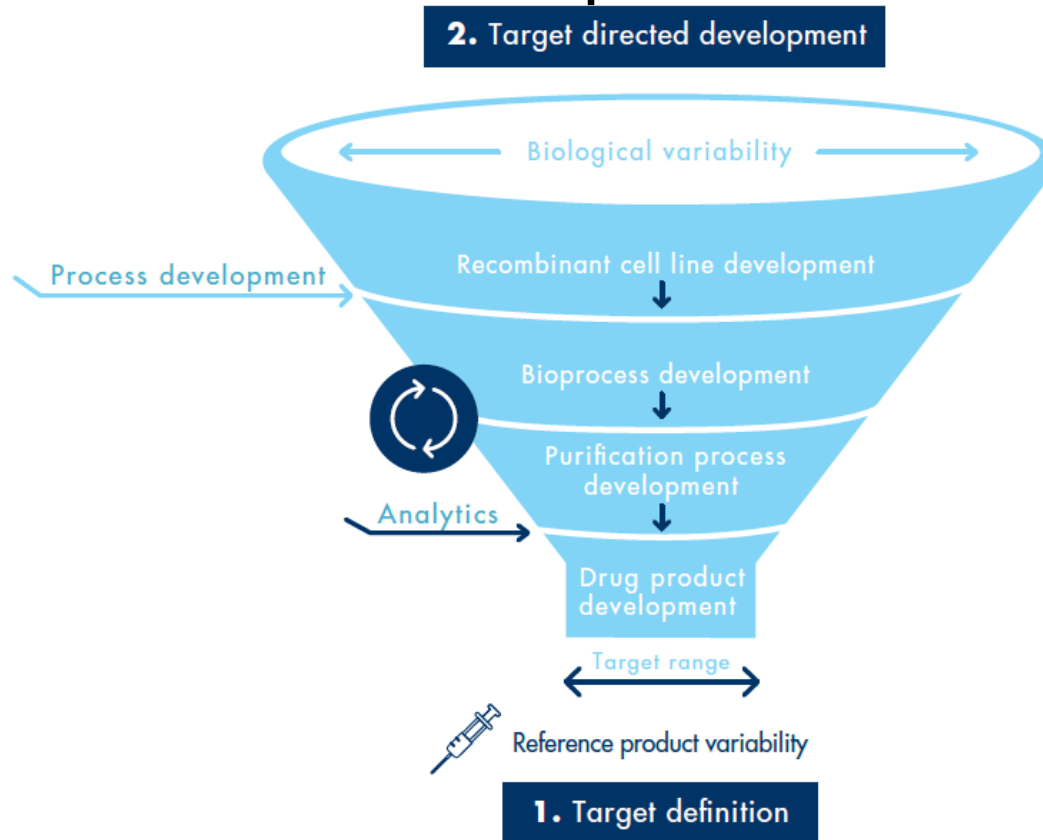
US Food and Drug Administration. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product 2015 [online]. Available from URL: [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf) [Accessed 2016 March 18].

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# Biosimilars are made to match

- Biosimilars are systematically developed to match the reference product

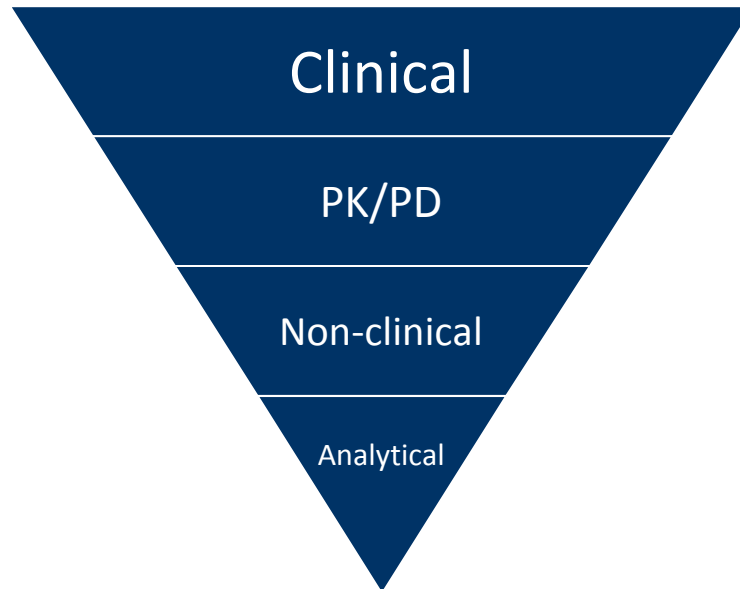


Adapted from McCamish M & Woollett G 2011. MAbs;3(2): 209–17.

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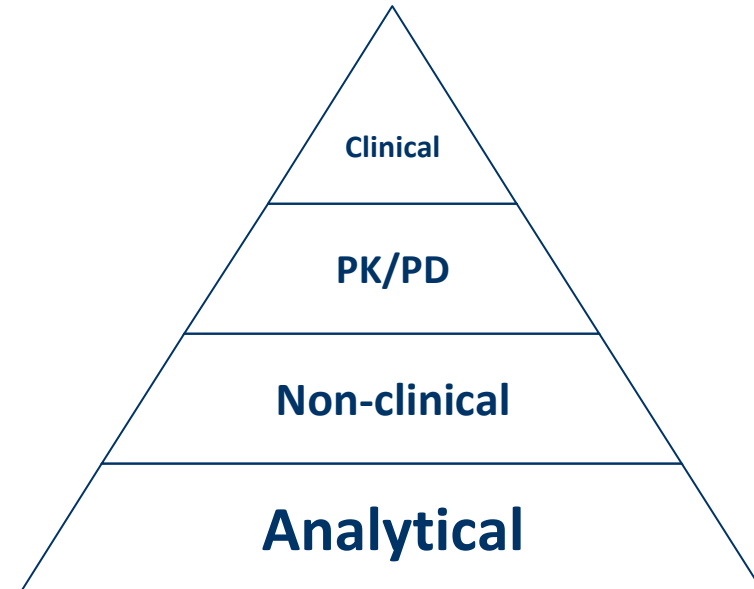
# Differences in development

