

Therapeutic Equivalent Biologics - Current Issues and Perspectives of Follow On Protein Products

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GENERIC BIOLOGICS COULD SAVE \$71 BILLION OVER 10 YEARS (2-15-07)

- Patient and insurer savings could reach \$3.5 billion in savings the first year generic alternatives are on the market.
 - The largest savings would come from anemia treatments, totaling \$40.7 billion over 10 years.
 - Eighty percent of patients with a growth hormone deficiency could switch to a generic biologic, saving \$27.7 million in the first year.
 - Half of multiple sclerosis patients could switch, saving \$678 million in the first year, and more than 25 percent of patients with diabetes could use a generic product and save \$797 million.
- Express Scripts said it supports H.R. 1038, the "Access to Life-Saving Medicine Act of 2007," which may be attached to the Prescription Drug User Fee Act reauthorization. The bill would establish a statutory pathway for the FDA to approve biologic license applications by giving the agency a way to measure the comparability of a biogeneric drug to its reference product without drug companies having to conduct costly and duplicative clinical trials.

French Law Disallows 'Generic' Biosimilars (2-19-07)

- French Parliament has adopted legislation which prevents biosimilar medicinal products from being classed as generics and bans the automatic substitution of one biological medicine for another.
- The new law to be introduced in France establishes a legal definition of "biosimilar" medicines that notes the potential variability of the active substance and differences in the manufacturing process that prevent the classification of biosimilars as strictly generic products and forbids the automatic substitution of one biological medicine for another at the pharmacy level without the express consent of the prescribing physician.
- *Analytical and preclinical tests are not sufficient to demonstrate the sameness of two biological products or that they are identical,* says the European Association for Bioindustries.
 - *A major concern when using biotech medicines is patient safety and drug efficacy," said Dr Carlo Incetti, President of European Biopharmaceutical Enterprises. "Because biosimilars are not exact copies of the reference products, they cannot have the exact same safety profile as the original biotech medicine."*

2006 FOP News

- **FDA under pressure to 'open the floodgates' for biologics**
 - Governors from four US states have petitioned the US FDA for clarity in their requirements for the production of generic versions of insulin and human growth hormone (hGH), the first step to opening the market up to generic biopharmaceuticals (August 17, 2006).
- **Zenotech Receives Marketing Approval for Generic GM-CSF, G-CSF**
 - Zenotech Laboratories has received two approvals in India for generic versions of Leucmax by Novartis and Neupogen by Amgen and Roche. Zenotech is exploring applying in Europe as well (August 9, 2006).
- **Biosimilar or Generic?**
 - The FDA has turned down Nasteck's generic version of the nasal spray Miacalcin for the treatment of osteoporosis because of the possibility of an interaction with a preservative (chlorobutanol) used in the formulation and the potential for immunogenicity, sparking heated debate in the US about whether calcitonin should be treated as a generic or a biosimilar drug (July 19, 2006).
- **BioPartners' Biosimilar Drug Knocked Back in Europe**
 - BioPartners has failed to bring Alpheon, its second biosimilar product into Europe after the EMEA issued a negative opinion on its interferon α -2a, recombinant hepatitis C drug, citing characterization, manufacturing and quality control concerns (July 3, 2006).
- **Approval Pathway for FOB Unlikely Until 2008**
 - Any legislative fix to the current FDA approval process for follow-on biologics is likely at least two years away because of other legislative priorities and the need for lawmakers to get up to speed on this issue, a Senate staffer says (June 26, 2006).

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2006 FOP News

- **Sandoz Gets TGA ('04), EMEA ('06) and US ('06) Approval for Omnitrope (rhGH)**
- **Biopartners Gets EC Approval for Valtropin**
 - Market authorization May 4, 2006
- **Biocon (India) will Introduce its Insulin Product**
 - Insugen to be sold in in Germany through a marketing partnership (May 5, 2006)
- **FDA reconsiders generic biologic guidelines**
 - After reassessing these product specific documents, FDA has decided that it would be more appropriate to publish guidances that are more broadly applicable to (follow-on protein products) in general. (April 6, 2006)

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Process / Comparability Challenges

- **Comparability of Biosimilars**
 - Combe *et al. Pharmacotherapy* 2005 Jul;25(7):954-62
- **Biosimilars are not truly equivalent.**
 - Products differed widely in composition, did not always meet self-declared specifications, and exhibited batch-to-batch variation
 - Clinical experience demonstrates dosing variability among patients
- **Manufacturing Changes Pose Challenges for Biogenics**
 - Product = Process ???
 - Accepted Variability of Glycosylation, Isoforms, Folding, etc.???

