Need for Better Insulins and Biosimilars

Lutz Heinemann
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Conflict-of-interest

• Lutz Heinemann

• Advisory Panel/Consultant: Biodel, Halozyme, InsuLine, Sanofi (only companies are listed that are relevant for the topic of my talk)

• Shareholder: Profil Institut für Stoffwechselforschung, Neuss, Germany; Profil Institute for Clinical Research, San Diego, US

• I own no stock at all!
1989 Michael Berger
Asked for better insulins!

Intensified insulin therapy in the 90s ...

M. Berger, EASD Annual Meeting Lisboa, 1989
Physiological insulin secretion in healthy individuals: An elusive goal!

Adapted from Kruszynska et al. Diabetologia 1987;30:16
Basal-bolus therapy = Re-create physiology (focus on PK, PD is relevant)
Regular human insulin: Slow onset, long duration of action

Glucose infusion rate (mg/kg/min)

Time (hours)

Regular insulin
- 6 IU
- 12 IU
- 24 IU

Insulin Analogues

[Diagram showing the structure of insulin analogues with labeled amino acids and chains, indicating fast-acting and long-acting analogues with different colors: yellow (Insulin lispro), green (Insulin aspart), pink (Insulin glargine), and gray (Detemir insulin).]
Rapid-acting insulin analogs: Better than regular insulin but not ideal

Glucose infusion rate (mg/kg/min) vs. time (h)

- Insulin aspart
- Regular insulin

n=24 healthy subjects

Overcome shortcomings of currently available prandial and basal insulins

- Prandial insulins = ultrafast-insulins (UFI)
- Basal insulins = ultralong-acting insulin (ULAI)
Novel approaches for ultrafast insulins

• Other methods to improve insulin absorption than rapid-acting insulin analogs
• Less research in this area for a while (patentability is more difficult)
• Novel approaches for sc applied insulin:
  - Intradermal insulin injection (Becton Dickinson, US)
  - Addition of excipients that keep insulin molecules monomeric (Biodel, US)
  - Addition of excipients that improve absorption (Halozyme, US)
  - Local heating of injection site (InsuLine, Israel)
TABLE OF CONTENTS
Current Issue, Volume 6, Issue 4, July 2012

EDITORIAL

» Future of Diabetes-Technology: Certificate of Competency for Insulin Pumps and Continuous Glucose Monitors
Lutz Heinemann, Gaby Faber-Heinemann, Ruth Roberts, John Walsh
Abstract / Full Text (PDF) / Purchase Article

» Symposium: Ultrastart Insulins
Co-Editors: Lutz Heinemann, Douglas Muchmore

» Ultrastart Acting Insulins: State of the Art
Lutz Heinemann, Douglas B. Muchmore
Abstract / Full Text (PDF) / Purchase Article

» Pharmacokinetics and Postprandial Glycemic Excursions following Insulin Lispro Delivered by Intradermal Microneedle or Subcutaneous Infusion
Elaine McVey, Laurence Hirsch, Diane E. Sutter, Christoph Kapitza, Sibylle Dellweg, Janina Clair, Kerstin Rebrin, Kevin Judge, Ronald J. Pettis
Abstract / Full Text (PDF) / Purchase Article

» Ultra-Rapid Absorption of Recombinant Human Insulin Induced by Zinc Chelation and Surface Charge Masking
Roderike Pohl, Robert Hauser, Ming Li, Errol De Souza, Robert Feldstein, Richard Seibert, Koray Ozhan, Nardini Kashyap, Solomon Steiner
Abstract / Full Text (PDF) / Purchase Article
Post prandial glycemic excursions with intradermal application

McVey et al. JDST July 2012
Time-action profile with monomeric insulin
Comparison of monomeric insulin with insulin lispro

Krasner et al. JDST July 2012
Post prandial glycemic excursions with improved absorption

Type 1

Type 2

Muchmore et al. JDST July 2012
Post prandial glycemic excursions with local heating