## 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

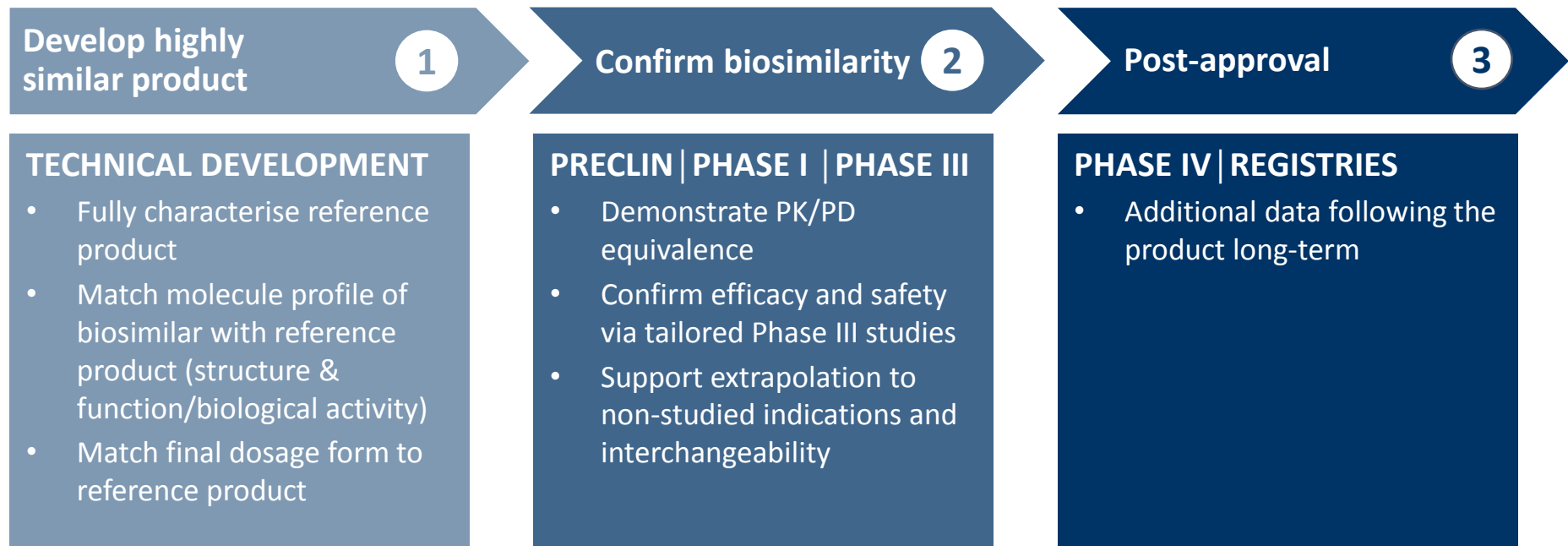
# Development approach for biosimilars is closer to originators than to generics

	Generic	New biologic	Biosimilar
 <b>Time to market (years)</b>	2–3	8–10	7–8
 <b>Clinical studies</b>	Bioequivalence studies in healthy volunteers	Phase I, II, III efficacy and safety studies	Comparative phase I pharmacokinetic and Phase III study
 <b>Patients (n)</b>	20–50	800–1000	~500
 <b>Post-approval activities</b>	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.

# Development process

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



McCamish M & Woollett G. Clin Pharmacol Ther 2010;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)

# 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

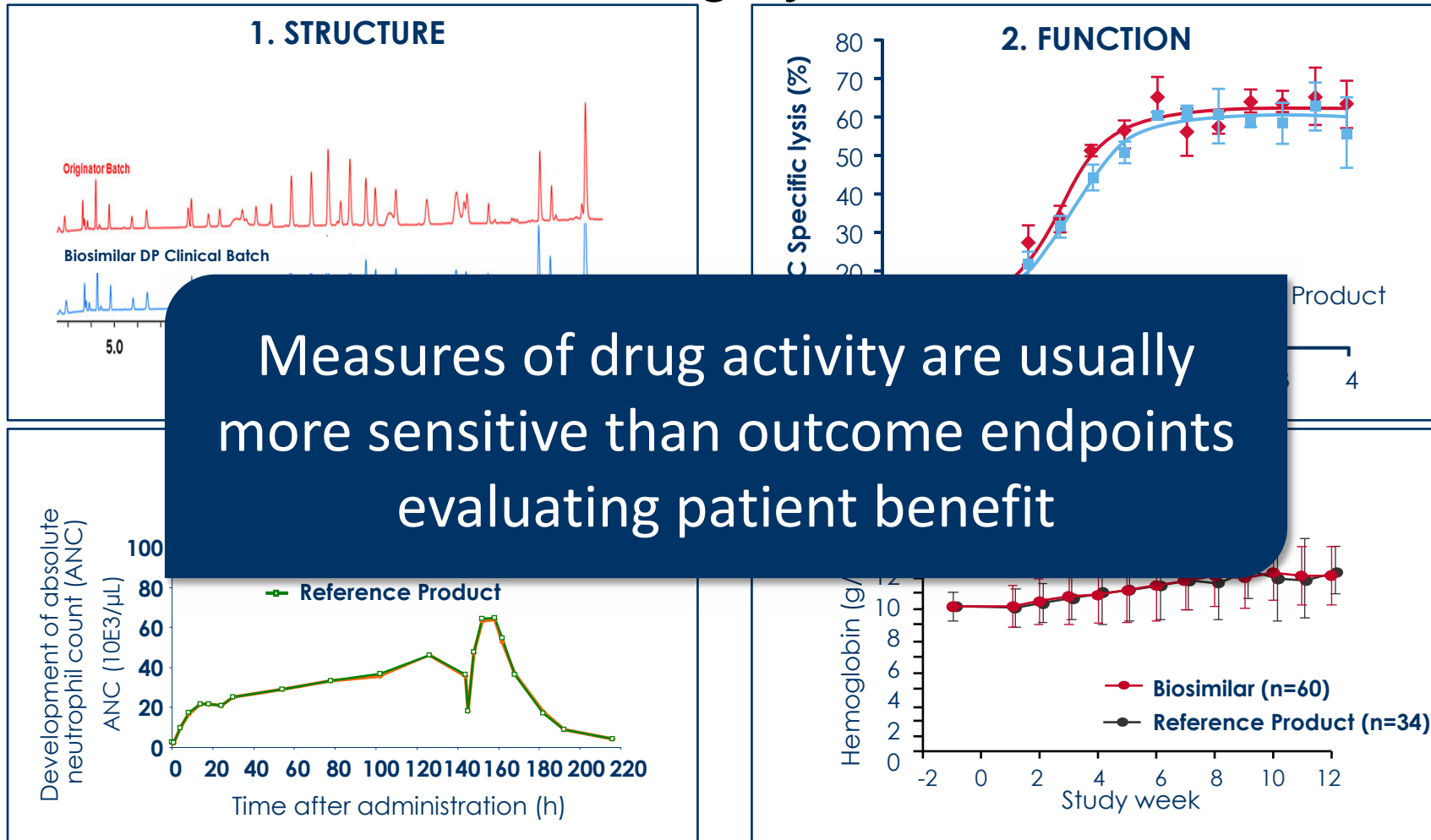
## COMBINATION OF ATTRIBUTES:

