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Biosimilars India 2009

Mapping Out The Latest Developments In European And U.S. Biosimilar Regulation – Achieving Cost-effective Compliance

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December 2, 2009

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Introduction

Terminology

Europe : Similar biological medicinal products (biosimilars)

US : 'follow-on protein products' or 'follow-on biologics', however, latest legislation- biosimilars

Similar versions of originator reference products containing recombinant DNA-derived proteins

Scientific discussion

Can biological products be replicated in a manner that ensures quality, safety and efficacy given their complex nature?

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How Has The EU Approached Biosimilars?

- All Biotech medicines are assessed by the European Medicines Agency (EMEA) which will issue a positive or negative scientific opinion to the EC for approval or rejection.
- European Parliament legislation provides 10 years of market exclusivity for innovator.
- EMEA's Regulatory Framework requires extensive testing demonstrating the same quality, safety and effectiveness as the reference (innovator) product before approval.
- EMEA takes a case-by-case approach requiring "differences between the similar biological medicinal product and the reference medicinal product will have to be justified by appropriate studies." Such studies will typically include clinical trials.
- Biosimilars are required to undergo post-marketing monitoring just like new innovative biologies.

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A Brief History of Biosimilars in the EU

Omnitrope® and Valtropin®

First approved biosimilars in Europe:

- Omnitrope® (Sandoz): Submission (01/07/04) ; EMEA (26/01/06) ; EC (12/04/06) + FDA approval (after litigation against the FDA)

- Valtropin® (Biopartners) : EMEA (23/02/06) ; EC (24/04/06)

First refused biosimilar in Europe:

- Alpheon® (Biopartners) : EMEA (negative opinion: 03/07/06)

- Characterisation, manufacturing and quality control concerns

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A Brief History of Biosimilars in the EU

The EU Omnitrope® story (1)

2001 : First attempt to obtain EU approval

- application to have the product considered for generic authorisation based on a detailed scientific bibliography

- accompanied by studies aimed at showing comparability with the reference product

06/2003 : Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion

European Commission (EC) decided not to follow the opinion

03/2004 : After legal action by Sandoz, EC publication:

CHMP had improperly accepted Sandoz' application as a bibliographical application based on the well-established use of the medicine, while at the same time it had accepted/required comparability studies to be performed

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A Brief History of Biosimilars in the EU

The EU Omnitrope® story (2)

Sandoz appealed the EC decision with the ECJ:

Sandoz contests that the performance of comparability studies implied that the legal conditions for the application of the bibliographical application procedure were not met.

Second attempt after new regulatory framework

- 01/07/04 : new submission

- 26/01/06 : CHMP positive opinion

- 12/04/06 : EC approval

Clear example of a need for a regulatory pathway

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Regulatory Pathway (EU)

EU Guidelines—3 Types

The Over-Arching Guideline

General Guidelines

Product Type Specific Guidelines

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Regulatory pathway (EU)

Overarching Guideline:

(CHMP/437/04) defining philosophy and principles:

> "***The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) is normally applied to chemically derived products. Due to the complexity of biological/biotechnology derived products the generic approach is scientifically not appropriate for these products. The similar biological medicinal approach,*** *based on a comparability exercise*, ***will then have to be followed.***

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Regulatory pathway (EU)

General Guidelines:

Two general guidelines covering quality (CPMP/BWP/3207/00) and pre-clinical/clinical issues (CPMP/3097/02) related to the assessment of marketing authorization application for biosimilars

Updated guideline on the 'comparability of Biotechnology-Derived medicinal products after a change in the manufacturing process - pre-clinical and clinical issues' replacing guideline CPMP/3097/02 and entering into force as from November 2007.