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The FOP Paradox

- The cost of developing a FOP may be greater than the cost of developing a new product
- Dependent on clinical criteria
 - Equivalence
 - Non-inferiority to reference product
 - Safe and efficacious
- What is the differential cost of equivalence/similarity/substitutability/switchability?
- How important is an “A” rating?
 - Room for Affordable TE Biologics Without an AB Rating
 - Multi-source biologics available now without any significant cost savings to patient/insurers

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Challenges

How can the industry prove pharmaceutical and therapeutic equivalence of multi-source, “follow on biologics”?

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Today's Discussion

- FOP Market Opportunities
- Definitions, Terminology and Regulations
- Therapeutic Equivalence
- EMEA Guidance
- Immunogenicity
- Label Considerations
- Future Perspectives and Conclusions

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Opportunities and Challenges

- Over \$20 Billion of Biotechnology-Derived Drug Products Losing Patent Protection Over the Next Few Years
 - Significant opportunity for generic manufactures and managed health care
- Significant Legal & Regulatory Challenges
- Registration Requirements and Process
 - Largely Undefined for PHSA Approved Products
 - No Provisions for an “ABLA”
 - Therapeutic Equivalence Issues

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Top Biotech Products

| Product | Active | Company | Approval Year | 2005 Sales \$ Millions* |
|---|-----------------------|--|---------------|-------------------------|
| Procrit®, Epopogen® | Epoetin- α | Amgen, J&J | 1989 | 6,000 |
| Aranesp® | Darbepoetin- α | Amgen | 2001 | 2,800 |
| Remicade® | TNF- α | JNJ (Centocor) | 1998 | 1,820 |
| Neupogen® | Filgrastim | Amgen, Inc. | 1991 | 1,503 |
| Enbrel® | Etanercept | ImmuneX | 1998 | 1,500 |
| Humatrope®, Nutropin® Satzene®, Tey-Tropin®, Norditropin®, Genotropin® | rhGH | Lilly, Genentech, Serono, Ferring, NovoNordisk, PU | 1987 | 1,500 |
| Rituxan® | Anti-CD20 Mab | Genentech | 1997 | 1,401 |
| Humira® | Adalimumab | Abbott | 2002 | 1,400 |
| Avastin | Bevacizumab | Genentech | 2004 | 1,100 |
| Intron A® | INF- α -2b | Schering Plough | 1995 | 857 |
| Avonex® | IFN- β -1a | Biogen, Inc. | 1996 | 797 |
| Betaferon® | IFN- β -1a | Schering AG | 1995 | 682 |
| Humulin® | 75%HIU/25%HRI | Lilly | 1992 | 630 |

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*IMS 1/2006

Terms / Definitions

- **Drug**
 - articles recognized in official compendia; intended for the use in the diagnosis, cure, mitigation, treatment and prevention of disease... [FD&CA]
- **Biologic**
 - Biologic Product - “any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product... applicable to the prevention, treatment, or cure of disease or injuries of man” [PHSA]
- **Biotech-Derived Drug Product:**
 - Proteins and polypeptides... produced from recombinant or non-recombinant cell-culture expression systems ... can be highly purified and characterized” ... [ICH Q6B Specifications]
- **Well Characterized Proteins**
 - The natural molecular heterogeneity, impurity profile, and potency is defined with a high degree of confidence.
- **“Specified biologics”** are biologics that are:
 - Therapeutic synthetic peptide products of 40 or fewer amino acids,
 - Monoclonal antibody products for in vivo use,
 - Therapeutic recombinant DNA-derived products (21 CFR 600.3(h)).
- **Follow-on Protein Pharmaceutical (Proposed Definition):**
 - A protein product which is intended to be a similar version or a duplicate of an already approved or licensed protein product

