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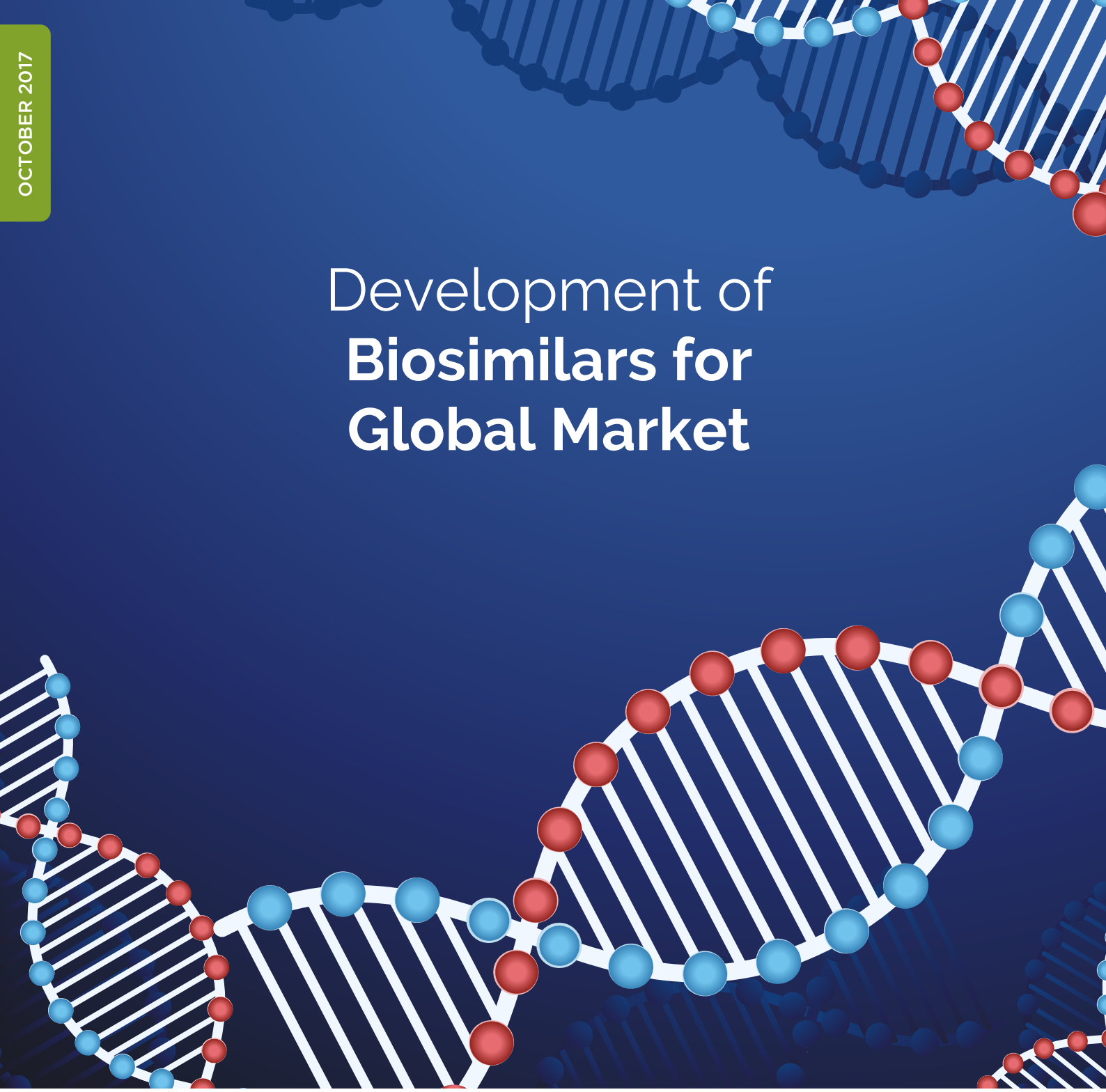
Development of **Biosimilars for Global Market**



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Science Integrity

Among Top 5 CROs for conduct of Biosimilar Clinical Trials Globally.[15]

Introduction

In the last 3 decades or more, the development of medicines from biological source has revolunised the way, we treat critical diseases, including Cancer, Inflammatory diseases and Complex Ophthalmic diseases. Biologics are produced in genetically-engineered living cells.[1]

Biosimilars are biologic medicines that are **highly similar to existing licensed biologic products with no clinically meaningful differences** in the terms of safety and efficacy.[2,3] However, the process of introducing a biosimilar to an innovator product is far more complex than the relatively straightforward process of introducing a generic equivalent to an innovator product based on a new chemical entity.

