Biosimilars: what's the problem?

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Biosimilars: what's the problem?

- Manufacturing
  - Understanding the regulations
  - Developing the analytical expertise
  - Showing that differences do not matter clinically
- Clinical
  - Knowing what they are
  - Knowing what they aren't
  - Having confidence that they're not inferior

Biotechnology

‘Any technical application that uses biological systems, living organisms or derivatives thereof to make or modify products or processes for specific use’

United Nations Convention on Biological Diversity 1992

Biologicals

- Whole blood and components
- Organs and tissue transplants
- Antibodies for passive immunisation
- Animal products
  - Heparin; insulin
- DNA technology
  - Factor VIII; Factor IX; insulin; erythropoietin
- Monoclonal antibodies

Advanced Therapies

- Gene therapy
  - SCID
  - Haemophilia B (Factor IX)
  - Gene editing
- Cell therapy
  - Stem cell therapy
  - Adoptive immunotherapy
- Tissue engineering
  - Expanded autologous cartilage cells

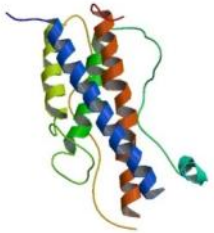
Biologicals

- Revolutionised treatment of some diseases
  - Cancers
  - Autoimmune disease
    - Rheumatoid Arthritis
  - Bleeding disorders
- May be more effective
- Potential to be more toxic

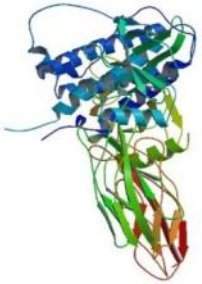
Biological Medicinal Products

- Developed and produced in living cells
- Relatively large, complex molecules
- Some manufactured by DNA technology
- Difficult to fully characterise
  - Variability of biological manufacturing processes
  - Inherent variability – ‘microheterogeneity’
  - Ancillary and process materials also biologics
    - Fetal bovine serum; cytokines

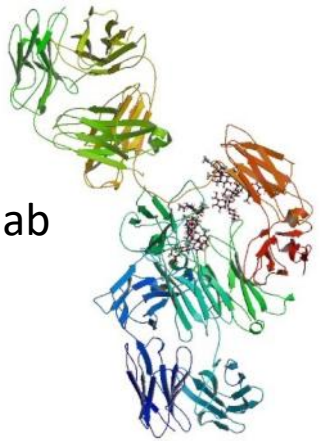
Complexity of Biologics



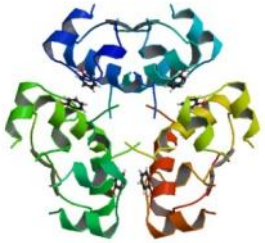
Somatotropin



Erythropoetin



Infliximab



Insulin

Blood

Retinal cells

Biosimilar medicines

- Expiry of data protection/patents
  - Allows development of biosimilar medicines
- Copy of an authorised biological (RMP)
  - Not innovative
  - Potential to bring substantial efficiency gains
- For marketing in the EEA
  - Reference medicinal product (RMP)
    - Must have been licensed by the EMA
    - On the basis of a full dossier

Biosimilarity

- Not the same as bioequivalence
  - Not a ‘biogeneric’
- Copy biological or follow-on biologicals
  - Compared to RMP – may be biosimilar
  - Not compared to RMP – not a biosimilar
- Biobetters or 2nd generation products are not
- Counterfeit medicines are not

RMP: reference medicinal product

Biosimilar medicines

- Somatotropin 2006
- Erythropoietin 2007
- Filgrastim 2008
- Follitropin 2013
- 1st biosimilar monoclonal antibodies
- Infliximab: RMP Remicade licensed 1999
    - Biosimilars: Remsima and Inflectra (September 2013)
- Rituximab: RMP Mabthera licensed 1998
    - Biosimilar: Truxima (February 2017)

Euclid of Alexandria (300BC)

Things that are equal to the same thing are equal to each other

…not true for biosimilars

Biosimilar

“The demonstration of comparability does not necessarily mean that the quality attributes of the… product[s] are identical but that they are highly similar and that existing knowledge is sufficiently predictive to ensure that any differences… have no adverse impact upon safety or efficacy of the drug product”

Inherent variability of Biologicals

- Needs to be carefully controlled
- Critical quality attributes
  - Impact on potency, safety, efficacy
- Critical quality parameters
  - Acceptance criteria (specifications)
- For each batch of product
  - Analyse physicochemical & functional properties
  - Ensure they remain within the set parameters

Inherent variability of biologicals

- Critical quality attributes
  - Purity, dissolution properties, glycosylation
- Critical process parameters
  - Filtration, particle size, cell culture process
- Variability inevitable
  - Acceptable if no change in safety or efficacy
- How much variability does that allow?

