Biosimilars: What, When and How
Things have got complicated…

<table>
<thead>
<tr>
<th>Simple Small Molecule</th>
<th>Small Molecule</th>
<th>Simple Biologic</th>
<th>Complex Biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Lipitor®</td>
<td>Insulin</td>
<td>Humira®</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 daltons</td>
</tr>
<tr>
<td>558 daltons</td>
</tr>
<tr>
<td>5,808 daltons</td>
</tr>
<tr>
<td>~148,000 daltons</td>
</tr>
</tbody>
</table>

![Molecular Structures](image)
Typical biologic - multiple variants

Even in a Single Protein Product There can be Multiple Product Variants

- Pyro-Glu (2)
- Deamidation (3 x 2)
- Methionine oxidation (2 x 2)
- Glycation (2 x 2)
- High mannose, G0, G1, G1, G2 (5)
- Sialylation (5)
- C-term Lys (2)

(9600)^2 \approx 10^8

2 \times 6 \times 4 \times 4 \times 5 \times 5 \times 2 = 9600
A complex process with multiple stages
Batch & process variation

Different Process or Different Batch = Different Product
Why do biologics change?

• There is unavoidable variation
  • Differences between batches
and there are
• Deliberate process changes
  • Lifecycle changes
  • Developmental changes
Batch-to-Batch variability
Manufacturing Process Changes

• Many factors drive these changes
  • Capacity (scale up or intensification)
  • Efficiency (site changes, facility modifications)
  • Technology (improve controls, reduce cost/risk)
  • Supplier changes and risk management
  • Regulatory trends (eg improve viral safety)
  • Pharmaceutics (improved formulations, containers, devices)
Process changes are the norm

The way biologics are manufactured has changed over time and continues to evolve.
Manufacturing Changes

EPAR changes according to risk category

No of changes with high risk
No of changes with medium risk
No of changes with low risk
Pre/Post Changes (2010) Rituximab
Process change → Comparability Exercise

Innovator Process Change
Governed by comparability guidance (ICH Q5E*)

Nature of Process Change
- Change filter supplier
- Move equipment within same facility
- Move to new production facility (same company)
- Change cell culture media
- New cell line or major formulation change

Risk Factor & Data Requirements
- Low Risk
  - Commonly implemented
  - Analytical data
  - Process studies
- Moderate Risk
  - Analytical data
  - Process studies
  - Stability data
- High Risk
  - Less commonly implemented
  - Analytical data
  - Process studies
  - Stability data
  - Clinical data

“Abbreviated” Comparability Exercise

“Comprehensive” Comparability Exercise
Generics vs. Biosimilars

Similar But

Not the Same

Biosimilar medicines, generic versions of biotech drugs, may not be exact duplicates.
Similar But

Not the Same

Biosimilar medicines, generic versions of biotech drugs, may not be exact duplicates
# Small molecules vs. Biologics

<table>
<thead>
<tr>
<th>Properties</th>
<th>Small Molecules (chemically based drugs)</th>
<th>Biologics (protein-based drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>Acetyl salicylic acid(^1) MW = 180 Da</td>
<td>Biologic monoclonal antibody MW = (\sim 150,000) Da(^5)</td>
</tr>
<tr>
<td>Size</td>
<td>Small(^2)</td>
<td>Large(^2)</td>
</tr>
<tr>
<td>Structure</td>
<td>Simple(^3) and well defined(^2,4)</td>
<td>Complex with many options for post-translational modification(^2)</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>Predictable chemical process; identical copy can be made(^2)</td>
<td>Each manufactured in a unique living cell line(^2) Similar but not identical copy can be made(^2)</td>
</tr>
<tr>
<td>Characterizations</td>
<td>Easy to fully characterize(^5)</td>
<td>Difficult to characterize fully due to a mixture of related molecules(^2)</td>
</tr>
<tr>
<td>Stability</td>
<td>Relatively stable(^2)</td>
<td>Sensitive to storage and handling conditions(^2)</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Lower potential(^2)</td>
<td>Higher potential(^2)</td>
</tr>
</tbody>
</table>

\(^1\) Commonly used as an analgesic and antipyretic.
\(^2\) Typically smaller in size.
\(^3\) Simple structure.
\(^4\) Well-defined structure.
\(^5\) Monoclonal antibodies are produced by a single clone of B cells.
Generics vs. Biosimilars

Lots of differences, however….