Biosimilars are being developed by an abbreviated route of development, that can help to have cost effective & more access to the potential patients.[4,5,6] With $67 billion in global sales of biologic medicines anticipated to go off patent by 2020,[7] even modest reductions in the cost of biosimilars products could have a meaningful impact on health care systems around the world.[8] For physicians and their patients, biosimilars provide additional therapeutic options.

Basic Difference between Biosimilars and Generics

	Biosimilars / Biologics Monoclonal antibody	**Generics Small molecule drug**
Size	Large: MW ~ 150,000 Da	Small: MW ~ 180 Da
Structure	Complex with many possibilities for post-translational modification	Simple and well defined
Manufacturing	Manufactured in a unique cell line; only similar, but not identical, copy can be made	Predictable chemical process; identical copy can be made
Characterization	Difficult to characterize	Easy to fully characterize
Immunogenicity	Higher potential	Lower potential
Stability	Sensitive to storage and handling conditions	Relatively stable

Biosimilars have fundamental differences from generic small molecule drugs. [9,10,11,12,13]

Biosimilars are not Generic drugs

Biosimilars are up to 1,000 times the size of small molecule generic drugs, and are far more structurally complex.[1] Additionally, biosimilars are manufactured in living cell lines using process that cannot be exactly replicated from one manufacture to the next.[10] Generics are manufactured purely via chemical synthesis, a wholly reproducible process. Therefore, a generic, unlike a biosimilars, is an exact copy of its reference product.

The underlying differences in size, complexity, and manufacturing processes are why biosimilars are fundamentally different from generics. One key reason a biosimilar cannot be identical to its reference biologic is due to post-translational modification such as glycosylation-the addition of glycans (carbohydrate groups) to a protein within the producing cell.[1] These are unique to each specific cell line and growth conditions and can have a profound impact on the molecule's biological effects, including drug clearance rates and immunogenicity.[14] Therefore, biosimilars are more complicated to develop and the regulatory pathway for approval is more complex than for generic drugs.[1]

Regulatory requirement for Biosimilar Development

Various emerging markets in Eastern Europe, Asia Pacific and Latin America are becoming important locations for biosimilars development in addition to the EU and USA, as sponsors pursue multinational programs to gain efficient access to appropriate patient populations. The use of multinational studies allows sponsors to submit for marketing authorization to a variety of regulatory bodies with a limited amount of clinical research.

As the regulatory landscape is evolving for biosimilar, the intriguing challenges for the biosimilar development companies and manufacturers are creating a unique recipe that serves all the regulatory authorities. Therefore, a deep understanding of the guidelines helps identify the "common" requirements that may satisfy the majority of the regulators. Note, there may be some "unique" requirements that you may need to research for some regulators.

The regulatory requirements are getting homogenized in last 3-5 years, with CMC & non-clinical requirements are more harmonized now. The clinical requirements are still heterogeneous, where the regulators decisions are influenced on

- **GCP practices**
- **PK and PD data requirement**
- **Statistical design:** Equivalence design (US FDA, EMA) vs non-inferiority design/ descriptive comparative data driven by Accessibility (mostly emerging market)
- **Local clinical data** (driven by difference in standard of care practice and/or pharmacogenomics issue).
- **Comprehensive Pharmacovigilance Plan**

A totality of evidence must be used to evaluate a biosimilar for market approval. Clinical studies involving biosimilars are carefully designed with sensitive subject populations and clinical end points to detect any potential meaningful differences between the biosimilars and reference product.[4,6]

Still there is a possibility to align the developmental strategy and make all incremental development research structured to key final destination (USFDA and/or EMA approval)