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Terminology

- Drugs – FD&CA
- Biologics - PHSA
- Follow On Biologic
 - Biogeneric
 - 2nd Generation Biologic
 - Subsequent-Entry Protein Pharmaceutical (SEPP)
 - Therapeutically Equivalent Biologic (TEB)
- Biosimilars
 - Similar Biologic Medicinal Product (EMA term)
 - Follow On Similar Biologics (Japan)
- Global Term Harmonization

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Drug vs Biologic

| | Drug | Biologic |
|---------------------------------|--|--|
| Active Ingredient | Typically well characterized small (< 5000) molecules. Stability / Impurities usually defined. | Often large macromolecules (> 5,000) with the potential for multiple forms (e.g. glycosylation), potential process/stability issues. |
| Manufacture | Typically chemically synthesized with high degree of purity and characterization. Can be analyzed from a structure function perspective. | Inherent Heterogeneity. Product Process Relationship. Activity may be affected by minor changes in bioprocessing and post-translational modifications. |
| Production | Typically a well defined synthetic pathway that can be scaled to relatively large quantities. | Potential for complex production process, scale up, purity, batch variability issues. Process yields can be small. |
| Dosage Form | Variable (oral, topical, inhaled, injections, etc). Established specifications Concentration determined by established test methodologies. | Usually an injectable solution. Potency more difficult to quantify. |
| Immunogenicity Potential | Usually too small to be considered immunogenic and are generally not recognized as "antigenic" by the immune system. Low batches to batch variability. | Variable, depending on the biologic. Immunogenic potential is high for macromolecules that are recognized as foreign, and can destroy the activity of the biopharmaceutical. |

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Generic Therapeutic Equivalence "A" Rating

- FDA classifies drug products as therapeutically equivalent if:
 - Products that are approved as **safe and effective**
 - Products that are **pharmaceutical equivalents**
 - contain **identical amounts** of the same active drug ingredient in the same dosage form and route of administration
 - Sameness (Seroquel vs. Shalal, Amgen vs. HRM, Avonex® Approval, Xigris®, etc.)
 - **meet compendial** or other applicable **standards** of strength, quality, purity, and identity
 - Products that are **bioequivalent**
 - Same rate and extent of absorption (C_{max} , AUC) to RLP
 - Products that are **adequately labeled**
 - Products manufactured in compliance with Current Good Manufacturing Practice (CGMP) regulations
- Will this Work for a Generic Biologic?

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Factors Impacting TE for FOP

- **Pharmaceutical Equivalence**
 - Structural Similarity
 - Analytical Capabilities
 - Structure-Function Knowledge
 - Manufacturing Process Design, Validation
- **Bioequivalence**
 - Monitoring Blood Levels May Not Be Sufficient
 - Structure-Function Knowledge (Multiple Functional Sites)
 - Ability to Determine Availability at Site of Action
 - Pharmacodynamics (Biomarkers)
 - Immunogenicity and AEs
 - Equivalence versus Non-inferiority

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RLD / AB-Rating / USP

- "AB" Rating Granted as TBE to Brand If Product has:
 - Same Rate of Absorption (C_{max})
 - Same Extent of Absorption (AUC)
- Reference Products Exist for:
 - Insulin, hGH, Heparin, hCG, Glucagon, etc.
 - Most Biologics Not Listed
- Official US Compendia
 - USP Guidance on BDP
 - <1041, 1043, 1045-1050 >
 - USP 29 monographs for Insulin, Somatotropin, Others
 - Need For RS and Monographs



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US Registration Pathways

- Products are **either**:
- **Approved as drugs** under FD&CA:
 - Insulin, hGH, Growth Hormone, Calcitonin, Glucagon, Menotropins, etc.
- Or **licensed** as biological products under PHSA:
 - Epoetin, Infliximab, Interferons, GCSF, etc.