• Some key similarities –
  • Both intended to be used in same way as originator
  • The intention of the manufacturing process for both is to produce a copy of the original
  • Proving clinical efficacy ≠ main driver (already done)

• The regulators have adapted existing guidance for these “copies” to facilitate regulatory approval

• The more complicated the molecule:
  • More testing required
  • More in depth the guidance
The EMA View

• From a scientific and regulatory point of view, the biosimilar is just another version of the active substance of the originator.

• The same scientific principles of the comparability exercise apply equally to
  • demonstrating similarity pre & post manufacturing process change
  • comparability exercise to demonstrate biosimilarity

• Critical quality attributes, i.e. those that affect function of the molecule, must be comparable.

• The cornerstone of this process is the extensive comparison of the physicochemical and functional characteristics of the molecules using up-to-date analytical tools.

• EMA regulators - extensive experience
EU approved biosimilars since 2004

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Company</th>
<th>Status</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnitrope®</td>
<td>somatropin</td>
<td>Sandoz GmbH</td>
<td>Authorized</td>
<td>4/12/2006</td>
</tr>
<tr>
<td>Epoetin Alfa Hexal®</td>
<td>epoetin alfa</td>
<td>Hexal AG</td>
<td>Authorized</td>
<td>8/28/2007</td>
</tr>
<tr>
<td>Silapo®</td>
<td>epoetin zeta</td>
<td>Stada Arzneimittel AG</td>
<td>Authorized</td>
<td>12/18/2007</td>
</tr>
<tr>
<td>Retacrit®</td>
<td>epoetin zeta</td>
<td>Hospira UK Limited</td>
<td>Authorized</td>
<td>12/18/2007</td>
</tr>
<tr>
<td>Tevagastim®</td>
<td>filgrastim</td>
<td>Teva GmbH</td>
<td>Authorized</td>
<td>9/15/2008</td>
</tr>
<tr>
<td>Ratiogastim®</td>
<td>filgrastim</td>
<td>Ratiopharm GmbH</td>
<td>Authorized</td>
<td>9/16/2008</td>
</tr>
<tr>
<td>Biogastim®</td>
<td>filgrastim</td>
<td>AbZ-Pharma GmbH</td>
<td>Authorized</td>
<td>9/18/2008</td>
</tr>
<tr>
<td>Zarzio®</td>
<td>filgrastim</td>
<td>Sandoz GmbH</td>
<td>Authorized</td>
<td>2/6/2009</td>
</tr>
<tr>
<td>Filgrastim Hexal®</td>
<td>filgrastim</td>
<td>Hexal AG</td>
<td>Authorized</td>
<td>2/7/2009</td>
</tr>
<tr>
<td>Nivestim®</td>
<td>filgrastim</td>
<td>Hospira UK Ltd.</td>
<td>Authorized</td>
<td>6/8/2010</td>
</tr>
<tr>
<td>Remsima®</td>
<td>infliximab</td>
<td>Celltrion Healthcare Hungary Kft.</td>
<td>Authorized</td>
<td>9/10/2013</td>
</tr>
<tr>
<td>Inflectra®</td>
<td>infliximab</td>
<td>Hospira UK Limited</td>
<td>Authorized</td>
<td>9/11/2013</td>
</tr>
<tr>
<td>Ovalex®</td>
<td>follitropin alfa</td>
<td>Teva Pharma B.V.</td>
<td>Authorized</td>
<td>9/27/2013</td>
</tr>
<tr>
<td>Grastofil®</td>
<td>filgrastim</td>
<td>Apotex Europe BV</td>
<td>Authorized</td>
<td>10/18/2013</td>
</tr>
</tbody>
</table>
Biosimilar Goal Posts (Target Range)

1. Define Reference Target
   - Understand the intrinsic variability across multiple batches of the reference

2. Development Process Directed by Reference Target Variability
   - Develop process toward biosimilarity within the bounds of the intrinsic variability

3. Ensure Biosimilarity to Reference Product
   - Leverage analytics at each stage to ensure biosimilarity
Can’t miss a gate.
The Biosimilar Data Package
The Role of Clinical Trials

Proving “highly similar” to reference product often requires multiple iterations of process change and physicochemical characterization.
New Biologic

Phase III study data

Phase III study data

Phase III study data
New Biosimilar

Phase III study data

Phase I study data
The purpose of the trials...