Category	EMA	FDA	Others
RMP	EU sourced RMP as comparator throughtout development, including all human studies	US Sourced RMP For structure function comparability Compared in >1 human study	Accepts EU/US RMP
CMC	A well executed CMC package utilizing 'state of the art' physicochemical & biological characterization for demonstrating comparability between RMP & TEST is fundamental to any approval strategy; 'Similarity' must be supported by robust regulatory science & quality rigor.		
Development Approach	Comprehensive	Sequential	Mixed
Biosimilarity	Assessment within "comprehensive evidence" framework	Assessment based on "totality of evidence"	Negotiable
Non Clinical	Emphasize on *in vitro* testing	Both *in vitro* and *in vivo*	
Clinical (PK/PD)	Designed keeping BE criteria in perspective; sensitive population		
Clinical (Safety, Efficacy)	Sufficient human exposure; therapeutic equivalence	Not efficacy - but "comparability"	Descriptive comparability or wider stat margin, risk based

The common principles includes discharging the risk at each of the development stages.

- 'Molecule' characterization' – strategic & crucial
- Reference product selection and distribution during comparability study is key.
- If the manufacturer has an early to launch strategy based on FTO, they need to be careful about clinical design, while taking leverage on statistical margin. This data can be structural and supportive to global development.
- Seek advice from both (EMA & FDA) to harmonize development-registration strategy. FDA & EMA willing to negotiate but "residual risk" judgment dependent

A systematic development plan ensures trigger of maximum investment, when majority of the risks are being discharged. Cliantha team has vast experience of Regulatory submissions/deliberations/presentations/scientific advice in various regions and successfully received the approval to conduct the study/market the product in the region. Along with that there is a panel of KOL, who have supported for global approvals for many years. One such KOL is **Dr. Hoss Dowlat (Germany) having more than 33 years of experience in Drug Development & Biosimilars in various therapeutic area.**

Cliantha Team Experience – Biosimilars

Phase	Indication	# Sites	# Patients	Services Performed	Current Status
III	Bevacizumab in Non Small Cell Lung Cancer(NSCLC)	30	Globally 478 (Currently, planned 225 patients recruitment from India)	India specific Regulatory services, Project Management, Site Management and Medical & Safety Management.	In other 22 countries another CRO is managing the study. DCGI approval is received and recruitment is ongoing
II	Non Small Cell Lung Cancer(NSCLC)	8	60	Full Scope	Under Regulatory review
III	Bevacizumab in Non Small Cell Lung Cancer(NSCLC)	33 sites in India,7 sites in Europe and 2 sites in South Africa	Globally **200** (Planned 165 patients from India, 25 patients from Ukraine, Hungary and Bulgaria and 10 patients from South Africa)	Cliantha is managing whole Global operation part of the study including Central Imaging, Central Lab for PK analysis and IWRS. Medical Writing, Data Management and Biostatics is managed by another Global CRO.	Approval in all 3 geographies is received and study is under hold due to strategic reasons
III	Rituxumab- Diffuse Large B Cell Lymphoma	12	73	Project Management, Site Management, Medical Monitoring	Recruitment and Follow up of patients is completed & final CSR is submitted to EU
III	Trastuzumab in Metastatic Breast Cancer	12	46	Medical Monitoring and strategic inputs for Recruitment	Study is completed and submitted to USFDA
III	Bevacizumab in mCRC	27	161	Project Management, Site Management, Medical Monitoring, Central Radiology	Recruitment is completed and CSR preparation is going on
III	Trastuzumab-Metastatic Breast Cancer	30	102	Project Management, Site Management, Medical Monitoring, Report Writing	Study has been completed and MA is also granted
III	Bevacizumab- mCRC	6	40	Project Management, Site Management, Medical Monitoring	Recruitment is completed and CSR preparation for EU is going on
III	FSH in Female Patients Undergoing Assisted Reproductive Technology	10	116	Full Scope	Recruitment is completed and CSR preparation is going on
III	G-CSF in all Solid tumors	6	104	Full Scope	Product is approved in India and Europe
III	Erythropoietin in Cancer Induced Anemia	6	60	Full Scope	Product is approved in India
III	Interferon in CML	3	40	Full Scope	Product is approved in India
PK/PD	PEG-GCSF Healthy Volunteers	1	90	Clinical Conduct	Study has been completed
PK/PD	Erythropoietin - Healthy Volunteers - SC Route	1	42	Full Scope	Study has been completed
PK/PD	Erythropoietin - Healthy Volunteers - IV Route	1	64	Full Scope	Study has been completed
PK/PD	Darbepoetin Healthy Volunteers	1	60 (Similar 2 studies)	Full Scope	Study has been completed

