Available online at *www.ujpronline.com*
Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

REVIEW ARTICLE

QUALITY EVALUATION OF BIOSIMILAR MEDICINES: AN OVERVIEW

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Article Info:

Article History:
Received: 1 February 2020
Reviewed: 13 March 2020
Accepted: 28 April 2020
Published: 15 May 2020

Cite this article:
KORKMAZ E, ÖZDEMİRHAN ME, ALGIN YAPAR E. Quality evaluation of biosimilar medicines: an overview. Universal Journal of Pharmaceutical Research 2020; 5(2):54-57.
https://doi.org/10.22270/ujpr.v5i2.390

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Abstract

Biosimilar medicines are biotherapeutics that are similar in quality, safety and efficacy to previously licensed reference biotherapeutics. The slightest change in any stage of production can cause differences in the product. Among the factors, affecting production can be listed as; host cell selection, fermenter type, ambient conditions, broth, substances used for cell culture, fermentation method and purification method. The similarity should be demonstrated by comparative quality, non-clinical and clinical tests. Research and development studies in the biopharmaceutical field bring diversity of quality control methods along with the formulation and manufacturing method of the biosimilars. Although there are some standardized and validated quality control methods given in the internationally recognized pharmacopoeias, there are many in house methods of biopharmaceutical product owners that can only be used as internal quality control methods by them. The main international sources for quality control methods of biopharmaceutics can be given as pharmacopoeias, International Organization for Standardization standards and Organization for Economic Co-operation and Development methods. In this review manufacturing process, regulatory guidelines and quality control of biosimilar medicines briefly are given.

Keywords: Biosimilars, biotherapeutics, manufacturing, quality control, pharmacopoeial methods.

INTRODUCTION

Biosimilar medicines are biotherapeutics that are similar in quality, safety and efficacy to previously licensed reference biotherapeutics[1]. Since the exact production method of the reference biological product is not known, different processes are mostly used in the production of biosimilar drugs. The slightest change in any stage of production can cause differences in the product. Among the factors, affecting production can be listed as; host cell selection, fermenter type, ambient conditions, broth, substances used for cell culture, fermentation method and purification method[2]. Good Manufacturing Practices-GMP requirements for biological and biosimilar products are higher than for small molecules. The similarity should be demonstrated by comparative quality, non-clinical and clinical tests[1,3]. While non-clinical tests can be grouped as physicochemical characterization, biological characterization, pre-clinical and pharmacokinetic-PK/pharmacodynamic-PD tests, clinical tests can be grouped as PK-PD tests, all reliability and effectiveness studies and clinical studies. Biosimilar products have high degree of similarity to the reference products, but they are not accepted as bioequivalent products[4]. Research and development studies in the biopharmaceutical field bring diversity of quality control methods along with the formulation and manufacturing method of the biosimilars under the biological/biotechnological medicines. Although there are some standardized and validated quality control methods given in the internationally recognized pharmacopoeias, there are many in house methods of biopharmaceutical product owners that can only be used as internal quality control methods by them. The main international sources for quality control methods of biopharmaceutics can be given as pharmacopoeias[5-9] International Organization for Standardization-ISO standards[10] and Organization for Economic Co-operation and Development-OECD methods[11]. Between the pharmacopoeias European Pharmacopoeia, United States Pharmacopoeia, British Pharmacopoeia and Japanese Pharmacopoeia are mostly accepted ones. In the scope of above mentioned pharmacopoeias the analyses of biological and biotechnological medicines can be grouped as physical, chemical, pharmacological and microbiological controls. Those include identity, quantity and potency tests, thermostability, viral control tests, total and bound protein and purity (impurity) controls, sterility

test, bacterial endotoxin and pyrogenicity test to prove their efficacy and safety. In this review, biosimilar medicines are briefly overviewed in the scope of regulations, manufacturing and quality control methods take place in the international standards such as pharmacopoeias.

Regulatory Guidelines for Biosimilars

Regulatory guidelines for biosimilars released by *European Medicines Agency*-EMA1, *U.S. Food And Drug Administration*-FDA[11] and *World Health Organisation*-WHO[12] are listed below.

European Medicines Agency

- ✓ Guidelines on Similar Biological Medicinal Products
- ✓ Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues
- ✓ Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Quality Issues
- ✓ Questions and Answers on Biosimilar Medicines (Similar Biological Medicinal Products).

U.S. Food And Drug Administration

- ✓ Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
- ✓ Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Product
- ✓ Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product.

World Health Organisation

- ✓ Guidelines for Evaluation of Similar Biotherapeutic Products-SBPs.

Manufacturing Process of Biosimilars

Basic steps for manufacturing process of biosimilars are presented in Figure 1 and the critical factors for these steps are given below2.

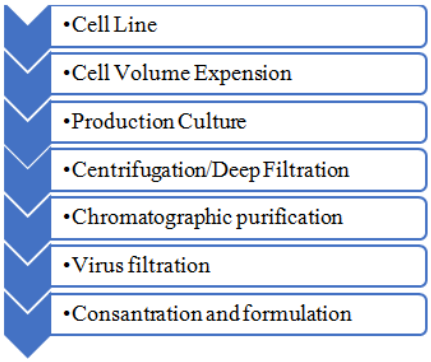

Figure 1: Basic steps for manufacturing process of biosimilars.