• The technology allows biosimilars to be fully characterised
• If critical product attribute differences are detected, the impact on receptor binding and other functional mechanisms can be assessed
• Functional integrity + performance can be assured before clinical studies.
• Clinical studies target “residual uncertainty”
• Studies not considered in isolation basis for “comparability”
  \[
  \text{\because } \text{Immunogenicity, Safety, Sensitive efficacy endpoints}
  \]
• Clinical studies are
  • designed to identify any unusual /unexpected issues
  • not sensitive enough to detect even moderate differences
Data requirements for a biosimilar

• The type and extent of clinical data requirements for biosimilars vary, and will depend on
  • the complexity of the active substance + ability to be characterised
  • the availability of an accepted surrogate end point to compare efficacy
  • the type and seriousness of safety concerns that have been encountered (reference product or substance class)
  • the possibility to extrapolate efficacy and safety data to other indications of the reference product,
    – (ie those which have not been studied for the biosimilar)

• However, a repetition of the entire development program of the reference product is
  • scientifically not necessary
  • could even be considered unethical
The European Public Assessment Report (EPAR) – CT-P13

- Summarises the regulatory assessment process for medicines to be used in the EU
- Five key elements for a biologic:
  - Analytical
  - Binding studies
  - Biological activity
  - Pre-clinical
  - Clinical (Residual Uncertainty)
Key Issues identified for CT-P13

• MoA – and implications for extrapolation
  • Additional data submitted
• Afucosylation and impact on Antibody Dependent Cell-mediated Cytotoxicity (ADCC)
  • Additional data submitted
• Safety in humans
  • Phase III studies
Potential MoA’s for anti-TNFs

Primary MoA

Neutralisation of soluble TNFα

Additional potential MoA’s - especially in IBD

Anti-TNF

tmTNF expressing cell

Apoptosis

Cytokine suppression

CDC

ADCC

Also induction of regulatory macrophages
Downstream impact of afucosylation

- A difference in afucosylation
- A difference in FcγRIIIa binding
- A difference in ADCC

A difference in safety?
A difference in efficacy?
Impact on extrapolation?
ADCC and IBD - relevant?

- CT-P13: lower level of afucosylated glycans, lower binding to FcγRIIIa
- Fc-mediated functions could be involved in the MoA. Further experimental data needed to confirm that the differences did not affect efficacy or safety in any of the applied indications
  - More data on the cell-based assays, sensitivity, more batches
  - Additional ADCC assays using a different source of effector cells
- Experimental models that are considered representative of the pathophysiological conditions and putative MoA performed
  - These provided convincing evidence that the difference detected had no clinically relevant impact on the efficacy and safety, in particular in IBD.
ADCC using whole blood

ADCC comparability using whole blood from CD patient #1 (V/F genotype)

ADCC Bioactivities (% Specific Lysis) for CT-P13 and Remicade® Containing Varying Amounts of Afucosylated Molecular Variants Using Whole Blood from CD Patient #1 (V/F Genotype)

CT-P13 antibodies with 5.5% (10B9301), 6.3% (10B0106) and 14.5% afucosylation and also Remicade® with that of 11.9% (1RMA65804) and 14.6% (1RMA61310) were used with whole blood from V/F CD patient as effector cells in standard ADCC assay at concentrations as indicated in the x-axis.
Infliximab safety

• 871 patients were included in the safety population

<table>
<thead>
<tr>
<th>Treatment-emergent SAEs</th>
<th>CT-P13</th>
<th>Remicade</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (% of pat with at least 1 TEAE)</td>
<td>181 (60.1)</td>
<td>183 (60.8)</td>
</tr>
<tr>
<td>Patients with drug related SAEs</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N (% of pat with drug-related infections)</td>
<td>17 (5.6)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>N (% of pat with infusion-related reactions)</td>
<td>3 (1.0)</td>
<td>6 (2.0)</td>
</tr>
</tbody>
</table>

• Pneumonia CT-P13: 5 vs. 0
  – 3 with predisposing factors

• Active TB: CT-P13: 7 vs. 1
  – 4 cases lacked diagnostic criteria or had pulmonary lesions
  – Overall rate similar to other studies

CHMP Conclusion: The CHMP concluded that the differences detected were not clinically meaningful, positive opinion issued in June 2013
Extrapolation

- The regulatory and scientific process of granting a clinical indication to a medicine without clinical efficacy and safety data to support that indication.