Freckmann et al. JDST July 2012
Better Basal Insulins = ULAI

Kruszynska Y et al. Diabetologia 1987;30:16
PD-Properties - Importance of Reproducibility + Mean Profile

A. Peaked mean profile, with high variability

B. Smooth, flat mean profile, with high variability

C. Smooth, flat mean profile, with low variability

Tolerable insulin range
Mean profile
Individual data
The Ideal Basal Insulin's: Key Characteristics

- Flatness: Flat, peakless profile => lower risk of hypoglycemia
- Duration/End of Action: Control of fasting BG with just one injection per day => ~ 24 h duration of action needed
- Variability: High predictability diminishes patient frustration and allows maximal dosing => less hypo- and less hyperglycemia
- Soluble
- Cheap
- No weight gain / no injection site reactions
Development of Basal Insulins

- Protamination (= NPH insulin)
- Shift iso-electric point of molecule to enable precipitation at pH 7.4
  - Insulin glargine
- Acylate with fatty acid ligands to enable depot albumin binding
  - Insulin detemir
Mathematical model: 24 h insulin

![Graph showing insulin levels over 24 hours with peaks and troughs every 24 hours.](image-url)
Mathematical model: 72 h insulin
Ultra-long Acting Insulins = Peakless Insulin
Insulin Degludec: Structure

$\text{Des(B30) LysB29( }\gamma\text{-Glu N }\varepsilon\text{-hexadecandioyl)} \text{ human insulin}$

A chain

B chain

$\text{desB30 Insulin}$

$\text{Hexadecandioyl}$

$\text{L-}\gamma\text{-Glu}$
Insulin Degludec Association: From Injection to Absorption

Jonassen I et al. Diabetes 2010; 59 (Suppl. 1): A11
Degludec: Mode of action

- **Capillary membrane**
- **Subcutaneous tissue**
- **Multi-hexamers**
- **Monomers**

**Degludec:**

- **Mode of action**
  - Dose of degludec is injected into the subcutaneous tissue.
  - Degludec forms multi-hexamers.
  - Multi-hexamers diffuse into the capillary blood.
  - Degludec binds to albumin in the blood.
  - Degludec reaches the cell membrane and binds to insulin receptors.
Insulin Degludec PK Profile
Single Dose and Steady State

People with type 1 diabetes (n=12)
0.4 U/kg once daily for 6 days

Jonassen I et al. Diabetes 2010; 59 (Suppl. 1): A11
Insulin Degludec Time-Action Profile: Steady State

Glucose infusion rate (mg/kg/min)

People with type 1 diabetes (n=12)
0.4 U/kg once daily for 6 days
Euglycemic clamp (Day 6)

Jonassen I et al. Diabetes 2010; 59 (Suppl. 1): A11
Insulin Degludec: PD-profile, Steady State (Type 2 Diabetes)

Nosek L et al. Diabetologia 2011;54(Suppl. 1):S429 (1055-P)
Intra-Individual Variability over Time

Heise T et al. Diabetes 2011;60(Suppl. 1):A263 (Abstract 960-P)
Intra-Individual Variability over Time

Intraindividual variability AUC-GIR$_{0-24h}$ (CV, %)

Heise T et al. Diabetes 2011;60(Suppl. 1):A263 (Abstract 960-P)
Conclusions

• Need for improvement in prandial and basal insulin formulations
• This should transfer into clinically meaningful improvements in:
  – Postprandial glycemic excursions
  – Flat metabolic effect
  – High reproducibility of the metabolic effect
• No product is on the market yet!
Biosimilar Insulin (BI)
Insulin manufacturing: New kids on the block!