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Regulatory pathway (EU)

Product Type Specific Guidelines:

Four product-specific guidelines (Insulin, Somatropin, GCSF, Erythropoeietin)

Address specific requirements to pre-clinical testing and clinical trials on a product type specific basis

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EU Progress to date: Regulatory approval in practice

Regulatory Standards

- 11 biopharmaceuticals now approved under biosimilar pathway
- Same regulatory agency as other current biopharmaceuticals
- With the same scientific rigor by the same committee (CHMP)
- Using the same regulatory systems and standards

Quality, Safety, Efficacy

- Manufactured to the same quality standards (GMP) as other current biopharmaceuticals
- Therapeutic equivalence with comparator biopharmaceutical proven
- Clinical efficacy and safety demonstrated in Phase III clinical studies with special attention to immunogenicity

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What Type of Data Does the EMEA Require?

Data required by EMEA in applications:

Quality Data--physicochemical characterization including analytical and quality control to establish same standard as reference;

Pre-Clinical Data-- *in vivo* and *in vitro;* PK/PD animal testing;

Clinical Data-- Phase I, II and/or III;

Pharmacovigilance—Phase IV and Post-Authorisation Safety Studies (PASS), including a Risk Management Plan (RMP)

The Safety and Efficacy of EU Biosimilars

Nicolas Rossignol, Administrator of the EC's pharmaceuticals on questions of safety for EU biosimilars:

"I don't judge case by case, but I have a message: we have promoted and developed with the European Medicines Agency a special biosimilars framework. So we are confident that if a product meets all the requirements and gets a marketing authorisation from the commission, it means that the product is as safe and effective as any other product authorized by the commission"

SCRIP World Pharmaceutical News 24 April 2008, reporting on EGA Meeting, London

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EU Biosimilar Approvals (marketed)

Biosimilar	INN	Reference product	Approval date
Omnitrope (Sandoz)	Somatropin	Genotropin (Pfizer)	12 April 2006
Valtropin (Biopartners)	Somatropin	Humatrope (Eli Lilly)	24 April 2006
Binocrit (Sandoz)	Epoetin alfa	Eprex/Erypo (Janssen-Cilag)	28 August 2007
Abseamed (Medice)	Epoetin alfa	Eprex/Erypo (Janssen0Cilag)	28 August 2007
Retacrit (Hospira)	Epoetin zeta	Eprex/Erypo (Janssen-Cilag)	18 December 2007
Silapo (Stada)	Epoetin zeta	Eprex/Erypo (Janssen-Cilag)	18 December 2007
Tevagrastim (Teva)	Fiegrastim	Neupogen (Amgen)	15 September 2008
Biograstim (CT)	Fiegrastim	Neupogen (Amgen)	15 September 2008
Zarzio (Sandoz)	Fiegrastim	Neupogen (Amgen)	6 February 2009
Fibrastim Hexal (Hexas)	Fiegrastim	Neupogen (Amgen)	6 February 2009

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Regulatory pathway (EU)

For overview of biosimilar guidelines and concept papers, see:
http://emea.europa.eu/htms/human/humanguidelines/biologicals.htm

For FAQ: see:
http://emea.europa.eu/pdfs/human/pcwp/7456206en.pdf

EMEA : These are open documents that can be discussed and amended ; learning process ; scientific advice is key

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A Brief History of FOBs in the US

No US regulatory pathway yet:

04/1999: Draft guidance on "Application covered by Section 505(b)(2) FDCA:

- this section could be used to obtain approval for therapeutic protein products and sponsors could make change to the reference product if the change were supported by clinical data

- goal : encouraging "different" generics;

Innovator industry intimidated the FDA by continuously filing citizens petitions challenging the use of Section 505(b)(2) FDCA to approve FOBs

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A Brief History of FOBs in the US

The US Omnitrope-story:

- 07/2003: 505(b)(2) Omnitrope application

- 2004: FDA declined that a decision could be made due to "unresolved scientific and legal issues"

- 09/2005: Sandoz files a lawsuit against the FDA for failure to take action on its pending application

- 04/2006: Court ordered the FDA to comply with its statutory obligation to act on the application

- 06/2006: FDA approval

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A FOB Legislative History

Legislative proposals :

Beginning 2006: legislation for follow on biologics was blocked by US biotechnology lobbyists

Beginning 2007: re-introduction of proposal by Congressman Waxman to create regulatory pathway

