Biosimilars in diabetes care

Professor Philip Home
Newcastle University, UK
Credentials and duality of interest

I have worked with the major insulin manufacturers and drug regulators on new insulins since 1980. I accept funding for advisory, education, and research activities from all the major insulin manufacturers (Eli Lilly, Novo Nordisk, Sanofi). I advise or speak for prospective manufacturers of biosimilar insulins and other biologicals (Antriabio, Biocon, Hanmi, Mylan, Merck (MSD)). I have been part of reimbursement review of biologicals in the UK.
Novo Nordisk, 31 October 2013

"Lantus loses patent protection in 2015, which will fundamentally "change the marketplace" for basal insulins"

Why? How? Does it matter clinically?
Background to the insulin market - highlights

- 355 Million people have diabetes globally
- The proportion depending on insulin varies markedly country to country, and within countries – 10-40% is often quoted
- Lantus sales are now US$~7.5 billion per year
- Novo Nordisk analogue sales are around US$6.8 billion per year
- Eli Lilly meal-time insulins are growing 7-8% a year
- Eli Lilly, Novo Nordisk, and Sanofi together have 99% of the global insulin market by value – value growth is ~15% per year
- Human insulins still have a large part of the market by volume

So why the interest in 'biosimilars'?

Kelly Close, Close Concerns newsletters, 2013
Patent expiry and manufacturers interested in the insulin biosimilars space

**Patent expiries**
- **Principle target**
  - insulin glargine (Lantus, 2014-2015)
- **Other targets**
  - insulin lispro (Humalog, 2013) and lispro premixes
  - insulin aspart (NovoRapid, 2012) and aspart premixes
  - human NPH insulin and premix

**Manufacturers interested**
- Biocon/Mylan, Eli Lilly, Gan & Lee, Merck (MSD)/Samsung, Sanofi, Wockhardt
Patent expiry and manufacturers interested in the insulin biosimilar space

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**Manufacturers interested**
- Biocon, Gan & Lee, Wockhardt
  - Sell copies of insulin in some countries
- Eli Lilly
  - Manufactures full range of insulins – introduced first biosynthetic insulin
- Merck (MSD)
  - No previous insulin product
- Sanofi (ex Hoechst)
  - >80 years experience of insulin

Biocon, Gan & Lee, Wockhardt
- Biocon/Mylan, Eli Lilly, Gan & Lee, Merck (MSD)/Samsung, Sanofi, Wockhardt
Biosimilar medications: focus on insulin

What are the clinical issues?

- Meaning and definitions – biologicals and biosimilars
- Making the distinction from generics
- Clinical problems with biologicals, biosimilars, and copies
  - where do the problems come from
- What is necessary to show biosimilarity?
  - comparative efficacy – PD studies, clinical studies, population choices, study durations
  - comparative tolerability and safety
  - role of immunogenicity
- Regulatory guidelines or lack of guidelines
- Prescribing, interchangeability and substitution
Biosimilar medications
Nature and definition

Biopharmaceuticals
- biological medical products derived from cell culture/fermentation processes producing target therapeutic proteins
- first example was recombinant human insulin (Eli Lilly, 1980)
- other examples: cytokines, monoclonal antibodies, other insulins
Biosimilar medications

Nature and definition

Biopharmaceuticals
- biological medical products derived from cell culture/fermentation processes producing target therapeutic proteins
- first example was recombinant human insulin (Eli Lilly, 1982)
- other examples: cytokines, monoclonal antibodies, growth hormone

Biosimilars
- biopharmaceuticals intended to be a clinically identical end product to another existing biopharmaceutical
- available clinical products include epoetin alfa, somatostatin

"a new biological product similar to an already authorized medicine . . . similar but not identical to the biological reference medicine"
Insulin glargine: by-product profile may arise from folding and cleavage

Krämer and Sauer, Brit J Diabetes Vasc Dis, 2010

Isolation of cells
Cell disruption (physical)
Isolation and purification
Folding
Enzymatic cleavage
Purification/concentration
Ion-exchange chromatography
Reversed phase chromatography
Crystallization and lyophilisation
Blending and filling

Typical operations – inclusion body process

Folding and cleavage can result in by-products

Chromatography defines purity

Degradation by-products can form late in the process
What aspects of manufacturing might affect the dissimilarity of biological products?

