

Regulatory and Scientific Perspectives on Biopharmaceutical Comparability and Follow-on Biologics

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Topics To Be Covered

- Introduction
- Manufacturing Changes and Comparability for Biopharmaceuticals
- Issues on Comparability Exercise
- Follow-on Biologics
 - Background, Regulatory and Scientific Issues
- Current Development on Follow-on Biologics in US and EU
- Conclusion

Biologics/Biological Products

Poorly characterized products Well-characterized products

- Traditional vaccines
 - Whole blood
 - Blood derivatives
 - Blood components
 - Allergenic extracts
 - Stem cells
 - Somatic cell and gene therapeutics
 - Toxins
- Natural proteins
 - rDNA-derived proteins
 - Monoclonal antibodies
 - rDNA-derived vaccines

Specified Biological Products

NDA's (FD&C Act)

- Insulin
- Growth Hormone
- FSH, LH, hCG, TSH
- Calcitonin
- PTH
- Aprotinin
- Imiglucerase
- Hyaluronidase

BLA's (PHS Act)

- Interferons
- t-PA
- Erythropoietin
- Monoclonal antibodies
- Enzymes

Product Characteristics

Product	Molecular Size	Subunits	Glycosylation
Insulin	52aa, 5.5 Kda	two	None
Somatropin	192aa, 22 Kda	Single	None
Epoetin alfa	165aa, 30 Kda	Single	Yes
Herceptin	1330aa, 150Kda	Multiple	Yes

Definitions

- **Comparability (ICH Q5E)**
 - Same manufacturer's products before and after manufacturing changes (FDA and Q5E)
 - Quality attributes are **highly similar(not necessary identical)** before and after a manufacturing change(Q5E)
- **Pharmaceutical equivalence (FD&C Act)**
 - Products from different manufacturers.
 - Drug products that contain identical amounts of **identical active ingredient**, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage form... (FDA, 21CFR 320.1(c)).

Evolution of Comparability Guidance

- General practices before 1996
- Comparability Document for specified products (FDA, 1996)
- Comparability Guideline (EMA, 2000 and 2003)
- CTD-Q Discussion (2001)
- PhRMA Concept Paper to ICH Steering Committee (Feb 5, 2002)
- ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (Step 2, 2003)

Manufacturing Changes

- **Production system**
 - New cell line
 - Master cell bank
 - Working cell bank
- **Fermentation/culture process**
 - Raw materials, cell culture conditions, scale, equipment, site change
- **Purification process**
 - Column/resin, reagents, scale, site, equipment
- **Drug product**
 - Batch size, container/closure, shipping, storage
- **Formulation and filling**
 - Excipient, equipment, change in manufac. Protocol, scale,, shipping
- **Manufacturing facility**
 - Site change, new site, and contract manufacturer

Comparability Testing

- **Quality Studies**
 - Physicochemical tests
 - Bioactivity/Potency assays
 - Stability
- **Non-clinical Studies**
 - PK/PD
 - Toxicology
- **Clinical Studies**
 - Efficacy
 - Immunogenicity

Incremental
or
Complementary



Comparability Exercises

- Molecular complexity
- Manufacturing process
- Degree of characterization
- Clinical indications
- Availability of safety data
- Availability of clinical data

- Quality Studies
 - **Physicochemical tests**
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Outcomes of Quality Assessments

- **Product is Comparable**
 - Product is indistinguishable or minor differences have no impact
- **Product is not Comparable**
 - Product identity has changed or Adverse affect on product quality
- **Insufficient Information**
 - Significance of differences are unknown or suspected differences can not be ruled out
 - Additional level of evaluation is needed

Clinical and Non-clinical Studies

- **Non-clinical studies**
 - Pharmacodynamic and pharmacokinetic studies
 - Toxicological studies
- **Clinical studies**
 - Immunogenicity studies
 - Efficacy studies

*Q5E discussion after Step 2

Definition of Follow-On Biologics

-subsequent versions of biologics independently develop after a pioneer's product. **It may, or may not, be intended to be molecular copies** of the innovator's product. They do, however, depend on the same mechanism of action and are **intended to be used for the same indication.** *BioPharma*
- A protein product with the **same amino acid sequence** and a similar enough production process and overall structure to appear on its face to be very similar to an already approved product or products. *Steve Galson, acting Director, CDER, FDA, May 5, 2004*