May 2007: Bush officially opposed any legislation paving the way for FOBs

September, 2007: Bill changing FDA provisions approved by Congress does not include regulatory pathway for follow-on biologics

November 2009: Pending Senate Health Reform Bill contains biosimilars pathway

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United States Follow-On Biologics Pathway

	Senate HELP	Eschoo amendment (HR 3200)	Waxman/Schumer (HR1427/S726)
"Biosimilar"	"Highly similar," notwithstanding "minor differences in clinically inactive components;" no clinically meaningful differences ins afety, purity & potency (animal tox, immunogenicity, PK)	"Highly similar," notwithstanding "mino differences in clinically inactive components:" no clinically meaningful differences in safety, purity & Potency (animal tox, immunogenicity, PK)	No clinically meaningful differences expected if treatment were initiated with biosimilar rather than reference product
Interchangeability	Biosimilarity + same clinical result + showing of safe switching (if given more than once)	Biosimilarity + same clinical result + showing of safe switching (if given more than once)	Biosimilarity + safe switching expected (if given more than once)
Guidance required	No	No	Yes, not tied to approval
Generic naming	Implied	No	Yes
Clinical trials	Yes, can waive	Yes, can waive	Discretionary, can waive
User fees	Yes	Not provided	Not provided

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United States Follow-On Biologics Legislation Comparison of Patent-Related Provisions

Features	Senate HELP	Eschoo amendment (HR3200)	Waxman/Schumer (HR1427/S726)
Obligatory	Yes	Yes	No
Disclosure of confidential information	Full application, and information describing the product and its manufacture	Full application, and a detailed description of the product, its manufacture, and materials used in its manufacture	Not required
Protection of confidential information	Detailed restrictions	Per FDA regulation	NA
Third party participation	No	Yes	No
Notice to FTC	No	No	Yes
Limitations on Declaratory Judgment	No DJ on "listed" patents until notification to market is received (if ABLA provided); Brand may DJ on any listed patent if applicant does not comply with requirements; IF ABLA not provided, brand can DJ on any patent	None	Brand may not DJ prior to marketing on patents no included in ABPA holder's notice; ABPA holder may DJ on a listed patent if not sued in 45 days
Penalties for not participating	Limitations on DJ Limitations on damages	None	None

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United States Follow-On Biologics Pathway

	Senate HELP	Eschoo amendment (HR 3200)	Waxman/Schumer (HR1427/S726)
Brand exclusivity	4 + 8 years (Add'l 12 years possible for structural changes that change safety, purity or potency)	4 + 8 years (Add'l 12 years possible for structural changes that change safety, purity or potency)	5 years for novel "major substance"; 3 years for modified "major substance" and a significant therapeutic advance
New indication exclusivity	None	None	6 mo. for "significant new indication"
Pediatric exclusivity	None	6 months	6 months
Follow-on exclusivity	Earlier of: •1 year after launch •18 mos. after litigation ends •42 mos. after approval if litigation on-going •18 mos. after approval if not sued	Earlier of: •1 year after launch •18 mos. after litigation ends •42 mos. after approval if litigation on-going •18 mos. after approval if not sued	Earlier of: •6 mos after launch •12 mos. after litigation ends •36 mos. after approval if litigation on-going •12 mos. after approval if not sued

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U.S. Patent Provisions – Features Common to All FOB Bills

- No "Orange Book" - listing is a private exchange between the parties
  - Applicant notifies brand of application
  - Brand responds with list of patents
  - Applicant provides "certification" & detailed statement
- No stay of approval pending patent resolution
- One year exclusivity for first to file application

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June 2009 Federal Trade Commission (FTC) Report

- a 12 to 14 –year regulatory exclusivity period was *too long* to promote innovation by these firms, particularly because they were likely to retain substantial market share after FOB entry.
- special patent procedures to resolve patent issues before FDA approval, were *not needed* and would undermine patent incentives and *harm* consumers.
- FOB manufacturers *do not need* additional incentives such as 180 day marketing exclusivity period.

