Challenges and its Resolution in Biosimilar Clinical Development

Chirag Shah Ph.D,PGDPM
Asso.Director & Head-Clinical Trials
Cliantha Research Ltd
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Challenges and for Biosimilar Clinical Development

- Opportunities
- Challenges
  - Scientific
  - Nonclinical
  - Clinical
  - Operational
  - Regulatory
  - Quality
- Conclusions
- Recommendations

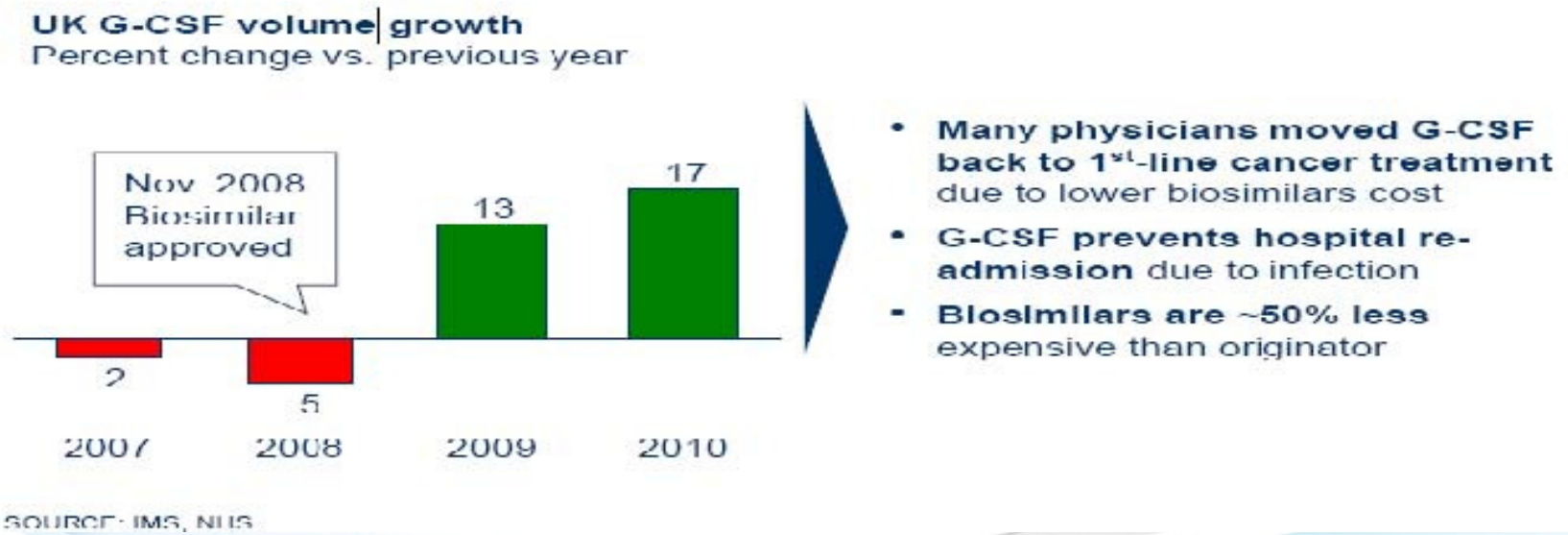
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Opportunities:

- Till 2019, 21 important biologics will loose patent protection
- Biologics represent cost effective opportunity for patients mainly for MABs in area of Oncology, Autoimmune diseases and cardiovascular diseases
- Biologics represent a total market value of more than $50 billion
- There are 150 marketed biologic products worldwide, with almost 500 products under development.
- The market opportunity is approximately $4 billion
- According to Data Monitor, the market of Biosimilars or follow on Biologics is estimated to reach $3.7 billion in 2015
- Currently, almost India is part of all biosimilar development plan due to more clarity on Regulatory guidelines

Biosimilars can improve Healthcare:

- Biosimilars can enable previously restricted therapies to become part of the accepted standard of care
- In the UK, patients have benefited from lower acquisition costs and improvements in the practice of medicine after the approval of a filgrastim biosimilar
- This has enabled the routine use of filgrastim (as a biosimilar) as a first-line treatment for the first time



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The potential impact of Biosimilars:

- A survey conducted in the European Union in 2010 found cost savings in 24 member states where biosimilars were marketed alongside their originators*
  - There was sustained price discounting in all countries, although this did vary at the country level
  - Values range from a 5% discount for filgrastim in the UK to a 53% discount for the same medicine in Denmark in 2009
  - The availability of biosimilars of somatropin, epoetin alfa, and filgrastim in Europe has led to price discounts relative to their respective originators ranging from 5–82%
  - The table below describes the mean price discount of biosimilar versions of the medicines listed relative to their originator products