Annual Sales and Patent Expiry

Brand Name (Generic Name)	Marketing Company	Sales (\$,millions)	Patent Expiry	Application
Rebetron™ (Ribavirin and Interferon alfa-2b)	Schering-Plough	1,361*	2001	BLA
Ceredase®(alglucerase)	Genzyme	537	2001	NDA
Cerezyme®(imiglucerase)	Genzyme	537	2001	NDA
Humulin®(human insulin)	Eli Lilly & Co.	1,137	2002	NDA
Novolin®(human insulin)	Novo Nordisk	260.4	2002	NDA
Intron® A(interferon alfa-2b)	Schering-Plough	361	2002	BLA
Avonex®(interferon beta-1a)	Biogen	761	2003	BLA
Humatrope® (somatropin)	Eli Lilly & Co.	303	2003	NDA
Nutropin®/Nutropin AQ® (somatropin)	Genetech	226	2003	NDA
Epogen® (epoetin alpha)	Amgen	2,034	2004	BLA
Procrit® (epoetin alpha)	J & J	1,720	2004	BLA
Synagis® (palivizumab)	Abbott	420	2005	BLA
Neupogen® (filgrastim)	Amgen	1,224	2006	BLA

Source: IMS Health, ABN AMRO estimates and FDA Orange Book

Regulatory Development

- **1996**, Generic menotropin by Ferring approved by CDER
- **1998-2001**, Draft guidance for follow-on growth hormone and insulin
- **2002**, Transfer of therapeutic proteins and Mabs to CDER
- **2002**, Omnitrope 505(b)(2) application (follow-on GH) by Sandoz
- **2003**, FDA follow-on biologics WG and proposed guidance
- **2004**, Genentech Citizen Petition, 2004
- **2004**, Pfizer Citizen Petition on Omnitrope in US
- **2004**, Delayed approval of Omnitrope NDA without deficiencies
- **2004**, FDA Follow-on Workshop (September)
- **2005**, DIA-FDA Follow-on Workshop (February)
- **2005**, EMEA guideline for biosimilar products and specific products
- **200?**, FDA's guidance or concept paper

Issues on Follow-on Biologics

- Patent and exclusivity of reference products
- Legal Authority under FD&C Act and PHS Act
- Abbreviated data requirements
 - Generic drug concept (ANDA)
 - 505(b)(2) NDA based on literatures or FDA's finding of safety and efficacy
 - Other approaches (BLAs)
- Interchangeability issues
 - Orange Book listing (NDA and ANDA products only)
 - Labeling (may be feasible for BLA products)
 - Non-interchangeable but same indications
- Scientific Issues and data requirements

Data Requirements For Drug Approval

	<u>FD&C</u> 505(b)(1)	<u>FD&C</u> 505(b)(2)	<u>FD&C</u> 505(j)	<u>PHS</u>
Application	NDA	NDA	ANDA	BLA
Pre-clinical	Yes	Yes/or No	No	Yes
Clinical	Yes	Yes/or No	No	Yes
CMC	Yes	Yes	Yes (PE)	Yes
PK & Bioavailability	Yes	Yes		Yes
Bioequivalence			Yes	
Labeling	Yes	Yes	Yes	Yes

505 (j) ANDA Not Appropriate for Biologics

- **NDA products (FD&C Act)**
 - Pharmaceutical equivalence is difficult to determine by physicochemical/biological tests alone for some proteins
 - Safety and efficacy studies may be required
 - Clinical or immunogenicity studies are beyond “limited confirmatory studies” allowed for an ANDA submission under 505(j)
- **BLA products (PHS Act)**
 - No legal basis for generic approvals under PHS Act

Examples for Abbreviated Approval

- 505(b)(j) and 505(b)(2) NDAs
 - Recombinant GH products-by 505(b)(1)
 - Menotropin by Ferring –505(j) and 505(b)(2)
 - Glucagon by Novartis-505(b)(2)
 - Hyaluronidase –DESI
- BLA
 - Biogen Avonex (interferon beta-1b), cell line change
 - Vaccines

D.C. Circuit in its decision on approval of Repronex, the generic version of menotropin:

The FDA has jurisdiction, and broad discretion, to determine sameness of two proteins, especially since the definition of “same” has been freed from any rigid conception of chemical identity....