- MVDA, mathematical algorithms

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

# Totality of the evidence

- Biosimilars must be highly similar at all levels



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 UK/MKT/SDZ/17-0027d(1) Mar 2017

## 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](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/11/WC500154186.pdf) access March 2017

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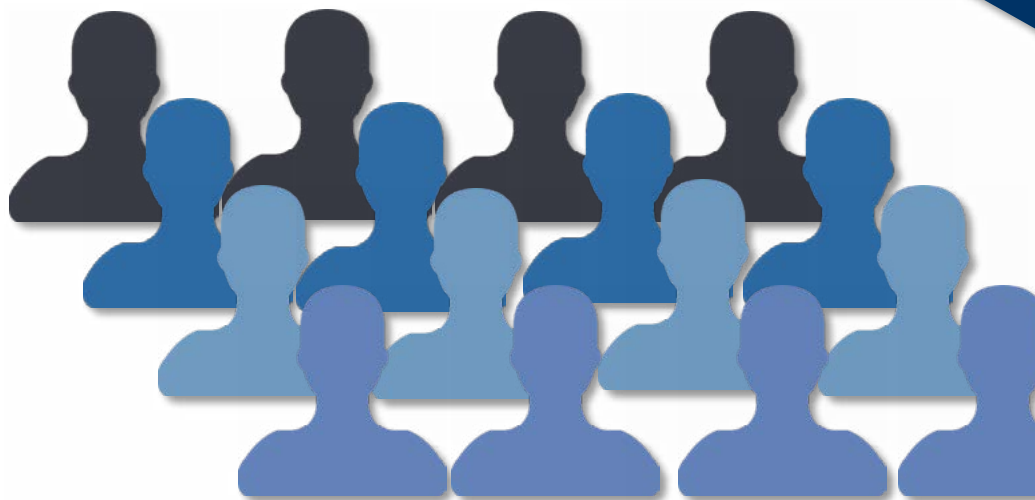
## Patient populations

- 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**



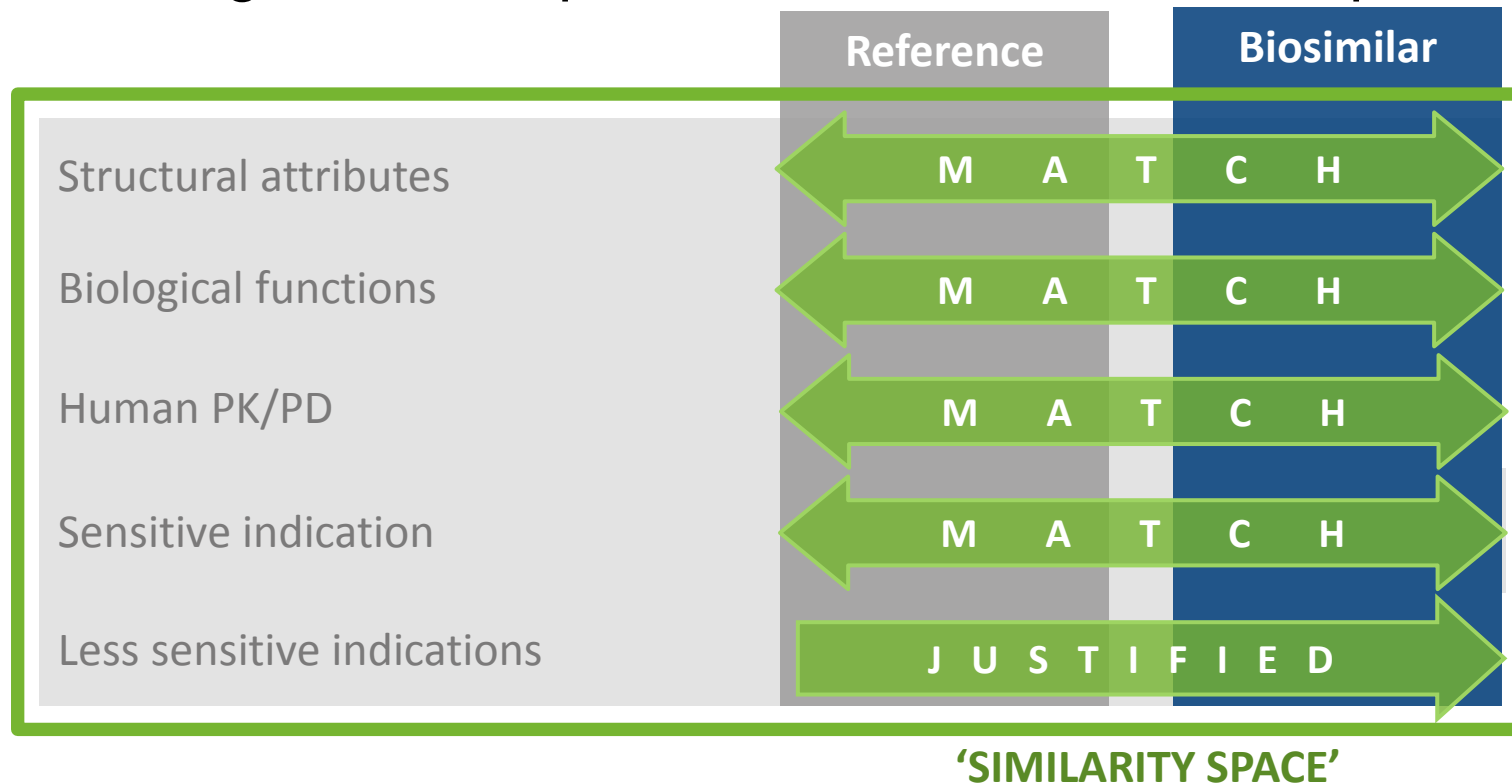
Homogenous populations have:

- Fairly consistent disease activity
- Less disease/patient confounders
- Minimal interpatient variability

**This means smaller sample sizes can be used**

# 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](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

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# 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<sup>1</sup>

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

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# Questions?