Difficulties with biosimilars

- The process defines the product
- Developers do not have access to
  - Originator companies' proprietary data
    - Details of manufacturing process
    - Active ingredients of reference medicine
- Will engineer own manufacturing process
- Critical quality attributes will not be identical
- Critical quality parameters will not be identical

The Great British Bake Off

- Technical challenge
  - Same ingredients
  - Brief instructions
  - No picture of end product

Quality target product profile

- Public data (EPAR; published literature)
- Data from extensive characterisation RMP
  - Multiple batches over longest time period
- Extent of variability of RMP defined
  - Clinical data to support lack of clinical effect
- Wider ranges for QTPP

RMP: reference medicinal product
EPAR: European Public Assessment Report

Comparability data

- Biosimilar final product
  - representative of proposed commercial process
- Differences identified
  - Consider impact on safety and efficacy
  - Impact on biological activity
  - Support arguments with data
    - Limited non-clinical and clinical trials

Interchangeability

- Switching versus automatic substitution
  - Biosimilars are similar but not identical
  - Potential differences in clinical profile

therefore

- Switching should be monitored
- Automatic substitution is not appropriate
- Brand names should be used

EU experience

Omnitrope	somatropin	Sandoz	Genotropin	Approval	Apr-06
Valtropin	somatropin	BioPartners	Humatrope	Approval	Apr-06
Alpheon	interferon alfa-2a	BioPartners	Roferon-A	Refusal	Jun-06
Abseamed	epoietin alfa	Sandoz	Eprex	Approval	Aug-07
Epoietin alfa Hexal		Hexal			
Binocrit		Medice			
Silapo	epoietin zeta	Hospira	Eprex	Approval	Dec-07
Retacrit		Stada			
Insulin Rapid Marvel	soluble insulin	Marvel	Humulin	Withdrawal	Dec-07 & Nov-12
Insulin Long Marvel	isophane insulin				
Insulin 30/70 Mix Marvel	biphasic insulin				
Tevagrastim	filgrastim	Teva	Neupogen	Approval	Sep-08
Ratiograstim/Filgrastim Ratiopharm		Ratiopharm			
Biograstim		CT Arzneimittel			
Filgrastim Hexal	filgrastim	Hexal	Neupogen	Approval	Feb-09
Zarzio		Sandoz			
Nivestim	filgrastim	Hospira	Neupogen	Approval	Jun-10
Epostim	epoietin alfa	Reliance GeneMedix	Eprex	Withdrawal	Mar-11
Remsima	infliximab	Celltrion	Remicade	Approval	Sep-13
Inflectra		Hospira			
Ovaleap	follitropin	Teva	Gonal-f	Approval	Sep-13
Grastofil	filgrastim	Apotex	Neupogen	Approval	Oct-13
Bemfola	follitropin	FINOX Biotech AG	Gonal-f	Approval	Jan-14
Truxima	rituximab	Napp Pharma	Mabthera	Approval	Feb-17

Avastin and Lucentis

- Are these biosimilar products?
- Are they used interchangeably?

What are they?

- Both are anti-VEGF monoclonal antibodies
- Mode of action
  - Anti-angiogenic
- Both developed by the same company
- Same parent mouse antibody

Avastin (Bevacizumab)

- Humanised monoclonal antibody
- Full length 149KDa
- Produced in CHO cells; glycosylated
- Monomer at pH ≤ 5.5
- Reversible aggregates dependent on
  - pH, temp, ionic strength
- Licensed for various types of cancer
- 25mg/ml
  - Vial sizes 4ml and 16ml

Lucentis (Ranibizumab)

- Humanised monoclonal antibody
- Fragment 48KDa
- Produced in *E Coli* cells; not glycosylated
- Licensed for wet AMD
- 10mg/ml
  - Vial size 0.23ml

Repackaged Avastin for AMD use

- Smaller volumes
- Silicone syringes
- Several UK ‘Specials’ manufacturers
- Repackaging may affect quality
  - Microbiological safety
  - Introduction of contaminants
  - Handling procedures

Performance in clinical trials

- Efficacy the same
- Concerns over safety
  - Endophthalmitis
  - Increased ocular pressure/inflammation
- Precise cause not yet identified
  - Possibly due to impurities
    - Microbiological
    - Silicone from syringe
    - Variable stability during handling
  - Possibly due to aggregates

Avastin and Leucentis

- Bevacizumab and Ranibizumab
- Not the same amino-acid backbone
- Clearly not biosimilar
- Cannot extrapolate data for new indication
- Quality concerns with repackaged Avastin
  - Many different specials sites involved
  - Difficult to gather meaningful data
- Off-label use only if no licensed product

Pharmacovigilance

- Accurate identification of product used
- INN not enough
  - May not have the same safety profile
  - May not have the same efficacy profile
- Product name must be used
  - Batch number may be needed
- ADRs must be linked to specific product

INN: International Non-proprietary Name

Information for prescribers

- Indicate that the product is a biosimilar
- State the reference product
- State which indications are approved
  - From clinical trials
  - By extrapolation
- Safety and efficacy data
  - From biosimilar
  - From reference product

Biosimilars

...give clinicians more information than the mere knowledge that they were developed for the same indication