- Host cell characteristics
  - Post-translational glycosylation
  - Effects on protein folding and structure
- Protein stability
  - Physical degradation
    - Protein aggregates
  - Chemical degradation
    - Deamination and oxidation
- Purification
  - Impurities
    - Host cell (e.g. lipopolysaccharides)
- Formulation and storage
  - Protein stability and final product may be affected by:
    - Excipients
      - Type used and sources
    - Containers
      - Type, filling, and closure

May affect:
- PK and PD
- Efficacy
- Immunogenicity
- Adverse events

Human insulin derivatives originating from fermentation synthesis in *S. cerevisiae*

courtesy of Novo Nordisk, 2010
Impurities (of unknown clinical significance) in marketed preparations of copies of insulin glargine

Owens et al, Diabetes Technol Ther, 2012
Problems with biologicals
*Example: epoetin alfa*

- Change in manufacturing of reference product
  - deaths from pure red cell aplasia
  - traced to change in manufacturing process
- Thailand: no requirement for clinical comparability for approval of biosimilars
  - Epoetin alfa: 14 products on the market
  - 30 CKD patients on SC biosimilar recombinant human epoetin
  - Sudden loss of effect
  - Positive for anti-recombinant human epoetin

*K Tungsanga, Ottawa, 2009*
Problems with biosimilars

Example: somatropin

- Early version of Omnitrope (Sandoz)
  - 57% of patients developed antibodies
- Problem was residual host-cell protein
- Purification process redeveloped

Source: EMEA, European Public Assessment Report
Problems with biosimilars: Presence of a thioether variant in a commercial somatropin medication

- Thioether variant found in some hGH products (up to ~30%)
  - found in Hormotrope, Yelit, Cryotropin
- Not detected by usual industrial monitoring methods

*Electrospray mass spectrogram from Lispi et al, J Pharm Sci, 2009*
### Guidelines for biosimilars – non-clinical evaluations

<table>
<thead>
<tr>
<th>Region / country</th>
<th>Non-clinical evaluation</th>
</tr>
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<tbody>
<tr>
<td><strong>European Union</strong></td>
<td></td>
</tr>
<tr>
<td>General biosimilars</td>
<td>Comparative physiochemical, biological and immunological properties including purity/impurities. In vitro studies in a relevant species</td>
</tr>
<tr>
<td>Insulin-specific</td>
<td>Comparative <em>in vitro</em> receptor binding assays; bioactivity</td>
</tr>
<tr>
<td><strong>United States</strong></td>
<td>As European general guidelines</td>
</tr>
<tr>
<td><strong>Canada</strong></td>
<td>As European general guidelines Repeat dose toxicity study</td>
</tr>
<tr>
<td><strong>Mexico</strong></td>
<td>Biocomparability studies (<em>in vitro</em>) required. In vivo studies may not be required. Repeat dose toxicity study</td>
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*Heinemann et al, work in progress, 2014*
# Guidelines for biosimilars – PK-PD studies

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<tr>
<td>General biosimilars</td>
<td>Comparative PK/PD studies – may sometimes be sufficient</td>
</tr>
<tr>
<td>Insulin-specific</td>
<td>Cross-over, preferably double-blind, insulin clamp studies (details given)</td>
</tr>
<tr>
<td><strong>United States</strong></td>
<td>Expect human comparative PK and PD studies - 'fundamental'</td>
</tr>
<tr>
<td><strong>Canada</strong></td>
<td>Comparative PK and PD studies (general guidance)</td>
</tr>
<tr>
<td><strong>Mexico</strong></td>
<td>Comparative studies are required when requested</td>
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*Heinemann et al, work in progress, 2014*
### Guidelines for biosimilars – clinical efficacy studies