## Patient Information Leaflet – Suggestions for Use

### Description

This leaflet is a 2 sided piece.

### **Side 1**

The first side is a general description about biosimilars. It aims to reassure and explain to patients, who are to be changed from a reference biologic to one of its biosimilars, the following:

- What a reference biologic means
- What a biosimilar is
- Some reassurance about how biosimilars are developed and licensed

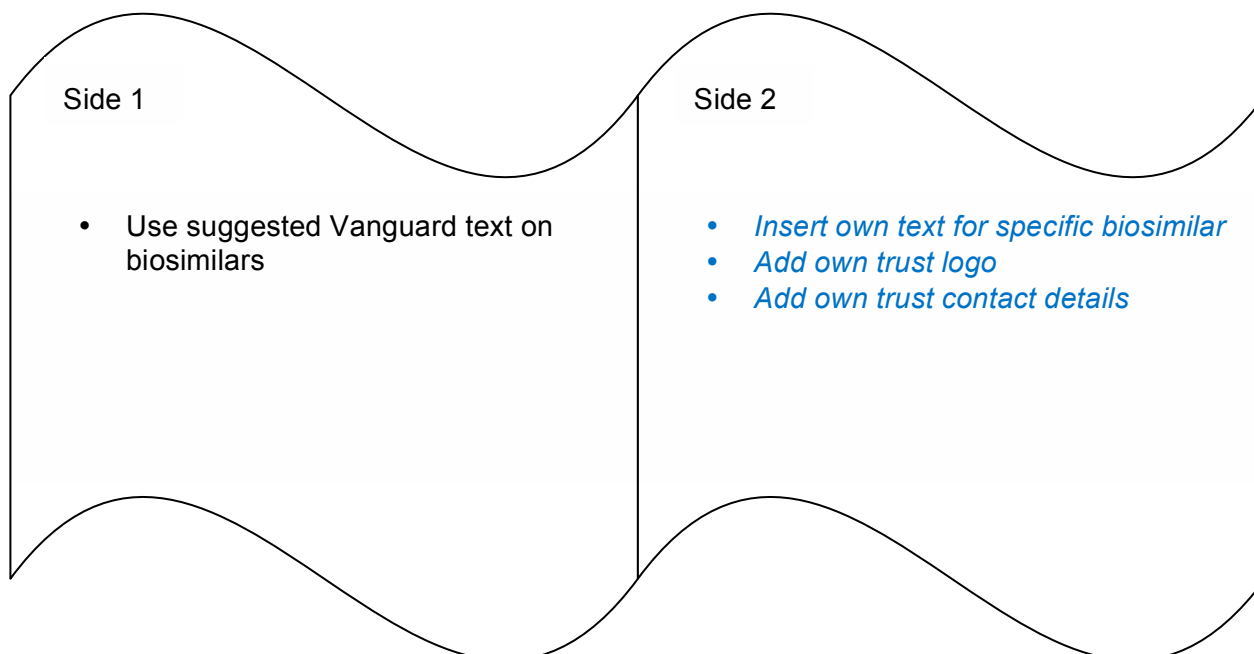
This description has been written by pharmacists from the Cancer Vanguard sites and approved by the wider Cancer Vanguard Biosimilar Adoption steering group. It has also been reviewed by the Royal Marsden Hospital patient information standards team.

### **Side 2**

The second side is intended for trusts to adapt for their own use to help uptake of any specific biosimilar through patient education.

Trusts may add their own logos and contact details having passed the document through their own PALS or information standards, where needed.

### How to Use



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### General Biosimilar Information Leaflet For Patients Changed from Biologic to Biosimilar

One of the medicines your doctor has previously prescribed you is called a biologic medicine. Instead of this biologic, your hospital now uses a biosimilar. This leaflet will help you understand more about biologic and biosimilar medicines, but if you have any questions please ask your pharmacist, nurse or doctor.

#### **What is a biologic?**

Biologic medicines are made by living cells in a controlled way, rather than being built as synthetic chemicals like regular medicines, such as tablets. Think of them in the same way that bread or yoghurt is made using living cells. The original biologics were first used to treat people with serious illnesses in the UK over 20 years ago and they have improved life for millions of people worldwide.

#### **What is a biosimilar?**

You may have heard of some medicines you take described as generics, for example supermarket own brand ibuprofen is the generic version of Nurofen<sup>®</sup>. Generics are exact copies of the original medicine and are relatively simple to copy and manufacture. The same idea applies to biosimilars, but it is not possible to make an exact copy of an original biologic medicine due to their size and the complex way they are made. Biosimilars are highly similar to the original medicine but not identical. They have been thoroughly tested to show no difference in terms of how the medicine works, its effectiveness and safety.

#### **How can I be confident that it will work the same?**

The companies that make biosimilars have to show the licensing authority very strict evidence of their effectiveness, safety and quality. Clinical studies have to be conducted in a large group of people to show that the medicine works just as well and is just as safe as the original biologic.

Biosimilars take several years and cost many millions of pounds to develop and prove that they work in the same way to the original medicine. This is another way biosimilars are different to generics. Generics do not need studies in people with disease and take much less time and money to develop.

#### **What are the benefits?**

You can expect to have the same results from your biosimilar as if you'd had the original medicine. Sometimes it is provided in a new device such as an injection pen or with a bigger range of strengths to make it easier for you to use.

There is a benefit to the NHS too. Biosimilars are usually provided at a much lower price than the original biologic. This helps the NHS provide complex medicines at better prices and improve treatment for people with conditions like yours.

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BLANK FOR YOUR OWN BIOSIMILAR TEXT

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## Cancer Vanguard

### Biosimilars Trust Policy – Template

#### Aim of this document:

*The document provides generic guidance and outline for the development of local trust policies in relation to the adoption of biosimilars in trusts. All trusts work in slightly different ways and have different processes with the goal of achieving similar outcomes. The document aims to highlight key points in the use and adoption of biosimilars, which can then be developed and adapted to individual trust needs and processes as appropriate. The focus of the template is on haematological and solid tumour biosimilars, however it can be adapted to biosimilars used in all therapy areas. The policy is seen as an overarching policy which will link into specific SOPs for individual biosimilar medicines.*

#### Summary:

##### What are biologics?

Medicines that are made or derived from a biological source and as such are complex with inherent variability in their structure. As biological medicines are derived from living cells or organisms there is always a small degree of variability in the manufacturing process, thus biologics may show a degree of variation from batch to batch of the product. This is also the case for biosimilars.