Mean discount in 24 EU member states	2007	2008	2009
Somatropin	25.4%	25.9%	14.1%
Epoetin	32.1%	17.3%	17.0%
Filgrastim	---	10.8%	35.0%

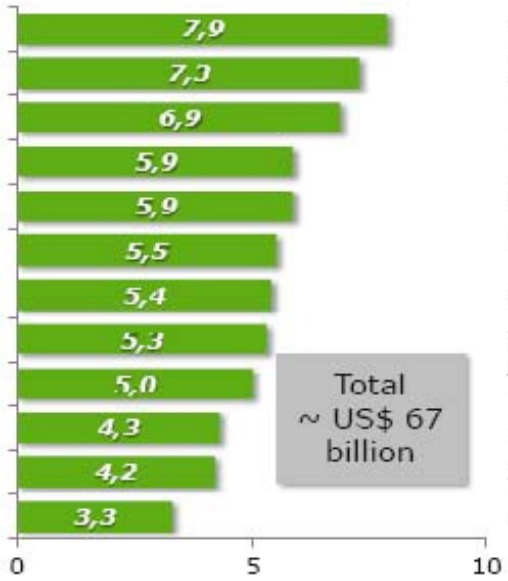
*Rovira J, Espín J, García L, and Olry de Labry A. The impact of biosimilars' entry in the EU market. 2011. http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_market_012011_en.pdf.

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Twelve compounds will present a US$ 67 billion opportunity

All these products will lose patent protection by 2020, but Enbrel whose US patent has been extended until 2028

Global Sales (MAT 12/2011), US$, Billion



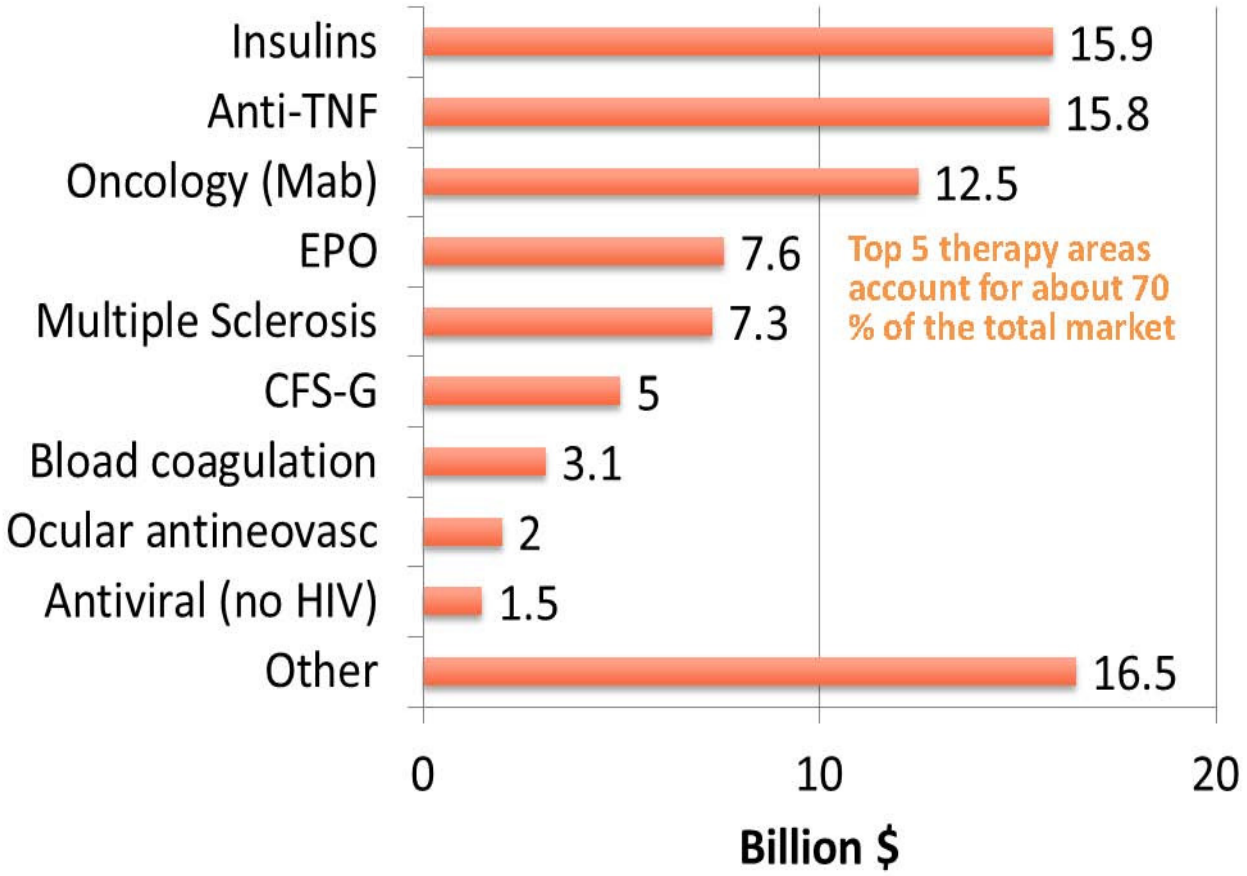
	EU expiry date	US expiry date
Adalimumab (Humira)	2018	2016
Etanercept (Enbrel)	2015	*2028 (extended)*
Infliximab (Remicade)	2014	2018
Insulin Glargine (Lantus)	2014	2014
Rituximab (MabThera)	2013	2016
Bevacizumb (Avastin)	2010	2017
Enoxaparin Sodium (Lovenox)	2012	Expired
Interf. Beta-1A (Rebif, Avonex)	2015	2015
Trastuzumab (Herceptin)	2014	2019
Pegfilgrastim (Neulasta)	2017	2015
Glatiramer Acetate (Copaxone)	2015	2014
Darbopoetin Alfa (Aranesp)	2016	2016