- “How can a biosimilar be given to a patient for an indication where there is no evidence?”

- Data ie EPAR is not what prescribers used to

- Decision to extrapolate
  - Extrapolation of Indications or Total Data Package?

- Depends on Totality of Evidence (new and old)

- Always case-by-case basis

- Prescribers: A leap of faith required?
The Extrapolation Principle

When I see a bird that walks like a duck and swims like a duck and quacks like a duck, I call that bird a duck.

(James Whitcomb Riley)*

*American writer, poet, and best-selling author.
Extrapolation

• It may be considered if biosimilarity has been shown
• Must be sound scientific justification
  • Clinical experience + available literature from the originator
  • MoA of the active substance in each indications
  • Evidence that the lead indication is representative of the other indications (safety and efficacy)
• Extrapolation is already widely exercised
  • Post manufacturing change or reformulation
  • Phase 1 biologics (EPO, GCSF, GH)
• Extrapolation principles apply equally to biosimilars AND biologics pre & post-change
Interchangeability, substitution & switching

- **Interchangeability** – Means moving freely between the available products ie like a generic
- **Not approved by EMA, down to each member state to decide**
  - Not an option in UK (c/f FDA regulatory position)
  - Batches pre and post manufacturing change will be considered “interchangeable”
- **Substitution** – changing product in pharmacy without telling prescriber – also not an option
- **Switching** – following a local agreement existing patients are switched to the biosimilar
The CT-P13 Trials

• PLANETRA & PLANETAS
• Phase III and Phase I
• PD and PK
• Different doses +/- MTX
• 24, 52, 102 weeks data collected
• Includes switching studies at week 52 (full data due)
• Results: similar, comparable, equivalent etc
CROSS-IMMUNOGENICITY: ANTIBODIES TO INFlixIMAB IN REMICADE-TREATED IBD PATIENTS SIMILARLY RECOGNIZE THE BIO-SIMILAR REMSIMA

• The cross-immunogenicity of Remsima vs. originator drug in IBD patients is unknown
• Sera of Remicade-treated IBD patients with measurable antibodies to Remicade were tested for their cross-reactivity to two batches of Remsima.
• 124 sera were tested. All 68 +ve anti-Remicade IBD sera were cross-reactive with Remsima.
• In -ve controls all 56 control sera which were anti-Remicade negative also tested -ve for anti-Remsima antibodies.
• Antibodies to Remicade in Remicade-treated IBD patients recognize Remsima to a similar extent,
• Suggests shared immuno-dominant epitopes on these two infliximab agents.
HTAs – Infliximab Biosimilar

• NICE
  • No HTAs but now a TAS
  • Future HTAs to include biosimilars
• SMC
  • Did a review for CT-P13 then changed their exclusion criteria
• AWMSG
  • Reviewed
# Gastroenterology vs. Rheumatology

<table>
<thead>
<tr>
<th>Rheumatology</th>
<th>Gastroenterology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide range of biologics</td>
<td>Limited range of biologics</td>
</tr>
<tr>
<td>Phase I and Phase III study</td>
<td>“Data” limited to posters / abstracts</td>
</tr>
<tr>
<td>New patient every year (maybe)</td>
<td>New patients every month (definitely)</td>
</tr>
<tr>
<td>Limited chances to initiate</td>
<td>Biosimilar in new patients possible</td>
</tr>
<tr>
<td>Switching presents a problem</td>
<td>Extrapolation is main barrier</td>
</tr>
<tr>
<td>Full publication of switch data needed</td>
<td>Need to understand extrapolation and the role of Phase III studies</td>
</tr>
</tbody>
</table>
Naming of Biosimilars

- INN or something else ie Infliximab - napp, delta, grsy
- Filgrastim biosimilar in the US = Filgrastim-sndz
- Epoetin
  - alpha, beta, theta, zeta vs Binocrit, Retacrit, Eporatio, Eprex, NeoRecormon
- Some Pharma not keen on INN – why not?
  - Pharmacovigilance & Patient Safety
  - Default generic prescribing
  - Something to differentiate biologics vs biosimilars?
  - Same convention for both?
- Need evidence the suggested naming convention safer
- Hospitals can brand name prescribe if needed to + EP
Biosimilar Glargine - Abasaglar