##### What are biosimilars?

Biosimilars are highly similar to the biological originator medicine (already licensed), shown by non-clinical studies (*in vivo and in vitro analysis*) and clinical studies to show no clinically meaningful differences from the originator biological medicine in relation to quality, safety and efficacy.

**To note:** Biosimilar medicines are **not** considered as generic to the originator biological medicines the two are “similar” and not identical. However in relation to licensing they have met stringent regulatory requirements based on a comprehensive scientific comparability exercise such that they do not have any clinically meaningful differences from the reference medicines in terms of quality, safety and efficacy.

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## 1. Background & scope

The policy has been developed in line with recommendations *[insert detail here, this may include different organisation e.g. Cancer Vanguard Guidance, BOPA position statement on biosimilars, NICE & others]*.

The use of biosimilars in cancer is set to increase exponentially in the next few years as patents of originator biologics expire. The adoption of biosimilars will help provide much needed savings to the NHS, which may be utilised to further benefit patient care (however introduction should not be driven purely by financial considerations). The purpose of the policy is to aid this early adoption process in order that the benefits can be realised early. The use of biosimilars will not alter the care provided to patients, with the patient seeing no change in the treatment experience.

Detailed guidance will be provided on the following topics:

- Adoption process for biosimilars including:
  - Considerations prior to adoption
  - Approach to homecare if required
  - Existing versus New Patients
  - Governance requirements and local approval
  - Informing and involving patients in introduction
  - Prescribing requirements
  - IT readiness
  - Pharmacovigilance and monitoring
  - Clinical outcomes monitoring
  - Tracking of any savings

The policy is overarching and should be used in conjunction with individual SOPs developed for the introduction and use of specific biosimilars at the trust.

## 2. Definitions:

**Biological medicine** – medicine derived from living cells or organisms, consisting of large highly complex molecular entities which may be difficult to characterise.

**Biosimilar medicine** – a biological product that is highly similar but not identical, to the licensed originator biological medicine and shows no clinically meaningful difference in terms of quality safety and efficacy.

**Generic medicine** - is identical or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use.

**Extrapolation** – the decision by the Regulator whether to extend the efficacy and safety data from an indication for which a biosimilar has been clinically tested to other conditions for which the reference product is approved.

**Interchangeability** – the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative or with the agreement of the prescriber.

## 3. Duties & Responsibilities

This policy applies to medical, nursing, pharmacy staff and other key staff involved in any aspects of providing biosimilar medicines to patients.

### Lead Consultant (and clinical team)

- Support the proposed biosimilar introduction, in the agreed patient groups and endorse the DTC submission on behalf of the clinical unit
- Carry out initial patient consultation with patients in lead up to biosimilar medicine adoption (see also specialist nurses and pharmacists)

### Pharmacy Department

- Coordinate and manage an effective implementation programme
- Specialist and unit pharmacists to be able to provide information on biosimilars to HCPs and patients
- Provide required detail for management of trust prescribing systems and aseptics unit work sheets (if required)
- Reporting on uptake of the biosimilar medicine following any biosimilar introduction and reporting financial savings realised from adoption
- Procurement of the selected biosimilar

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- If the biosimilar is to be delivered via a Homecare delivery service, coordination and requirements of a biosimilar introduction will need to be considered

### **Specialist nurses and specialist pharmacists (who have direct involvement with relevant patients)**

- Carry out initial consultation with patients in lead up to biosimilar medicine adoption
- Be available to answer patient questions and provide information regarding biosimilar medicines to patients and other HCPs should it be required

## **4. Core elements:**

### **Introduction of a new biosimilar**

*This section provides potential requirements to be taken into consideration when reviewing initial adoption of a biosimilar.*

#### **4.1 Considerations to be taken prior to adoption**

##### **General:**

*Points to be included in policy should include:*

- Does the biosimilar have the required licensed indications?
- Anticipated launch date and supply chain details
- Patient groups to be included:
- Adult and paediatric setting? Will the biosimilar be intended for all indications or only specific indications?
- Process to be adopted:
  - to be introduced by the Trust for existing patients
  - to be introduced by the Trust for new patients
  - both of the above
- Are the biosimilar presentations i.e. strengths, concentration & preparation the same as for the originator?
- Are the biosimilar stability once prepared and storage conditions the same as the originator?
- Are the biosimilar administration requirements the same as for the originator i.e. route and duration of administration?
- Are the required clinical outcomes data available prior to review by the trusts DTC?
- Are a number of biosimilars medicines for the same originator biological medicine anticipated to be launched around the same time by different manufacturers? If so a decision will need to be made on which will be adopted, and when, with an aim to avoid

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further changes in the short-term which may introduce risk and damage patient confidence (see also section 4.10 pharmacy purchasing).

- Possible resource implications of the adoption process. These may include:
  - patient counselling requirements
  - MDT education and training requirements
  - possible administration route change e.g. SC to IV
  - possible administration duration change
  - is the biological medicine given in the Homecare setting and will this have to be reviewed (e.g. for initial dosing or patient self-administration training)

## 4.2 Internal governance requirements

- DTC submission as per local requirements. The submission should include points highlighted in 4.1.

## 4.3 Commissioner position

Prior to undertaking the change from originator biological medicine to a new biosimilar medicine, the position of the commissioner e.g. NHSE should be sought, with adoption meeting the requirements of any NHSE initiative such as CQUINs within the required timeline.

## 4.4 Informing and involving patients in introduction

- Local decision on requirement to inform new patients once the biosimilar has been approved and adopted at the trust. For new patients this is not a change but a recommended treatment by a clinician.
- Required at point of initial adoption to inform and educate currently-treated patients. How this is carried out will be dependent on the biological medicine in question e.g. how often it is prescribed, in what setting it is given (IP, OP, or Homecare), and how the clinics are set up.
- Possible methods for informing and involving patients may include:
  - focus groups prior to adoption
  - one to one patient consultation by trained clinician, nurse or pharmacist in lead up to the adoption (feasibility will be dependent on how the clinic is coordinated at the trust)
  - the utilisation of a patient information leaflet with Q&A section and contact details of relevant HCP if patients wish to discuss further
  - patient letter to be sent out to patients explaining:
    1. the planned change

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2. how the decision has been undertaken
3. that clinical efficacy and safety have not been affected
4. that significant financial benefits will be achieved for the NHS and/or the Trust.