Scientific Issues

- **Comparative quality analysis**
 - Identity, structure
 - Bioassay
 - Purity, impurities
- **Pre-clinical studies**
 - Animal PK/PD
 - Animal toxicology
- **Clinical safety**
 - Immunogenicity
- **Clinical studies**
 - Efficacy, biomarkers, surrogate endpoints

Pharmaceutical Equivalence-Quality

- **Identical structure**
 - Primary amino acid sequences
 - Secondary structure, disulfide linkage
 - Tertiary and higher order structure
- **Post-translational modification**
 - Glycosylation
- **Biological activity or potency**
 - Clinically relevant or irrelevant
- **Impurities**
- **Manufacturing process (?)**

Growth Hormone and Insulin

- First two rDNA proteins approved in 80s with extensive human data available from multiple manufacturers
- Mechanism of drug action known and validated biomarkers available
- Small, simple, non-glycosylated and highly purified protein with proven structures and known impurities
- Physico-chemical tests and public reference standard (WHO and EP) available
- Clinically relevant bioassays

Follow-on GH Concept Under 505(b)(2)

Documentation	No claim of interchangeability	Claim of interchangeability
Chemistry Data	Comparative analysis	Rigorous comparative analysis
Bioassay Data	One comparative bioassay	Two comparative bioassays
Pharm-Tox	May be waived	May be waived
PK/PD	Comparative PK/Bioavailability studies to a listed drug	Rigorous comparative PK and PD studies to a listed drug
Human Immunogenicity Data	Comparative data	Comparative data
Efficacy Data from Clinical Trials	Efficacy data required (immunogenicity data obtained simultaneously)	Efficacy data <i>not</i> required

Same Products from Different Processes?

Producer	Tradename	Expression System	Product Identity, Safety and Efficacy
Genetech	Nutropin	<i>E. coli</i>	same
Lilly	Humatrope	<i>E. coli</i>	same
Novo Nordisk	Norditropin	<i>E. coli</i>	same
Serono	Saizen	Mouse cell line	same
Pharmacia	Genotropin	<i>E. coli</i>	same

Other Issues

- Court challenges on legality of 505(b)(2) pathway
- No official abbreviated pathway for BLA products.
- Wide ranges of protein complexity due to size and post-translational modifications
- Adequacy of analytical methodology
- Product and process-related impurities
- Clinical relevant biomarker for PK/PD
- Immunogenicity and safety
- Acceptance criteria for comparative quality studies

EMEA Biosimilar Policies

- 2002, 2003 two comparability Guidelines: quality, non-clinical and clinical issues.
- 2004 Delay of approval of Omitrope
- 2004 Guideline on Similar Biological Medicinal products
- 2004 Amendment- for less preclinical and clinical data
- 2005 Concept Papers-GH, EPO, GCSF, GH, Insulin
- 2005 Guidelines for GH, EPO, GCSF, GH, Insulin

2004 Guideline on Similar BMP

- Generic drug approach is not appropriate
- Biosimilarity has to be established by comparability exercises for highly purified products.
- Safety and efficacy data requirements are product-specific.
- A reference product has to be identified and used for comparability exercise.
 - similar molecular and biological form
 - same dosage form, strength and admin. route
- Pharmacovigilance

Dissimilar Non-Clinical Studies

Product	PK in vivo	PD in vivo	Toxicology
Iusulin	Insulin and IGF binding	Normally not required	1 repeat dose tox in rats, 4 weeks and local tolerance
GH	Comparative bioassay	Rat weight gain or Tibia growth assay	1 repeat dose tox in rats, 4 weeks
G-CSF	Receptor binding assay	Neutropenic and non- neutropenic rodent models	1 repeat dose tox in rats, 4 weeks
EPO	Receptor binding Cell proliferation	Erythogenic effects in animal models	1 repeat dose tox in rats, 3 months and local tolerance

Dissimilar Clinical Studies

Product	PK	PD	Efficacy	Safety
Insulin	1 single dose cross over in patients	Double blind cross over glucose clamp	Not needed	Immunogenicity SC 12 months
GH	1 single dose cross over	IGF-1 and IGFBP-3	2 powdered randomized confirmatory 6-18 month	Immunogenicity 12 months
G-CSF	1 single dose cross over	Neutrophil and CD34 cell counts	Two arm equivalence	Immunogenicity repeat dosing > 6monthd
EPO	1 single dose cross over	Reticulocyte counts	2 powdered randomized 3-6 month	Immunogenicity 300 patient, 12-months

Conclusion

- **No 505(b)(j) type approval in US and EU**
- **Current law and regulations may allow approval of products under NDA without legislations by Congress**
- **Abbreviated data requirements will be case-by-case and may involved non-clinical and clinical studies (EU), depending on:**
 - **Molecular complexity, degree of characterization, indications and safety concerns, e.g. immunogenicity**
- **Legislation by Congress is needed for products under PHS Act**
- **Biomarker and surrogate endpoints may be used for certain products**
- **Scientific guidance will be provided, but when ?**

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