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Legal Aspects

Statutes

Food Drug & Cosmetic Act



Public Health Service Act



Application

New Drug Application (NDA) 505(b)
Abbreviated NDA (ANDA) 505(j)

Biologic License Application (BLA) NSR

No ABLA

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FD&CA 505(b)(2)

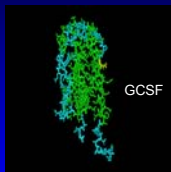
- Present ANDA Process Inadequate
- Available Option - 505(b)(2) – If RP Approved by 505(b)
 - All of the 505(b)(1) info (except original clinical data)
 - Reference to clinical data (add'l data may be needed)
- AB Rating? No
- WH Exclusivity? No
- Label? Partial
- User Fee Yes
- Awaiting Future FDA Guidance
- Existing Guidances
 - US & EMEA Guidances, Comparability, US & EU Compendia, etc.
- Legislative Changes? (FDAMA, PHS, WH Modernization)

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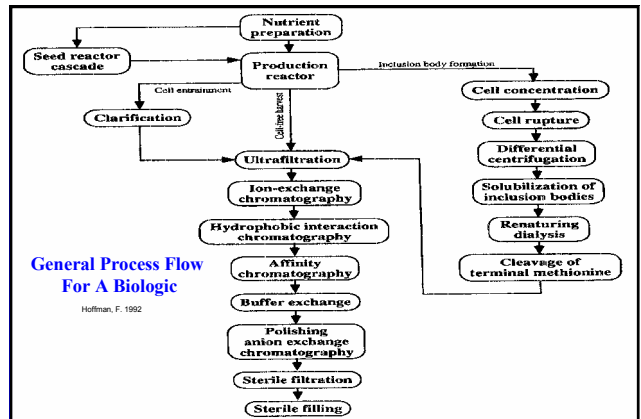
Scientific Attributes

• Biotechnology Products

- Can Be Complex
 - Inherent Heterogeneity
 - Product Process Relationship
- Physical/Chemical Characterization
 - Structure Confirmation
 - Purity / Impurity Profile
 - Modern Analytical Techniques
- Mature, Well Characterized Proteins
 - 2nd Generation Products



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Scientific Attributes

• Product Process Relationship

- Similar Expectations For Drug and Biologics
- API, FDF, Excipients, Adjuvants, Mfg. Materials
 - Qualification, Specifications, Validated Testing, QA
 - Analytical Methods and Process Validation
 - Process Analytical Technologies
 - Bioassays
 - Relevant Animal Models / Preclinical Animal Studies
 - Quality By Design

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General Classes of Proteins for Generic Development

| Class | Marketed Products | Polypeptide Backbone | Primary Sources Heterogeneity | Analytical Comparability | Process Comparability |
|-------------------|--------------------------------------|--------------------------------------|---|--|--|
| Simple Unmodified | Insulin hGH α ₁ IFN | homogeneous or limited heterogeneity | degradation, processing | less difficult, size-dependent | less difficult, size-dependent |
| PEGylated | PEGIFN _α 2a PEGIFtrast | homogeneous or limited heterogeneity | length of PEG, attachment site, degradation | more difficult but still very feasible | more difficult but still very feasible; PEGylation controlled chemically |
| Glycosylated | Epoetin Cetuximab Etanercept | homogeneous or limited heterogeneity | sugar chain sequences and branching; attachment site; degradation | challenging but feasible | challenging but feasible; glycosylation controlled biologically |

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Pharmaceutical Equivalence

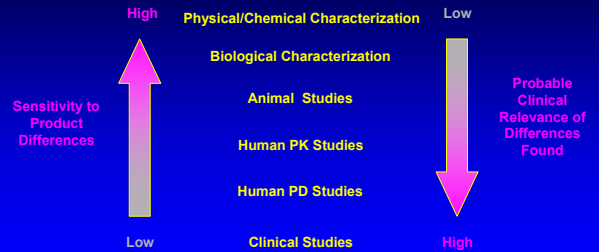
Product Complexity

| | | |
|----------------|-----------|----------|
| Human Insulin | MW 5808 | (51 AA) |
| Erythropoietin | MW 30,400 | (165 AA) |
| hGH | MW 22,125 | (191 AA) |
| TPA | MW 70,000 | (527 AA) |

No Penultimate Technique
 Address By Product Complexity & SE Experience
 Specifications, Monographs and Excipients / Adjuvants
 Structure Activity Data Base
 Quality Control / Quality Assurance / QbD