## 4.5 Prescribing requirements & interchangeability

It is recommended that biosimilar medicines be prescribed by brand name for example, “International Non-proprietary Name (INN) (Brand name®)” i.e. “Filgrastim (Zarzio®)” (see section 4.6. for electronic prescribing systems).

Prescribing by brand reduces the risk of one biosimilar brand being substituted for another without a review and due consideration by the prescribing clinician/team. This does not mean that a biosimilar medicine cannot be changed from one brand to another, however this needs to be done as part of a clinically led management process.

Biosimilars are interchangeable. Interchangeability is the practice of changing one medicine for another that is expected to achieve the same clinical effect. The decision to interchange is one that again requires review and due consideration by the prescribing clinician/team and approval via the local DTC.

Batch number must also be recorded as with all biologic medicines in case of requirement to report an ADR (*a local process dependent on prescribing systems should be adopted to ensure this*).

## 4.6 IT readiness

*Points to be included in policy should include:*

- If the originator biological medicine and biosimilar are both to continue to be used at the trust (e.g. in change over period or for different indications) the pharmacy systems clearly need to differentiate between the two (i.e. is brand name in the profile name). Systems will include dispensing and in some cases aseptic unit systems.

## 4.7 Patient Registration and consultation/ shared decision making

Following the adoption of a biosimilar at the trust it will be a local decision on how patients need to be consulted if a biosimilar change is to take place mid treatment. All new patients will follow the standard consent process as with the reference originator medicine.

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## **4.8 Pharmacovigilance and monitoring**

All biological medicines require additional monitoring for safety and any suspected adverse drug should be reported using the MHRA yellow card scheme, with the provision of the brand and the batch number.

## **4.9 Clinical outcomes monitoring**

As with all biologic medicines collection of clinical outcomes should take place, and after an agreed time period assessed to ensure quality of outcomes.

## **4.10 Monitoring patient satisfaction.**

A patient experience survey in the form of a short questionnaire may be carried out pre and post implementation of biosimilar to ensure that the patient experience has not been negatively impacted following the introduction of the biosimilar medicine. The finding may also assist in supporting future biosimilar adoptions if shared with patients and MDTs.

## **4.11 Pharmacy Purchasing requirements**

Close liaison with regional procurement leads should take place, in order to keep up to date with new biosimilar medicines:

- anticipated launch dates
- planned tenders and timelines
- product specifications
- pricing information

## **4.12 Tracking of savings and biosimilar adoption rate**

Following implementation of a biosimilar medicine tracking of:

- the drug acquisition cost savings should be monitored and recorded on a monthly basis to calculate savings achieved from the change (see appendix 3. for example).
- breakdown of:
  - number of new patients on the biosimilar
  - number of patients changed to the biosimilar medicine part-way through current treatment, for the approved indication
  - reasons identified for those patients that have not been changed
  - metrics and indicators in line with any NHSE requirements e.g. Medicines Optimisation and CQUINs

## **4.13 Evaluation of Service impact on the Trust of adopting a biosimilar**

Data should be collected through-out the change process in order to ascertain the resource impact of adopting the biosimilar in both new and mid-treatment change patients (*refer to Service impact tool on Biosimilar adoption process time line for further information*).

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*(papers utilised to complete this guidance & may further assist in development of local guidance):*

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## 6. Linked documents

*This will be different for individual trust and may include:*

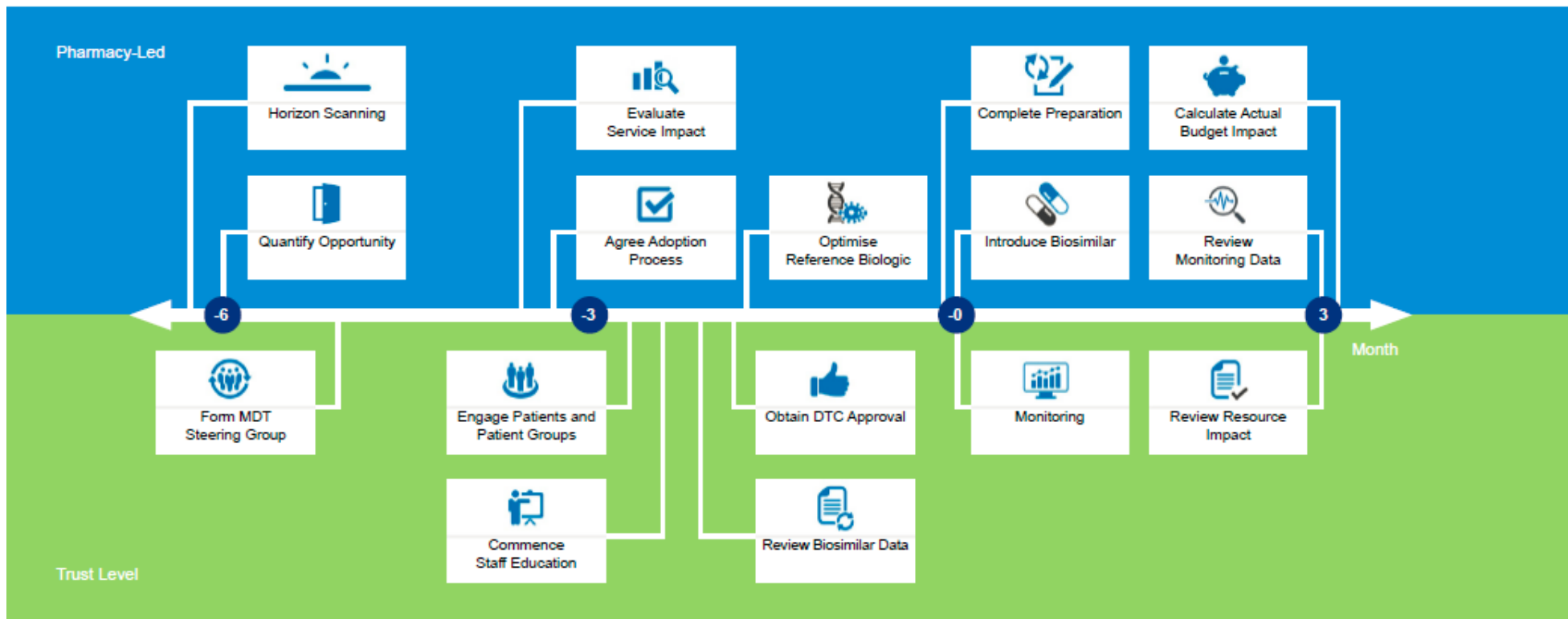
- Standard Operating Procedures for individual biosimilars
- Medicines Management Policy

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## Appendix 1. Biosimilar Adoption Process Timeline

### Biosimilar Adoption Process Timeline



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## Appendix 2. Biosimilars uptake tracker requirements

*(to note NHSE may provide a tracker in relation to any CQUIN requirements).*

The tracker will be used to provide details of biosimilar uptake and any associated savings made. Data from the tracker can be used to assist in reporting that CQUIN requirements on a local or national level have been met. It should initially be completed on a monthly basis. Once the adoption process has stabilised following initial uptake this may go to a quarterly review, although this should be agreed locally.

