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Human Insulin Biosimilars Are Not Explored Yet??

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Abstract: *"BIOSIMILARS" are the generic version of innovators product is the new buzz word in the pharmaceutical industry at present. Biosimilars are defined as complex structured, large molecules that are made from the living organisms and manufactured by complex processes, differ in many respects from chemically derived drugs. The first Biosimilars introduced in to routine clinical was recombinant human insulin registered in European region. The main focus is on regulatory issues why human insulin Biosimilars are not used worldwide??*

Currently there is a interest in the legislative debate around "BIOSIMILARS" in the European Union and US due to large,Lucrative market that it offers to the industry. The European Medicines agency leads in providing regulatory guidelines to this emerging industry. Several non - innovator insulins, including insulin analogs are readily available in many countries. Many of these lack rigorous regulations for bio similar approval and pharmacovigilance. Recently an application for a biosimilar recombinant human insulin was withdrawn by European medicines agency because of safety ,efficacy concerns.Therefore, every biosimilar should be assessed by well defined preclinical and clinical trials followed by post marketing pharmacovigilance programs. Framing of stringent guidelines and following them may lead to minimise safety ,efficacy issues of bio similar insulin. The pharmaceutical market is now allows the generic version of innovators product referred as "BIOSIMILARS" in Europe, "follow on pharmaceuticals "in US and Japan, "Subsequent entry biologics " in canada "Biocomparables" in Mexico. Future explore of biosimilars is Bio betters

Keywords*: Biosimilars,Bio betters.*

INTRODUCTION:

Biosimilars are biotechnologically produced by the host cells with high molecular weight and complex physico chemical properties .Biosimilars are administered parentrally and difficult to characterize. A biosimilar product is a biological product that is approved based on a showing its similarity to an FDA approved[1] innovator's product, and has no clinically meaningful differences in terms of safety and effectiveness from the innovator's product. Only minor difference is clinically inactive components are also allowed in biosimilar product. Biosimilars are larger in size than generics ,having several hundreds of amino acids, biochemically joined together in a defined sequence by peptide bonds to form polypeptide. Structurally biologics are more complex than low molecular weight drugs ,consisting of primary and secondary structures.

A human insulin biosimilars[2] are based upon the original formulation of the insulin molecule which is a non-glycosylated, di sulphide bonded hetero dimer made up from 51 amino acids of which 21 amino acids are in A chain and 30 in the B chain which is intended to treat diabetes mellitus. Incorrect dosages [3]of human insulin makes patient run the risk of going into hypoglycaemia(very low level of blood glucose level). Biosimilars are produced after the expiry of patent period of innovators product.

Difference between Generics and Biosimilars:

characteristics	Generics	Biosimilars
Product characteristics	Small molecules	Large complex molecules
	Often very stable	Stability requires special Treatment
	Typically taken orally	Produced by chemical synthesis
Production	Produced by chemical Synthesis	Produced in living organism
		Highly sensitive to manufacturing changes
		Often high production costs
Development	Very limited clinical Trials (only Bioequivalence studies)	Significant research and development (i.e. cell lines)
		Clinical trials to a limited extent
Regulation	Shorter registration procedures in Europe and the United states	Regulatory Pathway defined by the EMA

	Usually enjoy "substituability" status	Comparability status
		In the united states,law approved in March 2010,in force in october 2010
Marketing	No or limited detailing to Physicians	Detailing to (specialist)physicians required
	High price reduction	Lower price reduction
	Market substituion	

HISTORY:

Human insulin is the name which describes synthetic insulin which is laboratory output to mimic the insulin in humans. Though it is developed in 1960&70's ,it was approved for pharmaceutical use in 1982.

Before human insulin developed animal insulin ,usually a purified form of porcine insulin was used. Biocon was the first company that launched world's first recombinant injectable human insulin (insugen).

MANUFACTURING OF HUMAN INSULIN:

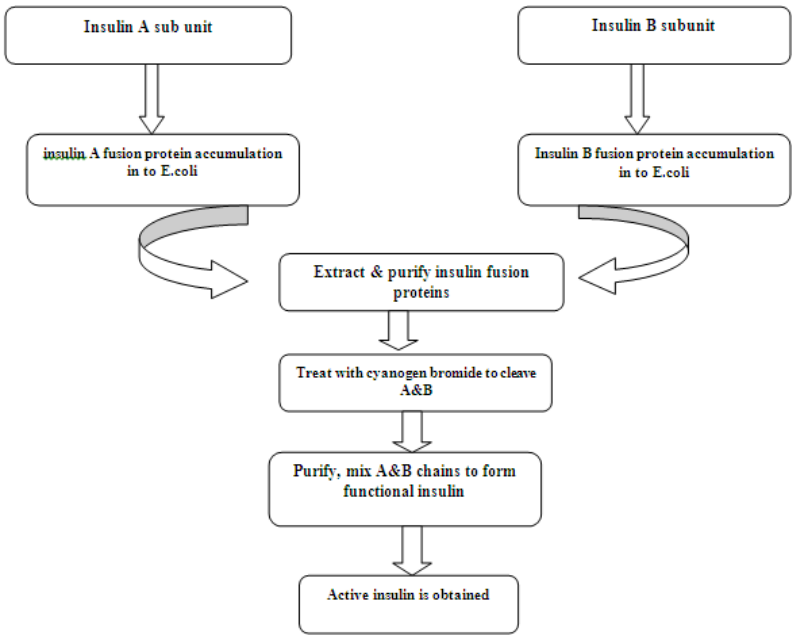
Biosimilars production is more complex process involving several steps. These are generally produces from living host cells such as yeast ,bacteria(E.coli[4], Saccharomyces cerevisiae).