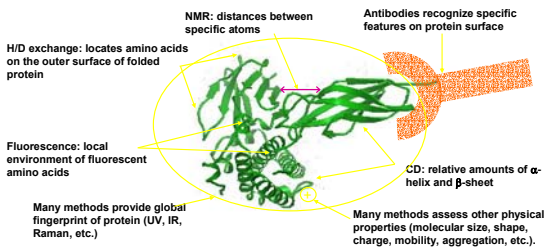
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Comparative Tools



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Analytical Methods for Assessing 3D Structure



View generated using AstexViewer™:
 Michael J. Hartshorn "AstexViewer™: An aid for structure-based drug design",
 Journal of Computer Aided Molecular Design 16 (12): 871-881 (2002), DLI-Ibetti 2006

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Factors to Consider

- Quality Attributes
 - 1°2°3° Structure
 - Multi-Subunit?
 - Post-Translational Modifications?
- Structure Function Information
- Heterogeneity
- Analytical Methods
- Impurity Profiles
- Formulation Components
- Stability
- Container Closure
- Potential Contaminants
- Potential Immunogenicity

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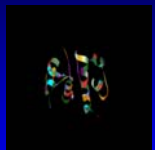
Impurities

- Process-Related Impurities
 - Media, HCP, Leachates, etc.
- Product-Related Impurities
 - Truncation, Mis-folds, Aggregation, etc.
- What is the Consequence of the Impurities at Their Given Concentrations?
 - e.g. Proteases, Catalytic Metals, Aggregate Inducers, Antigens, Adjuvants, Allergens, Antagonists, Agonists

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USP 29 Insulin/Insulin Human Monographs

- USP 29 Insulin Human
 - Enzymatic Modification of Insulin from Pork Pancreas
 - Microbial Synthesis Via Recombinant DNA process
 - NLT 27.5 USP Insulin Units/mg
 - Proinsulin NMT 10 ppm
- USP 29 Insulin Injection
 - Isotonic, Sterile Solution
 - Labeled Potency NLT 95.0 - 105.0% USP Insulin Units
- No TE Code for Insulin Listed in the Orange Book

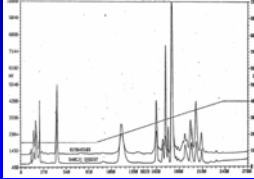


USP 29 Insulin Human
 USP 29 Insulin Injection
 USP 29 Insulin Human Monographs
 USP 29 Insulin Injection Monographs

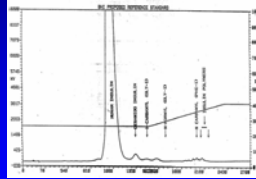
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Insulin Analysis

Peptide Mapping

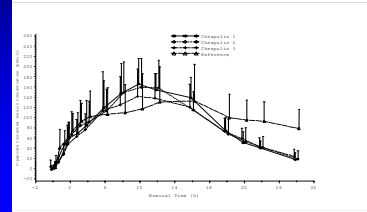


HPLC



Chui, 2003

Mean (+SD) C_{ptide} Corrected Insulin Concentration Time Profiles Following Subcutaneous Administration of Biosimilar Formulations 1, 2, 3 and Reference Marketed Long Acting Insulin



Clarke, 2006 NBC

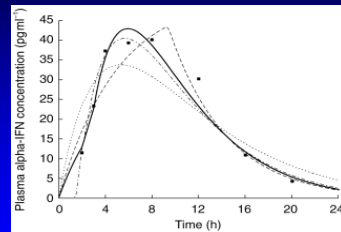
Interferon-α-2b

- E.Coli Production
 - single, non-glycosylated, polypeptide chain
 - 165 AA
 - 19,265 Dalton
- EP Monograph
 - Assay, Potency, ID, Host cell derived proteins, Host cell or vector derived DNA, PM, IEF, Impurities, Related Proteins, Endotoxins, Monomers, Aggregates, Deamidated/Oxidized Forms



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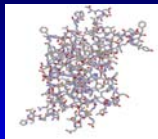
Interferon PK



Chatelut et al. *British Journal of Clinical Pharmacology* 47 (4), 365-371 (1999).