From initial adoption the tracker can be used to gauge success of the adoption programme, and predict when uptake by all patients anticipated to receive the biosimilar will be achieved. Detail of reasons why patients may not be receiving the biosimilar can be also be ascertained.

Information that should be tracked includes:

- Indication for which biosimilar has been approved for use\* (if more than one possible indication for use)
  - Number of vials of biosimilar used per month
- OR**
- Number of mgs (or other mass unit) used per month (if manufactured by a 3<sup>rd</sup> party provider)
  - Number of patients treated using biosimilar
  - Number of vials of originator biologic used per month (for same indication\*)
- OR**
- Number of mgs (or other mass unit) used per month (if manufactured by a 3<sup>rd</sup> party provider)
  - Number of patients treated using originator biologic

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## Biosimilars- Frequently Asked Questions

### 1. What is a biologic?

A biological medicine (commonly referred to as a “biologic” or “biopharmaceutical”) is a medicinal product made by or from living organisms, tissues, or cells and contains a biological active substance.<sup>1</sup> Most biological medicines in clinical use contain active substances made of proteins, they are often large, complex molecules. Common biologics, such as monoclonal antibodies, are typically 1000 times heavier than a small molecule such as ibuprofen<sup>2</sup>. Because of this complexity, their manufacture can only be done in living cells, not through chemical synthesis like most small molecules. Accordingly, they are difficult to make, and difficult to copy with EU legislation stipulating strict manufacturing requirements.

### 2. What is a biosimilar?

Medicines in Europe are regulated and approved by the European Medicines Agency (EMA). “Biosimilar” is a term that the EMA uses to designate that a medicine has been certified for use by a particular approval route. The correct use of this term is only with reference to biologics that have been approved in highly regulated markets, such as Europe, the United States, Australia, Canada or Japan, and that meet strict criteria of quality and comparability to their respective reference biologics.<sup>3-14</sup>

A biosimilar is a medicine highly similar to another biological medicine already marketed in the EU (the so-called ‘reference medicine’). Approved biosimilar medicines can only be marketed once the period of market protection (patent) of the reference medicine expires.

To be approved by this route the EMA defines a biosimilar as “a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product)”.<sup>3</sup> The EMA lists the following specific features of a biosimilar medicine<sup>15</sup>

- **Highly similar to the reference medicine**

The biosimilar has physical, chemical and biological properties very similar to the reference medicine. There may be minor differences from the reference medicine which are not clinically meaningful in terms of safety or efficacy. A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

- **No clinically meaningful differences compared with the reference medicine**

No differences are expected in clinical performance. Clinical studies that support the approval of a biosimilar confirm that any difference will not have an effect on safety and efficacy.

- **Variability of biosimilar and reference medicine kept within strict limits**

Minor variability is only allowed when scientific evidence shows that it does not affect the safety and efficacy of the biosimilar. The range of variability allowed for a biosimilar is the same as allowed between batches of the reference medicine. This is achieved with a robust manufacturing process to ensure that all batches of the medicine are of proven quality. When approved, its variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.<sup>16, 17, 18, 19</sup>

- **Same strict standards of quality, safety and efficacy**

Biosimilars are approved according to the same strict standards of quality, safety and efficacy as for any other medicine. By definition, biosimilars are required to have an identical amino acid sequence, the same route of administration and strength as the reference medicine.

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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.

### 3. What is a biomimic?

Biomimics, also called “non-comparable biologics”, “biocopies”, “intended copies”, or “non-regulated copies”, are copies of biological reference medicines that do not meet the strict regulatory requirements for biosimilar approval, such as those set up by the WHO, EMA or FDA, but are being marketed in some countries. These compounds do not fulfil the definition of a biosimilar.<sup>3-7</sup>

### 4. How are biosimilars developed?

The development of biosimilars is a systematic process with two key stages. The first stage consists of the thorough characterisation and understanding of the reference medicine (the “target”) which forms the basis of the target-directed development of a biosimilar. The second stage establishes biosimilarity between the proposed biosimilar and the reference medicine in a stepwise approach, the so-called comparability exercise.

### 5. Why isn't a biosimilar a generic medicine?

A biosimilar is not regarded as a generic of a biological medicine because the natural variability and more complex manufacturing of biologics do not allow an exact replication of the molecule. More studies are required for a biosimilar to be approved than for a generic medicine. For example; quality studies comparing the structure and biological activity of the biosimilar with the reference medicine, demonstration of biosimilarity using comprehensive comparability studies and clinical data in a sensitive indication. Owing to their complexity and rigorous scientific evaluation, biosimilars are much more costly and take longer to develop than traditional generic medicines – taking up to 8 years and upwards of \$300million vs. \$3million in investment to develop<sup>20</sup>.

### 6. How are biosimilars approved?

The EMA will approve a proposed biosimilar only if they are convinced that the presented “totality of evidence” is both substantial and sensitive enough to demonstrate that the biosimilar matches the reference medicine and that there are no clinically meaningful differences in terms of purity/quality, efficacy/potency and safety<sup>3,4</sup> “Totality of evidence” is a term used to describe the results of the entire development program for a biosimilar and involved data from analytical, preclinical and clinical studies. The non-clinical and clinical data needed to approve a biosimilar are different from those needed for a biological medicine with a new active substance. The biosimilar relies on the safety and efficacy experience gained with the reference medicine.

This is achieved with comprehensive comparability studies and pharmaceutical quality data. Comparability is a well-established scientific principle of regulatory science used after manufacturing changes to biologic medicines during their commercial life. Comparative trials are designed to confirm biosimilarity and clinical performance; they do not need to repeat all the pivotal studies to the reference medicine to prove safety and efficacy in humans but are designed to rule out clinically relevant differences in safety or efficacy between the biosimilar and the reference medicine and to confirm biosimilarity.