Not considered existing biosimilars such as Epoetin Alfa expired in EU, but still patent protected in US

Source: IMS MIDAS, 12/2011, IMS Patent focus

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Core therapy areas of Biologics:



IMS Health 2011

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Challenges in Clinical Development:

- Study Indication
- Study Design
- End points
- Inclusion and Exclusion Criteria
- Statistical consideration
- Immunogenicity
- Safety and Post marketing study requirement
- Reference Product
- Vendor Selection
- Operation Requirement
- Regulatory Requirement

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Phase I

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Biosimilar Phase I:

- Comparability NOT Characterization
- PK and PD endpoints
- Primary and secondary?
- Large inter and intra subject variability
- Standard bioequivalence criteria (i.e., 90% confidence interval within 80–125% for select PK parameters)
- Simultaneous evaluation of extrapolation ability of equivalence in PK to equivalence in PD and to equivalence in efficacy
- Bridging study with US and EU reference-3 arm studies
- Large sample size (>100)

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Study Design:

- Cross over or Parallel
  - Half life
  - Safety
- Dose
  - Prescribed dose or lower dose in the ascending part of the curve?
  - Single or Multiple doses
- Single dose administration or multiple dose?
  - Driven by PD and not PK

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PK Methods for Biosimilars:

- One or two assays?
- Which reference standard to use?
- Quality Control Samples?

- Immunogenicity ADA/NAb Methods

- One or two assays?
- Positive controls?
- Comparable activity and sensitivity?

PK Methods for Biosimilars:

- **One or Two Assays?**
  - One assay is recommended **Calibration Curve**
  - One of the two: Innovator or Biosimilar
  - Most likely the Biosimilar COA

- **Reagents**
  - Suitable and characterized for both Innovator and Biosimilar

- **Validation Samples and QCs for Method Validation:** Innovator and Biosimilar
- **Quality Control Samples for Bioanalysis:** Innovator and Biosimilar (blinded analysis)
  - Accuracy and Precision
  - Sensitivity
  - Selectivity
  - Stability in plasma

Operational considerations:

- Phase I unit with Biosimilar experience
- Bioanalytical knowledge and experience
- Phase I unit capacity: clinic and lab
- Phase I unit Quality
- Control variability
- Pharmacy IMP preparation
- Clinical conduct
- Sample processing and shipment
- Number of cohorts and bedsize

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Phase III

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Challenges in Clinical Development:

- Study Indication
- Study Design
- End points
- Inclusion and Exclusion Criteria
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- Safety and Post marketing study requirement
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- Vendor Selection
- Operation requirement
- Regulatory Requirement

Study Indication:

- Selection is very important
- Rituximab has 2 approved indications: Do we need to provide justification within same disease area e.g. Oncology indications and across different disease e.g. Oncology to RA

Study Design:

- Plan with standard of care e.g. background chemotherapy or cycles of treatment
- Comparative
- Double blind
- Parallel
- PK & PD
- Randomisation:2:1 or 1:1

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Study End Points:

- Incorporating right clinical end points for Clinical Trials, including Biomarkers or other surrogates predictive of clinical efficacy
- Acceptability of non conventional primary efficacy end point e.g. PFD or ORR Vs OS in oncology trials by prescribers

Inclusion and Exclusion criteria:

- Very important as it decides the patient population, for recruitment
- Detailed feasibility
- Streamline inclusion/ exclusion: Stay with the approved prescribed inclusion/exclusion
- Do you really need population PK?
- Can you overlap antibody and PK samples and with routine visits?
- Sensitive Homogenous Population: Indication not licenced,Indication of not commercial value
- Sensitivity of Assay: ICH E10: Adhere closely to the design of the trials used to determine that historical evidence of sensitivity to drug effect exists
- Aim is to establish non patient benefit but biosimilarity