Somatropin (C₉₉₀H₁₅₂₈N₂₆₂O₃₀₆S₇)

- 191 AA, 3087 atoms, 3119 bonds, 22,125 d
 - Human Sequence
 - *E. Coli*, Mammalian Cell, Transgenics
 - Formulation, Excipients, Packaging
- Orange Book
 - Seven Somatropin Listings
 - All BX Therapeutic Rated
 - RLD Are Not Available for All Strengths & Brands
 - Choose RLD Wisely for Comparability
 - Label / Delivery Device
- Patent Situations
 - API, Finished Dosage Form (2002 -2018)

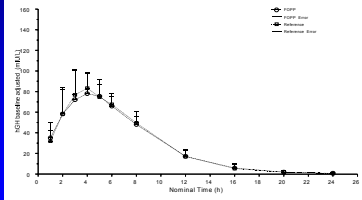


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Somatropin USP 29

- | API | Finished Product |
|---|---|
| • Packaging and Storage | • Packaging/Storage |
| • Labeling | • Labeling |
| • USP Reference Standards <11> | • USP Reference Standards <11> |
| • Identification <ul style="list-style-type: none"> - A (HPLC <621>) - B (Peptide Mapping <1047>) | • Identification <ul style="list-style-type: none"> - HPLC <621> |
| • Bacterial Endotoxins <85> | • Bioidentity |
| • Microbial Limits | • Bacterial Endotoxins <85> |
| • Water Method <i>lc</i> <921> | • Sterility <71> |
| • Chromatographic Purity <621> | • Chromatographic Purity <621> |
| • Limit of High Molecular Proteins | • Limit High Molecular Proteins |
| • Content of Protein <851> | • Assay - HPLC <621> |
| • Bioidentity - API or FP <ul style="list-style-type: none"> - Rat Weight Gain Test | |
| • Assay - HPLC <621> | |

Mean (+SD) Baseline Corrected hGH Concentration versus Time Profiles Following Single s.c. Injections of FOPP and Reference



Clarke, 2006 NBC

Product Comparability Protocols

- Comparability
 - AA Analysis (AA Sequence, 2°, 3° Structure, etc.), Peptide Mapping, Chromatography, Electrophoresis, Spectroscopy, Histochemical Analysis, Microheterogeneity, Glycosylation, Phosphorylation, Deamidation, Aggregation, Binding Studies, Bioassays, Degradation, Stability, etc.
 - Animal Models
 - Human PK / PD
 - Clinical Trial
 - FDA & ICH Guidances

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Avonex® Comparability

| Analysis | Result |
|-------------------------------------|--|
| Peptide Map | Similar t_R Corresponds to Natural Sequence |
| N-Terminal AA Sequencing | Corresponded as Predicted Sequence; Minor Form (des-1 (-methionine)) Detected in Varying Amounts in Both Products |
| BLAcore | Binding Virtually Identical |
| CHO EP / MS | 3 Major Glycoforms in Both Products Detected in equal proportions; Differences were Noted Between Minor Glycoforms |
| Immunoblot | 1 Major Band for Both Products; Differences in Minor Bands and IEF Gels (des-1 form) |
| HPLC | Similar t_R Difference in Deamidation. |
| Receptor Binding Assay | Equal |
| PK (AUC) | 112% (100 -126%) |
| Neopterin Production | 124% (99 -156%) |
| Phase IV PM Immunogenicity Study | Less than 9015 (5 vs 24%) |
| β -2 Microglobulin Production | 127% (96 -168%) |

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EMA Guidances

- General:
 - Overarching
 - Quality Issues
 - Nonclinical/Clinical
- Product-specific:
 - Human Insulin
 - Human Growth Hormone
 - GCSF
 - Erythropoietins

US FDA Guidances ? ? ? ?

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EMA Biosimilar Guidance Non-Clinical Studies

| Product | PK <i>in vivo</i> | PD <i>in vivo</i> | Toxicology |
|---------|--|---|---|
| Insulin | Insulin, IGF | Not Required | 1 repeat dose tox study in rats, 4 weeks and local tolerance |
| rhGH | Comparative bioassay | Rat weight gain or tibia growth assay | 1 repeat dose tox study in rats, 4 weeks |
| GCSF | Receptor binding assay | Neutropenic and non-neutropenic rodent models | 1 repeat dose tox study in rats, 4 weeks |
| EPO | Receptor binding Cell proliferation | Erythropenic effects in animal models | 1 repeat dose tox study in rats, 3 months and local tolerance |