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Other Regulatory Issues

INN for biosimilars:

INN = international, non-proprietary name

Managed by WHO ; Nomenclature based on scientific rules

Example: Omnitrope and Valtropin are the unique names required by EMEA, but Somatropin is the INN or scientific name for the active substance in both products

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Other Regulatory Issues

Interchangeability

Practice of switching one medicine for another

Hurdle of interchangeability will be higher than they already are for generics despite clear statements of equivalent effectiveness in biosimilars European Public Assessment Reports (EPARs).

Substitution-rules that require or permit switching from one medicine to another often at the retail pharmacy level;

For Example: in Belgium doctors can prescribe medicines by INN: (such as Somatropin) which may facilitate substitution of biosimilar product.

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Defining biosimilars - "Quality by design"

- Biosimilars are developed and manufactured according to the same quality standards as the original product
- Manufacturing process, including cell lines / production strains, developed to guarantee comparability with the original product.
- Comprehensive analytical tests at all stages of manufacturing process ensure quality remains unchanged.
- Preclinical and clinical studies complement and validate tests on comparability, efficacy and safety.
- Post-marketing studies (PMS/PASS) demonstrate long-term safety (pharmacovigilance)

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ICH Definition of Comparability (EU, US, Japan)

ICH Harmonished Tripartite Guideline

Comparability of Biotechnological/Biological Products Subject To Changes In Their Manufacturing Process

Q5E

Comparable:

A conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion.

Federal Register, Vol. 70, No. 125, June 30, 2005, pages 37861-37862

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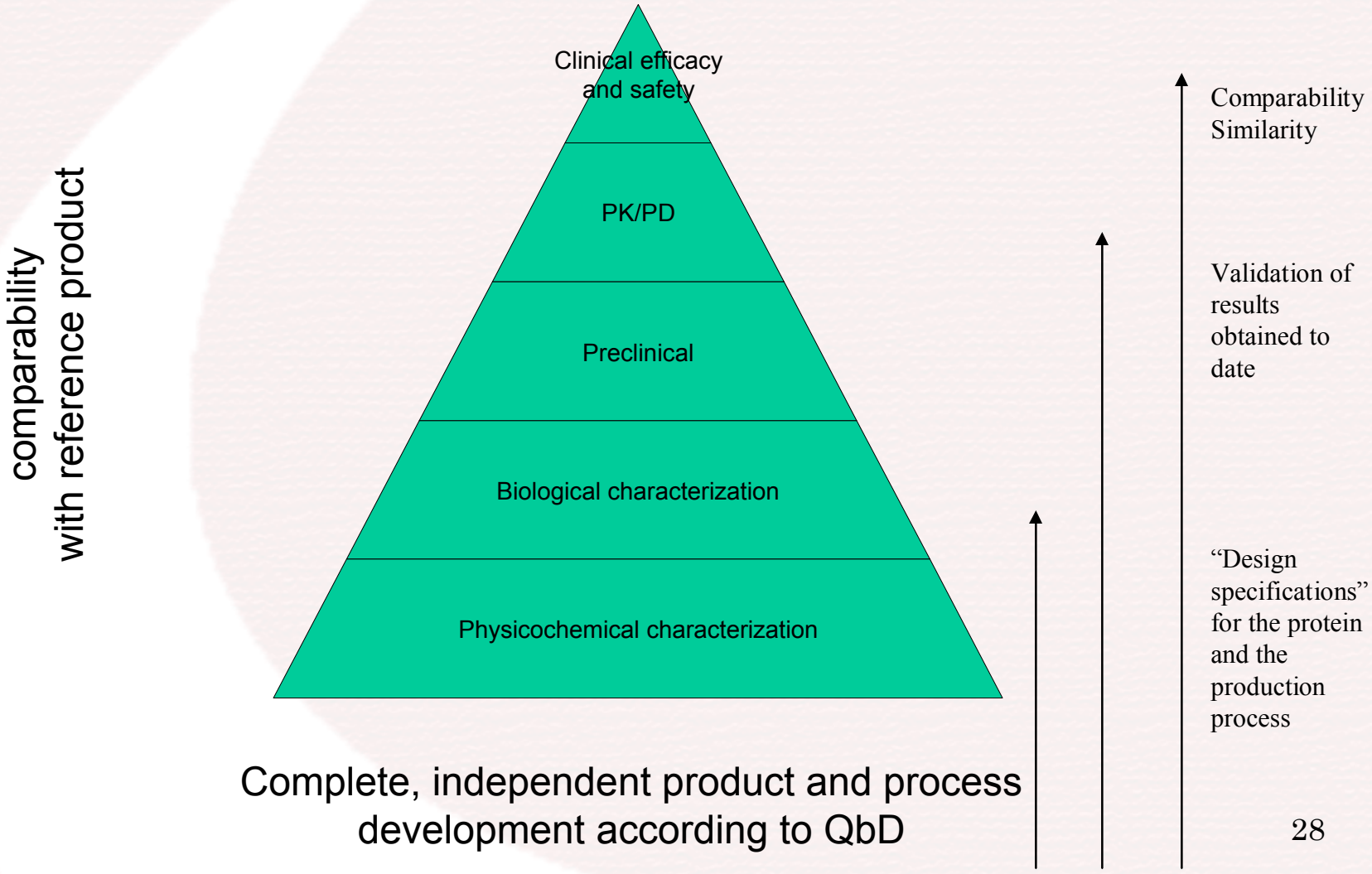
"The Comparability Exercise"