- New Hi-Tech insulin manufacturer: India, China, Ukraine, Poland etc. (not only human insulin, also insulin analogues, patents are expiring or not in place (e.g. glargine in India))
- Publications about biosimilar insulins?
- Biosimilar (what is this?): A complex world
- None is on the market in the EU/US that far
- This will change in the near future!?
- Approval process? (Focus on EU)
- Information about BI of one long-acting insulin analogue: insulin glargine
Publications (= Reviews) about BI

• Papers are more comments/reviews due to paucity of published data!
Potential impact of BI on the insulin market

• BI in the Indian market
  – Biocon introduced its insulin formulations in 2004
  – Prices of insulin significantly reduced upon introduction of BI
  – Price of injectable insulin is now $6.75 per 1000 IU (USA: $32 per 1000 IU)

• Forecast: BI’s and insulin analogues will erode $6.1 billion in brand sales in the US and Europe (France, Germany, Italy, Spain and UK) by 2018, saving healthcare systems $3.8 billion in the process
<table>
<thead>
<tr>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very sure</td>
<td>17.1 %</td>
</tr>
<tr>
<td>Somewhat sure</td>
<td>22.9 %</td>
</tr>
<tr>
<td>Unsure</td>
<td>17.1 %</td>
</tr>
<tr>
<td>Never heard of biosimilar</td>
<td>42.9 %</td>
</tr>
</tbody>
</table>

Results from a survey of 500 oncologists (May 2007)
Confusion of terms

- Biosimilars - this term is favored in the EU
- Follow-on biologics (FoBs) – was favored in the US (sometimes named as Follow on Proteins (FOPs))
- Subsequent Entry Biologic (SEB) - Canada
- Similar Biotherapeutic Products (SBP) - WHO guidance, RBP = Reference Biotherapeutic Product
- Similar Biological Medicinal Products (SBMPs) – term used in Australia
- Biopharmaceuticals
- Biopharmaceutical products not subject to regulatory approval (‘B-NSRA’)
- Bioidenticals - Same product
Biosimilars are not generics

Chemical product
e.g. Aspirin®

Chemical synthesis

Branded chemical product

Generic

Biologic
e.g. Insulin

Different manufacturing processes may result in different products

Originator biologic

Biosimilar

Insulin manufacturing has become more sophisticated

Pork/beef insulin production

Semi-synthetic human insulin

Recombinant human insulin

Short-acting insulin analogue

Long-acting insulin analogue

Insulin: By-product profile influenced by folding and cleavage

5. Isolation of cells
6. Cell disruption via homogeniser
7. Isolation and purification of fusion protein
8. Folding
9. Enzymatic cleavage
10. Prepurification and concentration via adsorption

E. coli cell
Inclusion body
Fusion protein
Preproinsulin
Insulin

Typical operations for inclusion body processes

Folding conditions influence by-product pattern
Cleavage enzyme: specificity & selectivity
BI are complex and identical copies cannot be made

• Subtle differences between BI and reference products could be expected
• Manufacturing of BI is a complex, multi-step process (Product can’t be identical, despite identical technological standards!)
• Different manufacturing processes may result in different products (“The Process is the Product”)
• Current analytical tools do not have the sensitivity to detect all differences between different products

Physico-chemical “similarity”

Challenges in making the product

**Active Ingredient:** Heterogeneity (e.g. glycosylation); deamidated-, oxidized-; N/C-terminal-deleted products

**“Pure” product:** Aggregates, degradation products; host cell proteins, infectious agents; purification-process related impurities etc.

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**Primary Structure**
- Molecular mass: Native/Reduced
- A/B chain sequencing: MALDI-TOF

**Secondary Structure**
- Peptide Mapping: LC-MS
- 2D NMR
- Circular Dichroism

**Higher Order Structure**
- Solution NMR
- Fluorescence Spectroscopy
- Bioassays: cell based / Animal based

**Size**
- SE-HPLC
- SDS-PAGE

**Charge**
- cIEF

**Potency**
- Cell based
- Animal based
- HPLC

Regulatory requirements reflect the complexity of biosimilars

- Stringent regulatory requirements needed for biosimilars vs. Generics
- Legislation enforced in EU since 2004 with:
  - Overarching guidelines and guidelines for specific therapeutic classes are established
  - Substitution of biosimilars is a national prerogative
- Guidelines are still under development in many countries outside the EU