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EMA Biosimilar Guidance Clinical Studies

| Product | PK | PD | Efficacy | Safety |
|---------|-------------------------------------|---------------------------------------|---|-----------------------------|
| Insulin | 1 single dose crossover in patients | Double blind cross over glucose clamp | Not Required | Immunogenicity SC 12 months |
| rhGH | 1 single dose crossover | IGF-1 and IGFBP-3 | At least 1 adequately powered, randomized, parallel group clinical trials 6-18 months | Immunogenicity 12 months |
| GCSF | 1 single dose crossover | Neutrophil and CD34 cell counts | Two arm equivalence Extension to other indications | Immunogenicity > 6 months |
| EPO | 1 single dose crossover | Reticulocyte counts | 2 adequately powered, randomized, parallel group clinical trials. | Immunogenicity 12 months |

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Product-Specific Guidances: Other Points

- Pharmacovigilance
- Extension to other indications
- Actual studies required depend on comparability outcome
- Varying guidance on acceptance criteria: most to be justified on clinical grounds
- Suggest combining study objectives where feasible
- Each guidance considers particular characteristics of the product/patient/history

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Immunogenicity

- Different Classes of Protein can be Immunogenic
 - Animal, Human, Human Recombinant Proteins
 - Antibody Therapeutics
 - Murine, Chimeric, Humanized
- Molecular Structure
 - novel epitopes, glycosylation, aggregation, degradation, oxidation, deamidation
- Product Impurities
- Formulation
- Dose, Route, Frequency of Administration and Duration of Therapy
- Immune Status of the Patients, Disease
- Immunomodulatory Properties of the Protein

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Therapeutic Proteins Inducing Antibody Responses

| Molecule | Indication | Antibody Incidence | Antibody related side effects |
|---|-------------------------|--------------------|-------------------------------|
| rhINF- α -2a | Hepatitis | 30-50% | Loss of Efficacy |
| Chimeric Anti-TNF MAb | RA, Crohn's | 10-57% | Reduction in Efficacy |
| Recombinant Human Glucocerebrosidase | Type1 Gaucher's Disease | 13% | None reported |
| Recombinant Human α -galactosidase | Fabry's disease | 88% | None reported |
| Murine anti-CD3 Monoclonal Antibody | Organ Transplantation | 80% | Loss of Efficacy |
| rh-Erythropoietin | Anemia | Rare | Pure red cell aplasia |

Thorpe 2005
Koren 2006

Assessing the severity of potential antibody related side effects (Risk Assessment)

| More Severe | Less Severe |
|---|--|
| Endogenous version Unique activity Sole therapy Life threatening disease | No endogenous version Redundant activity Other therapies Non life threatening disease |
| Repetitive treatment Non immunosuppressed subjects | Single dose treatment Immunosuppressed subjects |

Mire-Sluis, A.R., IIR Immunogenicity Conf. 2004

Immunocomparability

Comparisons will likely vary, dependent upon:

- Drug class (ex. Antibody vs. Cytokine)
- Indication
- Route, dose and frequency of administration

Using current technology, will require combinations of:

- Appropriate and relevant biochemical analyses
- Appropriate and relevant bioassay(s)
- Clinical trials (full or abbreviated, depending on other factors)

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Labeling

- Can One Indication Extend to the Other Indications?
- Labeled Adverse Events, Immunogenicity
- Can a FOPPP Manufacturer Inherit All or Parts of the Reference Label?
 - Is this a violation of trade secrets?
- Can the FOPPP:
 - Be substituted for the reference product?
 - Are they interchangeable?
 - Be "switched" during therapy?

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Omnitrope

- PK in healthy males and females
- Pediatric Growth Hormone Deficiency (GHD)
 - RCT (n = 89, n = 44 OMNITROPE™, n = 45 other somatotropin for 9 months, SC dose of 0.03 mg/kg. OMNITROPE™ and the somatotropin comparator showed similar effects on growth during the 9 months of treatment.
- Adult Growth Hormone Deficiency (GHD)
 - Randomized, placebo-controlled clinical trials with somatotropin have been conducted in adult GHD patients. In these trials, beneficial changes in body composition (LBM, TBW, L/F, TBF, WC, BMD) were observed at the end of a 6-month treatment period for patients receiving somatotropin as compared with the placebo patients.

