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CHALLENGES FOR BIOSIMILAR GENERICS

29 October, 2014

Dr. Vivek Kashyap

709-710 Tolstoy House, 15-17 Tolstoy Marg, New Delhi-110001, India
T: +91 11 2371 6565 / F: +91 11 2371 6556 / mail@lexorbis.com / www.lexorbis.com

Types of Challenges

- Regulatory
- Commercial
- Patent
- Next Generation/Improved Biopharmaceuticals

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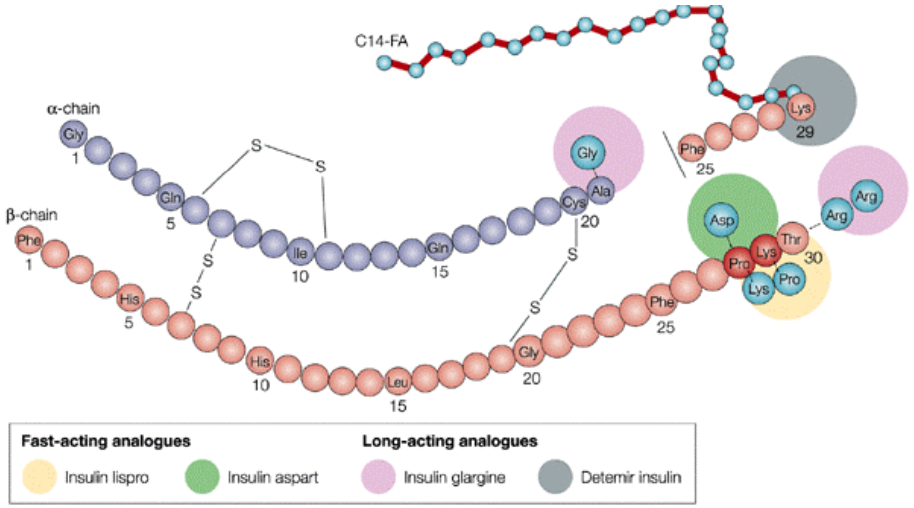
Challenges from Next Generation/Improved Biopharmaceuticals

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Diabetes Drugs

- Insulin Types
  - Human Insulin
  - Insulin Analogs
    - Rapid Acting Insulin
    - Long Acting Insulin
    - Ultra Long Acting Insulin
  - Insulin Delivery Devices

- Novo Nordisk, Sanofi, Eli-Lilly



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Insulin Analogs-Evolution

- Rapid-Acting Insulin
  - Insulin Lispro [Eli-Lilly; US5514646 (1993); US5474978 (1994)]
  - Insulin Aspart [Novo Nordisk; US 5618913 (1994); US 5866538 (1997)]
  - Insulin Glulisine [Sanofi; US 6221633 (1998); US 6960561 (2003)]

- Long-Acting Insulins
  - Insulin Glargine [Novo Nordisl-DK113585(1985); Hoechst-DE372665(1987); Hoechst-DE3837825(1988); Novo Nordisk-DK91098(1998); Novo Nordisk DK200000932 (2000); Aventis Pharma-DE10227232 (2002)
  - Insulin Determir [Novo Nordisk-US5750497(1993); US5866538(1996); US6011007-Div(1993) and US6869930 (1993)]

- Ultra Long Acting Insulin [Novo Nordisk-WO2005012347 (2003)]
  - Insulin degludec

- Liraglutide: GLP-1 [Novo Nordisk-US6268343(1997); US6458924 (1996); and US7235627 (1996)]

- Insulin Pens

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Summary

- Next Generation/Improved Biopharmaceuticals
  - Better Efficacy
  - Better Safety
  - Broad and Varied Patent Protection
  - Better Delivery Systems

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Further Development of Insulin Analogs

- Insulin Lispro (Eli Lilly)-Product by Eli Lilly
  - Pediatric Indications >3 yrs
  - Plug-in Development's : Basal Insulin + Improved Version of Glargine
- Insulin Aspart - Novo Nordisk Product
  - Pediatric Indications >2 yrs
- Insulin Glargine (Long Acting Insulin)
  - Effect on Cardiovascular and Cancer
- Insulin determir-Product by Novo Nordisk
  - B-classified drug for pregnancy
  - Approved for use with other insulin analogue

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Further Development of Insulin Analogues (Contd..)

- Insulin Degludec- Novo Nordisk Product
  - High half-life of >24 hrs (twice as much of Glargine)
  - Nocturnal Hypoglycemia
  - Overall Hypoglycemia

- Liraglutide
  - Long-acting glucagon-like peptide-1 agonist (GLP-1 agonist)
  - Advantages of Liraglutide
    - It acts in a glucose-dependent manner (meaning it will stimulate insulin secretion only when blood glucose levels are higher than normal. Consequently, it shows negligible risk of hypoglycemia).
    - It has the potential for inhibiting apoptosis and stimulating regeneration of beta cells (seen in animal studies).
    - It decreases appetite and maintains body weight-Controls Obesity.
    - It lowers blood triglyceride levels.

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Summary

- New/Multiple Indications
  - New patient populations
    - Paediatric
    - Pregnancy
  - New disease conditions
    - Safe with other disease conditions
      - Pregnancy safe
    - Delivered for controlling/treating other disease conditions, for e.g. Liraglutide

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Summary

- New form of administration of same product
  - Parenteral
  - Oral
  - Injectable

- Change in molecular structure
  - Pegylation, Glycosylation, carboxylic chains, etc.
    - Insulin Determir
    - Insulin Degludec
    - Liraglutide

- Biologic Combinations
    - Premixed Insulin Analogs
    - Insulin analogs + GLP-1 peptides
    - Luveris + Gonal-F (FSH Hormones)

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Other Challenges

- Data Exclusivity Protection
  - Protects against copy or near copy of innovator molecule
  - High up-front investment (Process Engineering and Manufacturing)
    - USA-12 yrs
    - EU- 8 yrs (+2 yrs. Market exclusivity + 1 yr. new indication)
    - Japan- 6 yrs

- Outlook of physicians and patients
  - Brand Loyalty
  - Physicians Recommendations
    - Trust and believe that biosimilars are an effective, safe and cheaper.

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Strategies for Biosimilars

- Gather Patent Information
  - Identify patents
    - Product, Formulation and Process
    - Identify patent that might cover bio-betters
- Check for Data Exclusivity and patent coverage Expirations of Innovators
  - Data Exclusivity is not monopoly protection
    - Filing of Biosimilar Licensing Applications without data of reference molecule. e.g. Human Growth Hormone
- Freedom to Operate
  - Understand the state of the art
  - Understand the relevant patent portfolio of the innovator pharmaceutical manufacturer
  - Seek analysis of proposed biosimilar in view of the patent claims of others
- Consider License Agreements

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Strategies for Biosimilars

- Patents by Biosimilar Generics
  - Formulations not imparting “clinically meaningful differences”
    - Improved formulation properties
      - Storage stability
      - Flowability
      - Change of excipients
      - Solubility
  - Improved Manufacturing process
    - Different cell line
    - Altered nucleic acids
    - Altered culture conditions
    - Improved purification
    - Improved sterilization

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Thank You!

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