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<td>European Union</td>
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<tr>
<td>General biosimilars</td>
<td>RCTs usually required</td>
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<tr>
<td>Insulin-specific</td>
<td>No anticipated need for specific clinical efficacy studies</td>
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<tr>
<td>United States</td>
<td>Required if residual uncertainty from pre-clinical and PK/PD studies</td>
</tr>
<tr>
<td>Canada</td>
<td>Critically important with few exceptions</td>
</tr>
<tr>
<td></td>
<td>Not required for human soluble insulin products</td>
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<td>Mexico</td>
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*Heinemann et al, work in progress, 2014*
Important clinical findings in assessment of biosimilar insulin

- What is the most sensitive clinical population?
  - type 1 diabetes – C-peptide negative
- What duration of study is needed?
  - >6 months
- What measures should be used?
  - pre-injection (for basal) or post-meal challenge (for prandial) glucose
  - hypoglycaemia – CGM at night
  - $\text{HbA}_{1c}$ and durability to 9-12 months
- Antibodies to insulin (cross-reacting); and to host-cell proteins
Biosimilar insulins: 
What should clinicians be looking for?

- Since no set of evidence (eg glucose clamp studies) has the statistical power to ensure biosimilarity to the levels needed by people with diabetes:
- Review the package of clinical outcomes: eg for a basal insulin
  - PK 24-h AUC, Cmax, Tmax
  - PD – but likely to be weak data – have multiple studies been performed?
  - HbA1c – but averages high and lows, and tends to target in treat-to-target studies
  - pre-injection SMPG – but problem for evening injections
  - hypoglycaemia rates – but power often low
  - reputation of manufacturer (insulin and/or biologicals)
  - immunogenicity and analytical results

This seems to be the approach suggested by the FDA (general not insulin-specific)

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Biosimilar insulins:
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*FDA Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,*


- Competently performed PK and PD studies – glucose clamps
- Comparative studies (to reference insulin) in an adequately powered population of people with type 1 diabetes
- Other clinically supportive comparative studies (type 2 diabetes, specific populations)
- Adequate duration of study to determine antigenicity in people with type 1 diabetes
- Assurance of manufacturing competency and consistency
- A good price, if the above conditions are met
PK findings for a new insulin glargine (Lilly) compared to glargine Sanofi in healthy people

Insulin concentration (pmol/l C-peptide corrected)

Zhang et al, ADA poster, 2014
PK findings for a new insulin glargine compared to glargine Sanofi in people with T1DM

Heise et al, ADA poster, 2014
PD findings for a new insulin glargine compared to glargine Sanofi in people with T1DM

Heise et al, ADA poster, 2014
PK/PD findings for a new insulin glargine compared to glargine Sanofi in healthy people

Zhang et al., ADA poster, 2014

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<td>0.3 U/kg</td>
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<td>glucose infused (PD; mg/kg)</td>
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Top line results of the phase 3 Lilly glargine vs Sanofi glargine results in T1DM and T2DM

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<td>FPG SMPG (mg/dl)</td>
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<td>Hypoglycaemia (events/person-yr)</td>
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*Blevins et al, ADA oral, 2014; Rosenstock et al, ADA oral, 2014*
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**difference: -1 (-10, 9) mg/dl**

*Blevins et al, ADA oral, 2014; Rosenstock et al, ADA oral, 2014*
Biosimilar insulins

Other issues for clinicians and payers

Interchangeability
- Can a patient be switched from the reference insulin to its biosimilar?
- Can I change my practice seemlessly to use a cheaper biosimilar?

Substitution
- Can a pharmacist dispense a prescription for a proprietary insulin with an approved name insulin?

Traceability
- How is the side effect profile of a biosimilar to be established in practice if it is prescribed by the approved name (WHO INN)?
Biosimilar medications: Conclusions

- Biosimilar biologicals are increasingly coming our way.
- Development requires a pre-clinical and clinical package of comparability to the reference product.
- Difficulties in the performance of pharmacodynamic and clinical studies and their interpretation are to be expected – sensitive clinical studies are critical.
- Clinician's will need to review the totality of evidence.
- Access to manufacturing quality data is not available, and it is unclear that regulators will do the necessary continuing monitoring of this.
- Substitution and interchangeability of biosimilar products will be subject to debate.
Thank you for your attention