rhGH Labels - AEs

- **Humatrope**
 - As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein. During the first 6 months of Humatrope therapy in 314 naive patients, only 1.6% developed specific antibodies to Humatrope (binding capacity \geq 0.02 mg/L). None had antibody concentrations which exceeded 2 mg/L. Throughout 8 years of this same study, two patients (0.6%) had binding capacity $>$ 2 mg/L. Neither patient demonstrated a decrease in growth velocity at or near the time of increased antibody production. It has been reported that growth attenuation from pituitary-derived growth hormone may occur when antibody concentrations are \geq 1.5 mg/L.
- **Omnitrope**
 - As with all protein drugs, a small number of patients may develop antibodies to the protein. Growth hormone antibody with binding capacity lower than 2 mg/L has not been associated with growth attenuation. In some cases when binding capacity is $>$ 2mg/L, interference with growth response has been observed.
 - Preparations of OMNITROPE contain a small amount of host cell *Escherichia coli* peptides (HCP). Anti-HCP antibodies are found in a small number of patients treated with OMNITROPE, but these appear to be of no clinical significance.
 - Incidence of drug-related treatment-emergent adverse events occurring in $>$ 5% pediatric patients with GHD during first 15 months of treatment (N=44)

How Same Is "The Same"?

Optimally:

- Same critical quality attributes
 - 1'2'3' Structure
 - Post-translational modifications (?)
- Same potency, concentration, dosage form
- Impurities, Levels
- Similar Rather Than Identical

Is the Variation Clinically Meaningful?

- Despite lot to lot variability, as well as process evolution over time, clinical safety/efficacy are maintained
- Human system does not appear as sensitive to these variations that are inherent to a biologically based manufacturing process
- Products for which the human body is sensitive to small variations tend to be screened out (abandoned) during the development process
- Appropriate Risk Assessments

Process = Product ?

Is it possible to produce the same product by two different methods?

In theory, yes.

Hurdles:

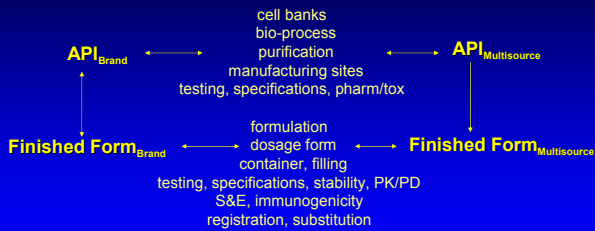
- Making the same product.
- Demonstrating that it is the same
 - Molecular complexity
 - Heterogeneity
 - Critical quality attributes



Peptides, LH, FSH, Insulin, hGH, Glucagon, Hyaluronidase, Calcitonin Salmon, INF- α , β *, GM-CSF*, EPO*

MAbs, Blood Factor (e.g. VIII), Others

Biologic Comparability



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"Primum non nocere"

The physician's motto of "first, do no harm" is high on the list of biotech arguments. "I would propose that there is a heavy burden [on the follow-on biologics manufacturer] to prove that there is no impact on safety,"

Bruce Kuhlik, PhARMA.

Pathways / Conclusions

- Therapeutic Equivalence
 - Pharmaceutical Equivalence
 - IPPQ, Process / Product Validation / PAT / GxPs
 - Monographs, Specifications, Testing, RS
 - Valid, Reliable, Harmonized Analytical Techniques
 - Clinical Equivalence
 - Animal and Human Studies
 - Relevant bioassays
 - Qualified biomarkers
 - Reference "Listed" Product
 - Immunogenicity
 - Pharmacovigilance
 - EMEA Guidances / FDA Guidances
 - Label Considerations

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Pathways / Conclusions

- Global Unified / Harmonized Regulatory Filing
 - CBER - CDER - OGD Harmonization
- Statutory Amendments and Legislation
 - HR 1038/S4016 Access to Life-Saving Medicine Act - PHSA
- Product Complexity and Knowledge Base
 - Well Characterized Proteins VS Complex Proteins
- Guidance from FDA
- ICH / USP / International Guidances
- Sound Science
- Understand Your Product
 - Assurance of Safety and Efficacy to the Patient, Pharmaceutical and Medical Community
 - Gained with Time

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