Guideline on similar biological medicinal products 2005: CHMP/437/04
Robust regulatory framework for biosimilars is established in the EU

Overarching Guidelines (CHMP/437/04)

Quality Guidelines (CHMP/49348/05)

Non-clin. and Clin. Guidelines (CHMP/42832/05)

Immunogenicity Guideline (CHMP/14327/06)

- r-Human Soluble Insulin Guidance (CHMP/32775/05)
  - Short acting
- Somatropin Guidance (CHMP/94528/05)
- r-GCSF Guidance (CHMP/31329/05)
- r-Erythropoeitin Guidance (CHMP/301636/08)
- LMWH Guidance (CHMP/118264/07)

# EMA requirements for biosimilars compared with originator biologics

<table>
<thead>
<tr>
<th>CMC*</th>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
</table>
| ● Drug substance  
  – Manufacture  
  – Characterisation  
  – Control  
  – Reference standard  
  – Container  
  – Stability  
  ● Drug product  
  – Description  
  – Development  
  – Manufacture  
  – Control  
  – Reference standard  
  – Container  
  – Stability  
  ● Comparability data  
  – Analytical comparison with reference product | ● Pharmacology  
  – Primary pharm.  
  – Secondary pharm.  
  – Safety pharm.  
  – Interactions  
  ● Pharmacokinetics  
  – ADME  
  – Interactions  
  ● Toxicology  
  – Single dose  
  – Repeat dose  
  – Genotoxicity  
  – Carcinogenicity  
  – Reproduction  
  – Local tolerance | ● Pharmacology  
  ● Pharmacokinetics  
  – Single dose  
  – Repeat dose  
  – Special populations  
  ● Efficacy and safety  
  – Dose finding  
  – Schedule finding  
  – Pivotal  
  – Indication 1  
  – Indication 2  
  – Indication 3  
  – Indication 4  
  ● Risk management plan |

*Chemical, manufacturing and control
EMA requirements for soluble BI

• Non-clinical studies
  – In vitro pharmacodynamic studies:
    - Bioassay for affinity
    - Insulin- and IGF-I-receptor binding assay
    - Tests for intrinsic activity
  – Toxicological studies:
    - At least 1 repeat dose toxicity study (≥4 weeks), including toxicokinetics
    - Special emphasis on determination of immune responses
    - Local tolerance study in at least 1 species

Specifically for recombinant human soluble insulin biosimilars; Source: EMEA Guidance on similar biological medicinal products containing recombinant human soluble insulin 2005:EMEA/CHMP/BMWP/32775/2005
EMA requirements for soluble BI

- Clinical studies
  - Pharmacokinetic studies:
    - Single s.c. dose cross-over study with biosimilar and reference product preferably in type 1 diabetes
  - Pharmacodynamic studies (key in demonstrating comparability!):
    - Time-effect profile of hypoglycaemic response
    - Double-blind, cross-over, hyperinsulinemic, euglycaemic glucose clamp study

Specifically for recombinant human soluble insulin biosimilars; Source: ²EMEA Guidance on similar biological medicinal products containing recombinant human soluble insulin 2005:EMEA/CHMP/BMWP/32775/2005
EMA requirements for soluble BI

• Clinical safety
  – Immunogenicity (main safety concern!):
    - Requires studies of sufficient duration
    - i.e. clinical studies of ≥12 months duration using s.c. administration
    - This study should incorporate a comparative phase of at least 6 months duration that is completed prior to market authorisation

• Pharmacovigilance plan:
  - Applicant should present a risk management programme / pharmacovigilance plan

Specifically for recombinant human soluble insulin biosimilars; Source: EMEA Guidance on similar biological medicinal products containing recombinant human soluble insulin 2005:EMEA/CHMP/BMWP/32775/2005
Regulatory framework for biosimilars in the US