Researchers or manufacturer's need the human protein that produces insulin. Researcher's can get this through an amino -acid sequencing machine that synthesizes the DNA. They must know exact order of insulin's amino -acid sequencing (the nitrogen -based molecules that line up to make up proteins).There are 20 common amino acids. Manufacturer's or researcher's input insulin's amino acid ,and the sequencing machine connects the amino acids together .And also they grow bacteria on large tanks and nutrients required for growth of that bacteria so that large tanks of insulin can be easily synthesized. Various instruments are necessary to separate and purify the DNA such as centrifuge along with various chromatography, electrophoresis and X-ray crystallography. Differences between innovator's and non-innovator's can be identified analytically.This provides strong argument for caution before automatic substitution of conventional products.
Human insulin is of 2 types. They are

1.Short acting :Humulin 's',actrapid.

2.Immediate acting: insuman basal.

PRODUCTION OF HUMAN INSULIN[5]:



QUALITY CONTROL:

After the complete human insulin is synthesized, the structure and purity of human insulin batches are tested through several different methods. High performance liquid chromatography is used to determine impurities in the insulin if any present. Various separation techniques ,such as X-

ray crystallography, gel filtration, gel electrophoresis and amino acid sequencing has to be performed. Manufacturer's also test the vial's packaging to ensure it is sealed properly or not. Manufacturing for human insulin must comply with national institute of health procedures for large scale operations.The united states food and drug administration, European medicines agency must approve all manufactured insulin

RECALL OF HUMAN INSULIN BIOSIMILARS:

Human insulin biosimilars are recalled mainly due to safety and efficacy issues which are araised due to inferior in framing, and following the stringent.

Stringent guidelines to be followed to minimise safety ,efficacy issues as per EMA:

The EMA requires that biosimilars undergo comparatibiity studies of both innovator and non innovator product to provide the evidence that the biosimilar is similar in quality ,and efficacy to that of refernce product.One of the main concern was that inproper in intake of insulin with different brands may cause hypoglycaemia. Therefore it is mandatory to ensure the effects of any insulin product in clinical use are highly persistent and anticipated.The EMA requires atleast one pk single dose studies that compares human insulin biosimilar with innovators product ,using parentral mainly sub cutaneous administration, mainly in patients with type -1 diabetes. Clinical activity also must be assessed such as comparative Pharmacodynamic study ,double blind cross -over to demonstrate the products response profile.

Overarching Guidelines:
Guideline on similar biological medicinal products[6].
Guideline on similar biological medicinal products containing biotechnology derived proteins as active substances[7](Quality issues).
Guideline on similar biological medicinal products containing biotechnology derived proteins as active substances[8](non clinical and clinical issues) .
2.Specific guidelines are framed for Recombinant erythropoietins, Recombinant G-CSF,Recombinant human insulin,Low molecular weight heparins, somatropin,Recombinant interferon alfa & beta,Monoclonal Antibodies.
3. Draft specific guidelines for revision of guideline on low molecular weight heparins
4.Other guidelines for comparability of biotechnological/biological
Comparability of biotechnology derived medicinal products after a change in the manufacturing process.
Immunogenicity assessment of monoclonal antibodies intended for invivo clinical use.
Immunogenicity assessment of biotechnology derived therapeutic proteins[9].
Concept paper on the revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant granulocyte colony stimulating factor& on immunogenicity assessment of biotechnology derived therapeutic proteins.
Draft concept paper on the need for a reflection paper on statistical methodology for the comparative assessment of quality attributes in product development.

CONCLUSION:

Biosimilars has become new buzz word in the pharmaceutical industry .Though it has become a familiar word to pharma industry at present the problems of biosimilars are not discussed around the globe. Although biosimilars started their journey in the pharma market the biosimilars manufacturers must have capability to manufacture a consistent product has to be proven. since they are complex structure they are difficult to manufacture and also they are very senstive to heat and stability issues also has been araised.And also their are no stringent guidelines for many countries to produce biosimilars. Thus framing of stringent guidelines and following them for the approval of biosimilars may minimise the issues of safety and efficacy of human insulin and may increase its utilization to patients.

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