Biosimilars Bioanalysis

We are a full service lab that provides solutions for large molecule bioanalysis. The large molecule bioanalysis is quite challenging because of its large size and complexity. It requires three different assays; a PK, Immunogenicity and Biomarker assay.

The PK assays are utilized for accurate and precise determination of Drug Concentration in Biological Metrix.

The production of endogenous antibodies against an administered biologic (immunogenicity) may also play an important role in its pharmacokinetics. Hence, immunogenicity assessment becomes a necessity in large molecule development. The immunogenicity assays have its own challenges in being semi quantitative and determination of statistically stringent cut point value.

For a majority of biotherapeutics, an initial assessment of immunogenicity typically involves the three tiered approach. A screening assay is complemented by confirmatory assay, which may then be supplemented by an assay for quasi quantitation of the amount of antibody present.

Any confirmed positive antibody is checked for its neutralizing capability in cell-based or non cell-based neutralizing Antibody (Nab) assay.

The biomarker analysis presents numerous challenges as it is an endogenous molecule. Regulatory guidances for biomarker method validation are still evolving. In most cases, a fit-for-purpose validation approach is used. We have a CAP accredited lab which is specialized and experienced in the field of biomarker analysis. The lab is equipped with BD FACS Caliber and other immune-systems to expedite biomarker analysis. **Being a CAP accredited lab, with FDA and EMA experience puts us in a unique position to cater to the needs of biomarker assessments.**

Analyte	Sensitivity	Method	Status
Levothyroxine	3.5 µg/dL	ELISA	Validated
Lio thyronine	0.5 ng/mL	ELISA	Validated
Erythropoietin	3.5 mIU/mL	ELISA	Validated
Bevacizumab	2.0 µg/mL	ELISA	Validated
Follicle stimulating hormone (FSH)	30.0 pg/mL	CMIA	Validated
Erythropoietin Immunogenicity assay	248.48 ng/mL	ELISA	Validated
Insulin Like Growth Factor-I (IGF-I)	0.094 ng/mL	ELISA	Validated
Growth Hormone	75.0 pg/mL	ELISA	Validated
Tissue factor pathway inhibitor (TFPI)	31.25 ng/mL	ELISA	Validated
Enoxaparin Sodium Anti Factor IIa	0.030 IU/mL	Chromogenic	Validated
Enoxaparin Sodium Anti Factor Xa (Chromogenic assay)	0.050 IU/mL	Chromogenic	Validated
Enoxaparin sodium Anti Factor Xa (Clotting assay)	0.075 IU/mL	Clot based	Validated
LMWH for APTT	NA	Clot based	Validated
LMWH Anti Factor IIa	0.030 IU/mL	Chromogenic	Validated
LMWH Anti Factor Xa	0.050 IU/mL	Chromogenic	Validated
Hep test (LMWH by Anti-Xa)	0.075 IU/mL	Clot based	Validated
Hemolytic potential of drug	-	Chromogenic	Validated
Ghrelin	46.875 pg/mL	ELISA	Validated
Leptin	2.000 ng/mL	ELISA	Validated
Adiponectin	0.1 ug/mL	ELISA	Validated
CD 34	-	Flow cytometry	Validated
GCSF	250.0 pg/mL	ELISA	Developed
Adalimumab	110.0 ng/mL	ELISA	Developed
Teriparatide	20.0 pg/mL	ELISA	Developed
Trastuzumab	2.0 ug/mL	ELISA	Developed
Rituximab	1.5 µg/mL	ELISA	Developed
Bevacizumab immunogenicity assay	124.0 ng/mL	ELISA	Developed
Adalimumab immunogenicity assay	100 ng/mL	ELISA	Developed
GCSF immunogenicity assay	-	ELISA	Developed
Trastuzumab immunogenicity assay	100 ng/mL	ELISA	Developed
Glucose	25 mg/dL	Chromogenic (GOD-POD)	Developed
Peg-GCSF	250.0 pg/mL	ELISA	Under Development
Her2	78.1 pg/mL	ELISA	Under Development
Etanercept	100 ng/mL	ELISA	Under Development
Iron sucrose	20 µg/dL	Chromogenic (ferrozine)	Under Development
Rituximab immunogenicity assay	-	ELISA	Under Development