Reference listed drug approved under

**Public Health Service Act**
- CBER
  - E.g.: Vaccines, Blood products, Allergenic products, Gene therapy

**Food, Drug & Cosmetic Act**
- CDER
  - E.g.: Monoclonal antibodies, Cytokines
  - E.g.: Insulins, Menotropins, Growth factors

505(b)2 Abbreviated pathway
- Already used for approval of a follow-on growth hormone

No legal pathway
- New legislation under preparation

Requirements based on chemical, pharmacological and clinical complexity

CBER: Center for Biologics Evaluation & Research; CDER: Center for Drug Evaluation & Research; FDA website: [http://www.fda.gov](http://www.fda.gov)
Regulatory pathways proposed for BI in US

- New regulatory guidelines were published in 2012 by the FDA
- Legal pathway established by amending section 351 of the Public Health Service Act
- The Senate committee on Health, Education, Labor and Pensions (HELP) voted for a 12-year period of data exclusivity in November 2009 (HR 3962)
Insulin administration devices add to the complexity of BI

Insulin biosimilar

Disposable pen

Insulin pump

Syringes/needles

Cartridges for reusable pen

*Presentation refers to both formulation and packaging (i.e. cartridge, concentration, excipients)
Insulin glargine copies

• Copies of Insulin Glargine are marketed in some countries outside Europe (e.g., India & China)
• These products have been registered in countries where no specific biosimilar guidelines are in force.
A biotechnology breakthrough in Diabetes

Wockhardt launches new insulin (Glaritus) in India. First in the world after innovator

Mumbai, 10 Feb, 2009

Pharmaceutical and biotechnology major Wockhardt has announced the launch of its new insulin (Glaritus), a recombinant long acting human insulin analogue. Wockhardt is only the 1st company in the world after the innovator to launch this new insulin (Glaritus) that works slowly for over 24 hours. Currently, the worldwide market for this insulin (Glaritine) is $2 billion. As per ORG IMS, the current market for analogues in India is Rs. 120 crores growing at 37% per annum. This new insulin (Glaritus) has been successfully clinically tested on 300 diabetic patients for safety & efficacy parameters and is approved by the Drug Controller General of India.
Biocon Ltd., India / Basalog®
(cooperation with Pfizer stopped!)

January 25, 2008
Publication: The Economic Times

BIOTECH major Biocon plans to launch four biosimilar drugs worth a billion dollars each in global markets in the next two years. It is in advanced stages of talks to acquire or enter into strategic tie-ups with several regional marketing and distribution companies for the launch. The company is also making a $50-million expansion for its contract research unit, Syngene.

"We plan to launch GSCF, Reteplose, Streptokinase and insulin drug Glargine which are biosimilars or generic versions of biotech drugs, each with a market size of a billion dollars at the innovator’s price. While two of the drugs have gone off patent, the other two will soon lose patent protection. Ideally, we would look for collaboration with equity stake with the regional partner, "Biocon VP-finance, Chinappa MD told ET."
Does biosimilarity mean interchangeability and substitution?

- **Interchangeability**
  - The practice of switching one medicine for another provided that medicines are equivalent in a given setting

- **Substitution**
  - Refers to a national policy which permits the switch from one to another medicine that has been demonstrated to have the same quality, safety and efficacy
  - Substitution typically occurs at retail or hospital pharmacies

*European Generic Medical Association. EGA Handbook on biosimilar medicines 2008; *proposed definition, no world-wide common definition*
Biosimilar insulins: Key points

• BI are on their way
• Small differences in the manufacturing process may result in “different” products
• Clear guidelines for market approval in EU, US
• Regulatory authorities recognize the risks of BI
• Concerns are quality, efficacy and safety
• Immunogenicity: most important safety issue
• Clinical trials and pharmacovigilance help guard against immunogenicity
• Personal comment: The (insulin) world will look different in 10 years from now.