- Human insulin molecule is a non-glycosylated, disulphide-bonded heterodimer containing only 51 amino acids.
- Considerably smaller than a mAb eg Infliximab 1328 AAs
- Characterisation is much easier
- Five Phase 1 studies: PK (glucose clamp) and PD, range of doses, healthy volunteers + T2DM.
- Two Phase 3 studies
  - ELEMENT-1: 52-wk P3, open-label, 535 patients T1DM
  - ELEMENT-2: 24-wk P3, double-blind, 756 patients T2DM
- No need for specific efficacy studies with biosimilar insulins
- Endpoints used e.g. HBA1c, not sufficiently sensitive to demonstrate biosimilarity.
Biosimilar Glargine - Abasaglar

- So efficacy studies evaluating HBA1c not generally anticipated.
- Two Phase 3 studies did report on HbA1c levels + other parameters
  - 7-point self-monitored blood glucose profiles and the data on intra-patient blood-glucose variability, basal and prandial insulin dose, and weight.
- Did not, in themselves, demonstrate biosimilarity
  - Were supportive evidence of clinical biosimilarity
  - Key output of the P3 studies = safety and immunogenicity datasets
- Quality, safety and efficacy all demonstrated
  - CHMP recommended granting of the MA
- Only real issues are delivery device and price.
Biosimilar Etanercept – SB4

- Two clinical studies
- P1 PK (healthy volunteers) – poster only
  - PK + Safety, immunogenicity and tolerability
- P3 PD (RA) – published in full
  - Efficacy, PK, Safety, Immunogenicity
- EPAR will be published prior to launch Feb 2016
Phase I - Results

- **PK similarity demonstrated**
  - SB4/US-ETN/EU-ETN
- **Well tolerated, comparable safety**
- **Lower ADAs for SB4 vs. Etanercept**
Biosimilar Etanercept SB4 – Phase III

- PD and safety in RA, 596 pts
  - SB4 vs. Enbrel, 24 weeks and beyond
- ACR 20, 50, 70, DAS28 + safety, immunogenicity, PK
## Safety

The table below shows the incidence of safety-related adverse events (ISRs) in two groups: SB4 50 mg (N=299) and ETN 50 mg (N=297).

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>SB4 50 mg N=299</th>
<th>ETN 50 mg N=297</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>21 (7.0)</td>
<td>15 (5.1)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>15 (5.0)</td>
<td>14 (4.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>14 (4.7)</td>
<td>15 (5.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (4.3)</td>
<td>8 (2.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (3.3)</td>
<td>10 (3.4)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>7 (2.3)</td>
<td>8 (2.7)</td>
</tr>
<tr>
<td>Viral infection</td>
<td>7 (2.3)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>6 (2.0)</td>
<td>33 (11.1)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>6 (2.0)</td>
<td>9 (3.0)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6 (2.0)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5 (1.7)</td>
<td>7 (2.4)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>4 (1.3)</td>
<td>8 (2.7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (1.3)</td>
<td>7 (2.4)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>4 (1.3)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (1.0)</td>
<td>10 (3.4)</td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (0.7)</td>
<td>10 (3.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (0.7)</td>
<td>7 (2.4)</td>
</tr>
<tr>
<td>Injection site rash</td>
<td>2 (0.7)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1 (0.3)</td>
<td>7 (2.4)</td>
</tr>
</tbody>
</table>
Results

• ACR 20 and DAS28 – equivalent
• Safety profile – comparable
• Inj site rxns – 3.7% SB4 vs 17.2%
  – ?different formulation and container closure system
  – No correlation with ADAs
• PK – similar
• ADAs – higher for Etanercept than seen previously (assay related)
  – But transient and non-neutralising
What’s next?

• Nothing else currently logged with EMA
• We’re waiting for
  • Adalimumab,
    – The “Carlsberg” of biologics?, reformulated version due soon
  • Also Rituximab, Trastuzumab, Bevacizumab
• Multiple biosimilars of the same “Brand”
• Resolution of the naming issue
• Education of prescribers
  • Extrapolation, role of Phase III studies
• Fighting inertia is key
Summary

• Biologics are inherently versions of themselves
• Biosimilars are versions of biologics
• Not identical but close enough
• Wave 2 of the biosimilars is now upon us
• It is a complex area but worth getting to grips with
• A big opportunity for the NHS
X-ray crystallography analysis of a section of the biosimilar and Remicade molecules. Superimposition of biosimilar (green) and Remicade (red).