### 7. What is extrapolation?

Extrapolation is the scientific and regulatory process of granting a clinical indication to a medicine without conducting a clinical efficacy and safety study to support that indication.<sup>9</sup> Extrapolation is a well-established principle that is applied to all biologic medicines, reference or biosimilar, if they undergo a major change in their manufacturing or a change in formulation. To confirm the biologic remains as safe and effective after the change, clinical data may be required by the regulatory authority. These are

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typically generated in one indication and then, taking into account the overall information gained from the comparability exercise, extrapolated to the other indications.<sup>9</sup>

This process is also applied to biosimilars in their licensing. After a full characterisation of the molecule in both *in vitro* and pre-clinical settings, where it must be proven to be equivalent to the reference medicine, clinical trials are conducted to confirm the analytical work already completed. The clinical trial populations are carefully chosen and confirmed with the regulatory agencies in order to demonstrate the critical attributes of the biosimilar molecule are equivalent to the reference medicine. Since the aim of these studies is to confirm comparability of the molecules and not to prove that the biosimilar works in every disease state, as this has already been demonstrated by the reference medicine, the number of studies that are required is less and the data can be extrapolated to indications not studied.

## 8. Can biosimilars be used with the same confidence as the reference medicine?

Yes. Authorised biosimilars are as safe, and efficacious as their reference medicines.<sup>11</sup> Safety monitoring of biosimilars follows the same requirements that apply to all biological medicines<sup>21</sup> for example collecting spontaneous ADRs and submitting PSURs and as with all new biological medicines additional monitoring is in place indicated by the black triangle.

The European commission (EC) has expressed its confidence in the quality of biosimilars. Their 2013 consensus document “What you need to know about biosimilars” states that “biosimilar medicinal products have been used safely in clinical practice in the European Union since 2006”.<sup>18</sup> Over the last 10 years the EU monitoring system for safety concerns has not identified any relevant differences in the nature, severity or frequency of adverse effects between biosimilar medicines and the reference medicines over 400 million patient days of experience<sup>22</sup>.

## 9. Why aren't biosimilars 100% identical with their reference medicine?

All biologics, be it the biologic reference medicine or the biosimilar, are made by living organisms which are naturally variable and so have a certain inherent degree of minor variability of the biologic system (“microheterogeneity”). This minor variability must fall within the acceptable range to ensure safety and efficacy during the manufacturing process.

Because of microheterogeneity, two biologics produced in isolation of one another cannot be identical, not even two batches of any biologic - reference medicine or biosimilar - are formally 100% identical.<sup>15,16</sup> This may happen because the manufacturing processes are modified during the commercial life of the biologic medicines but importantly, this inherent variability can be detected using sensitive analytical tools and is tightly controlled during the manufacturing process, with limits and specifications agreed with the regulatory authorities to ensure the consistent safety and efficacy of the biologic and the biosimilar.

## 10. Is the immunogenicity of biosimilars different from the reference medicine?

No. Immunogenicity, the ability of particular substance to provoke an immune response, must be equivalent.<sup>23</sup> A biosimilar will not be approved if there are any doubts that the immunogenicity is not comparable to the reference medicine, as a biosimilar must be equivalent in terms of safety.<sup>4, 10, 24, 25</sup>

Many biological medicines are intended for long term management of chronic conditions and difference biologicals with slight differences may be used over time. A harmful immune response is unlikely after a manufacturing process change because comparability studies prove that the batch from the new process is of the same quality and free of impurities or aggregates that can trigger immunogenicity. Similarly, harmful immunogenicity is unlikely after switching between biologicals<sup>26</sup>

## 11. Are biosimilars less effective because they are cheaper?

No, biosimilars must be just as effective as their respective reference medicines.<sup>11</sup> They are less expensive than the reference biological because they benefit from a tailored clinical development and the option for extrapolation of indications. Therefore, biosimilars have a less cost-intensive overall development programme.<sup>17</sup> This is the main reason they can be marketed at a lower price.

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## 12. Why are biosimilars prescribed by brand name?

It is important for traceability that all biological medicines, including biosimilars, can be identified by trade name (brand name) and batch number. This is particularly important in cases where more than one medicine exists on the market with the same INN. In line with EU requirements for ADR reporting, this ensures that any biological medicine can be identified, if any product specific safety concern arises.

## 13. What is switching?

Switching is the decision of the treating physician to exchange one medicine for another medicine, with the same therapeutic intent, in patients who are undergoing treatment.<sup>18</sup> For example, transitioning the patient from the reference medicine to the biosimilar.

Switching is a vernacular term that is not defined in law or regulations. In the UK any decision to transition a patient from one biological medicine to another, including a biosimilar (or vice versa) should involve the prescriber in consultation with the patient.

## 14. Is switching of patients who are treated with a reference medicine to a biosimilar medicine (and vice versa) safe?

No medicine can be considered as safe. Biosimilars are developed to be highly similar to their respective reference products and are approved only if they are proven to be as safe and as effective as the reference molecule. They must have no clinically meaningful differences in terms of safety, efficacy or quality. Under guidance of a physician; a treating physician is the best suited individual to make this decision, patients treated with a reference product can be safely transitioned to a biosimilar. Based on the currently available data, switching between a biosimilar and its reference biologic does not appear to impact efficacy/safety, immunogenicity or traceability in case of an adverse event. Traceability pertains to whether the adverse event has been caused by the reference medicine or the biosimilar.<sup>27-40</sup> Transitioning patients should involve the prescriber in consultation with the patient.

## 15. What is interchangeability?

From a regulatory perspective, different definitions and requirements for interchangeability apply across geographies. In the EU, interchangeability describes the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.<sup>18</sup> In the EU, the regulation of interchangeability is governed by the individual EU Member States.

## 16. What is substitution?

For any medicine, including biosimilars, there are two different types of substitution that can occur: automatic substitution and substitution. Automatic substitution is the practice of dispensing one medicine, instead of another equivalent and interchangeable medicine, at the pharmacy level without consulting the prescriber.<sup>41</sup> Substitution is the practice of dispensing one medicine, instead of another equivalent and interchangeable, with consultation of the prescriber. In Europe, the EMA has left the decision of automatic substitution and substitution to the decision of individual member states. In the UK automatic substitution of biological medicines, including biosimilars, is not permitted. Prescribing by brand name reduces the risk of one biologic brand being automatically substituted by the pharmacy for another, without a review and due consideration by the prescribing clinician.

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