Comparability with the reference product must be ensured at all levels.



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Overcoming Key Regulatory Hurdles When Navigating European and U.S. Regulatory Framework

EU Development	Requirements	US Development
√	rigorous physico-chemical and biological comparison with reference product of both regions ↓	√
√	appropriate comparative pre-clinical testing with reference product of both regions ↓	√
√	rigorous comparative PK/PD clinical phase I studies with reference product of both regions ↓	√
	comparative clinical phase III studies with reference product from one region only (against either EU or US reference product) √	

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GMP Issues at the Clinical Trial Stage

Given that there are currently no US regulations specifically pertaining to Follow-on Biologics, it is likely that the FDA will follow the lead of the EMEA and expect Biosimilar manufacturers to comply with good manufacturing practices ("GMPs") during all clinical product phases, beginning with early Phase I clinical trials. (GMPs cover the manufacture, processing, packaging, holding, testing, and quality control of drugs and biologics.)

Companies starting Phase I clinical trials for biologics must comply with facility and equipment qualification requirements and validate "safety related processes" (e.g., sterilization, viral clearance) to ensure that the product will consistently meet established specifications. Biosimilar manufacturers also need to establish and develop quality systems covering all aspects of development, including change controls, failure investigations and software validation.

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Good Manufacturing Practices/Quality System Regulation for Biologics (assuming that FDA makes these same requirements applicable for FOBs):

- After market approval, the manufacture, transportation and storage of drugs/biologics must adhere to GMP requirements.
- The GMP regulations for finished pharmaceuticals (drug or biological products) are found at 21 C.F.R. Parts 210 and 211.
- The GMP regulations include requirements pertaining to: equipment qualification; process validation; design controls; change and document controls; personnel responsibilities; production and process controls; purchasing controls; acceptance activities; and corrective and preventative actions.
- Important early stage issues include: facility design review; establishing/developing systems; and conducting assessments to verify status against FDA requirements.
- The GMP regulations are not prescriptive, and manufacturers are given some discretion in interpreting and applying the requirements.
- Companies must develop their own procedures and controls for manufacturing processes that meet the GMP requirements

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Challenges Ahead

Will US Healthcare Reform Pass?

Pharmacovigilance

Pricing and Reimbursement

Second Generation Biologics (monoclonal antibodies)

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Thank You

Special Thanks to:

Teresa Stanek Rea
(Washington DC)
Cathy Burgess
(Washington DC)
Kristof Roox
(Brussels)

QUESTIONS?