The lab also has a unique and diverse collection of vaccine assays to support vaccine testing needs. We offer the expertise available for fast and complete vaccine testing, including:

- **Traditional immunoassays**
- **Neutralization assays**
- **Cell-mediated immunity methods**
- **Bacterial functional assays**

Our vaccine experience includes

- Tetanus toxoid IgG
- Measles virus IgG
- Mumps virus IgG
- Rubella virus IgG
- Diphtheria toxoid IgG
- Varicella zoster IgG
- Bordetella Pertusis IgG
- Typhoid vaccine (Anti-S Typhi Vi) IgG
- Influenza virus H1N1, H3N2 and Type B-10 Brisbane, Type B-12 Massachusetts IgG detection was done by haemagglutination and haemagglutination inhibition method.

Biosimilars Speaking Engagement:

- Dr. Shaifali Gupta presented a poster titled "Challenges in Biomarker method validation: A practical approach towards QC preparation and case studies" at the 11th WRIB (Workshop on Recent Issues in Bioanalysis) at Los Angeles in Apr'17.
- Soumen Chakraborty presented a poster on "Bioanalytical Challenges in developing and validating a biomarker assay for Tissue Factor Pathway inhibitor (TFPI) using commercial kit" at APA-India in Feb'17.
- Dr. Shaifali Gupta delivered a lecture on "Biosimilars Bioanalysis; Challenges and Solutions" - presentation was done at the 49th Annual Conference of Indian Pharmacological Society held at PGI Chandigarh in Oct'16 and at APA- India, in Feb'17.
- Dr. Shaifali Gupta, Head - ELISA Lab presented a poster titled "Challenges in estimation of FSH for pharmacokinetic study by Architect i1000 (CMIA based clinical lab instrument) and commercial kits" which won the Best Poster Award at the "10th Workshop on Recent Issues in Bioanalysis (WRIB)" during in 19-21 April'16 at Orlando, USA.
- Dr. Shaifali Gupta delivered a talk on "Occurrence of Anti - erythropoietin antibodies and detection" at the 16th Annual Conference of International Society of Pharmacovigilance held at Agra in Oct'16. The abstract (P100) has been published in Adis journal, Drug Safety (Vol. 39, No.10).
- Mr. Soumen Chakraborty, presented a poster on "An acid dissociation Bridging ADA assay for immunogenicity assessment of Bevacizumab" at the "7th Annual Immunogenicity and Bio-assay summit 2015" in November'15 at Baltimore, MD, USA.
- Dr. Shefali Gupta, Head - ELISA Lab has presented a poster on "Method Development of PK/PD & Immunogenicity methods of Bevacizumab" in "9th Workshop on Recent Issues in Bioanalysis(WRIB) at during 16-19 April'15 Miami, Florida, USA.
- Dr. Chirag Shah, Associate Director & Head- Clinical Trials has delivered the lecture on "Challenges in Clinical Development of Biosimilars" in "3rd International Conference of Biosimilars 2014" during 27-29 October'14 at Hyderabed, India.

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About Cliantha

Cliantha Research is a global Contract Research Organization (CRO) providing integrated clinical offerings in Early Phase (Phase I/IIa), Late Phase (Phase II-IV), Biosimilars, Clinical Endpoint Trials, Bioequivalence (BA/BE), Oncology, Dermatology, Respiratory, Allergy, Bioanalytical, Biometrics, Regulatory Services and Personal Healthcare services. Our services have science at its foundation that is developed through regular and systematic training of the Cliantha Team.

For detailed information about Cliantha's biosimilars experience & capabilities, please visit us at **www.cliantha.in or** write to **cshah@cliantha.in**

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