Statistical Consideration:

- Sample Size
- Equivalence Test
- Cross Over or Parallel design
- Primary and Secondary End Points
- Determination of Margin:Inferiority,Superiority
- Scaled average bioequivalence criterion
- Concept of reproducibility as a measure of determining, whether it is necessary to require second trial, when the results of first trial is highly significant

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Immunogenicity:

- Safety assessment and Immunogenicity requirement can be different with all regions
- Some Agencies accept follow ups after 6 months, while others require 12 months or more
- Inconsistencies between regions with regard to the methodology used for measuring immunogenicity and hence interpretation of the data

Safety & Post Marketing:

- Safety profile may differ due to
- Dose
- Frequency
- Disease
- E.g. Rituximab RA and Oncology
  - Different dose
  - RA- more immune response
- DSMB
- Post marketing large safety studies?
- Post Marketing conditions as per Pharmacovigilance requirement in EMA & USFDA

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Safety Data (As per EMEA/CHMP):

- Safety profile may be different, even if the efficacy is shown to be comparable (in terms of nature, seriousness, or incidence of adverse reactions)
- Prelicensing safety data should be obtained in a number of patients sufficient to address the adverse effect profiles of the test and RMP
- Sponsor should prepare a Risk Management Programme / PV plan
- Data should be collected from a sufficient number of patients to characterize the variability in antibody response

Pharmacovigilance & Traceability:

- Regulations are being tightened to improve identification and traceability of biologic medicines
- In 2012, the European Commission introduced a pharmacovigilance directive
- A legal requirement for EU Member States to take all necessary measures to clearly identify the biological medicines that are prescribed, dispensed and sold in their country
- The FDA has also made the broader conclusion that, the use of distinguishable non-proprietary names will help post-marketing safety monitoring, allowing better traceability of medicines in the case of an adverse event
- The use of brand names alone was determined to be insufficient, as brand names are often not used by healthcare professionals for prescribing, and many pharmacovigilance systems do not require them

Reference product:

- Source as early as possible in Large quantity
- EU or US
- Check country requirements for importation
- If cannot get CoA- own analysis but impact on time
- Explore packaging and distribution options to minimize wastage, Blinding can be option
- Supply chain continuity
- Drug Accountability via IVRS, if product unblinded at pharmacy level- control cost of unblinded monitoring team
- Controlling drug wastage

- Reference Product: Clinical studies should use batches produced using the final manufacturing process.

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Vendor Selection:

- Central Laboratory
- Central Imaging
- IVRS/IWRS
- EDC
- eTMF

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Operational Challenges:

- Site/Investigator Selection
- Reference product
- Patient Recruitment : Education &Country selection
- Study design considerations

Operational Challenges: (Contd…)

- Patient recruitment is a key stepping stone to commercial success
- Shortage for Investigators and patients
- Same disease indication
- Even if different indication, research resource stretched
- Need for Quality sites
- Investigator interest

Operational Challenges: (Contd…)

- Ethics Committee and CT approvals
- Innovative designs with non-conventional end points
- Competition with other biosimilar as well as disease area
- Standard of Care evolving
- Patient consent
  - Why enter the study, if I will get the “approved” drug any way?
  - Too many visits e.g. population PK/PD studies in patients
  - Low recruitment rate- large number of countries and sites
  - High cost
- Include information about biosimilars in protocols, ICF etc..
- Educate Physicians and Patients on the benefits of taking part in Biosimilar
- Tools to maximize recruitment per site and reduce cost

Regulatory Consideration:

- Selection of reference products for a given country
- Data requirements necessary to demonstrate comparability for marketing approval
- Whether clinical trials must be conducted in the country in order to obtain local marketing approval
- US and EMA require detail PK and PD data. PK data at one dose or two dose may be required
- PK data to be reviewed before granting the CT approval

Conclusions:

- Biosimilar Clinical Development has challenges;

- High Clinical cost, resource and time
- Patient Recruitment challenges
- Different Regulatory Requirements
- Manufacturing capabilities
- Commercial difficulties
- Competition
- Experienced Partner CRO team with Biosimilars experience

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Recommendations:

- Plan complete programme and not one study
- Plan Global from day one
- Consult Regulatory bodies and experts at planning stage
- Optimize design and operation
- Develop simple charts/diagrams
- Streamline inclusion/exclusion
- Develop programmes and processes around helping sites with chart reviews and setting up referral network
- Grant fees- expectation is higher than standard
- Focus messages on therapeutic benefit
- Interactive tools with all stake holders will benefit the biosimilar trials

Remember- it's a Biosimilar NOT NCE

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Thank You

cshah@clianthatrials.com

www.clianthatrials.com

USA CANADA INDIA

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