Critical factors that are effective on the success of the manufacturing steps are given below.

Cell line selection

- Mammalian
- Bacteria
- Yeast

Cell culture process development

- Oxygen levels
- Lactate production
- Temperature
- pH
- Osmolality
- Duration

Purification process

- Column chromatography
- Filtration
- Centrifugation

Formulation

- Buffer conditions
- pH
- Ionic strength
- Excipients amounts
- The final formulation (liquid, frozen liquid or lyophilisate)

Quality Control of Biosimilars

Under the class of biological and biotechnological medicines the biosimilars are analysed for below given tests and surveillance in terms to prove their quality[13].

Characterization

Characterization of biological and biotechnological medicines are evaluated according to the ICH Q6B guideline[14].

- **Physicochemical Properties**
  - Composition determination
  - Physical determination
  - Primarly Structure determination
  - Heterogenity (activity, efficacy, safety)
- **Biological Activity**
  - Biological Assay (animal based, cell culture based, biochemical assay)
  - Potency
- **Immunochemical proporties**
  - Affinity
  - Avidity
  - Immunoreactivity
- **Puritiy, impurity, and contaminants**
- **Quantity**

Stability

The effect of temperature, humudity, accelarated and stress conditions, light, container/closure system, stability after reconstitution of freeze-dried product variables on stability is evaluated in terms of the following parameters, which are indicated in the ICH Q5C guideline[15];

- Potency
- Purity and Molecular Characterisation
- Other Caracteristics;
  - Visual appearance (colour and opacity for solutions/suspensions; colour, texture and dissolution time for powders).
  - Visible particulates (solutions or after the reconstitution of powders or lyophilised cakes)
  - pH,
  - Moisture level (powders and lyophilised products).
  - Sterility testing or alternatives (e.g., container/closure integrity testing)

- Effect of additives (exipients, stabilisers, preservatives etc.) have to been evaluated.

Comparision Studies for Manufacturing Quality

Comparability of biotechnological/biological products subject to changes in their manufacturing process are presented in ICH Q5E Guideline interms of non-clinical and clinical studies[16].

- Pharmacokinetic-PK
- Pharmacodynamic-PD
- PK/PD
- Clinical efficacy
- Specific safety
- Immunogenicity
- Pharmacovigilance

Table 1: Pharmacopoeial methods for quality control of biopharmaceuticals.

General Tests	Specification	Measurement
	pH	Calibrated pH meter
Identitiy and Heterogeneity	Dissolved molecule concentration	Osmolality
	Charge paternity Molecule weight Primer structure	Ion-Exchange Chromatography
	High level structure	Nuclear Magnetic Rezonanse-NMR, circular dichroism
	Glycolysation heterogeneity	Gas Chromatography/monosaccharide structure analysis with Mass Spectrometry, oligosaccharide analysis
	Amino terminal determination of protein	N terminal sequencing and HPLC
	Carboxy terminal determination of protein	C-terminal sequencing with a combination of peptide mapping and electrospray ionization-mass spectrometry/mass spectrometry
Purity and Impurities	Fragments and isoforms	SDS-PAGE (reduced and non-reduced) HPLC, ultra-HPLC, liquid chromatography/mass spectrometry
	Deamidation products	IEF, Ion exchange chromatography, peptide mapping
	Dimers and large aggregates	Size exclusion chromatography, ultracentrifuge, SDS PAGE
	Post-translational modifications	Peptide mapping, Liquid Chromatography-Electrospray Ionization/Mass Spectrometry
	Host Cell proteins	SDS PAGE, immunological tests
	Related proteins	SDS PAGE, immunological tests, HPLC, liquid chromatography/mass spectrometry
	Production-based impurities	Gas chromatography/mass spectrometry
Potens	Validated biological potency tests	Potens
Quantity	Protein content	UV scanning

Since the quality control of biopharmaceutical products has a great prospect in terms of the safe access to treatment that patients need the quality of them must comply with relevant internationally accepted criteria. Quality in biopharmaceutical products is a broad concept covering all aspects that affect the efficacy and safety of these products. All of the measures that require the assurance of biopharmaceutical quality constitute the quality assurance system. The Quality Assurance system consists of Quality Management-QM, Quality Assurance-QA and Good Manufacturing Practices-GMP and Quality Control-QC. As quality control and analysis of biopharmaceutical products are a part of GMP, quality control analyses should be carried out using validated methods appropriately to ensure the quality of the product. Biopharmaceutical products are subjected to quality control criteria and analysis within the scope of internationally accepted standards and guidelines specified or guided, including formulation, place and form of use. The quality control analyses made in biopharmaceutical products are mentioned below in the general framework within the scope of biopharmaceutical forms. Biological/ biotechnological product analysis in pharmacopieas can be grouped as below and can be given in detail in Table 15-8;

• Biological activity by cell culture method,

• Qualification and quantification by the Enzyme-Linked Immunosorbent Assay-ELISA and High Performance Liquid Chromatography-HPLC methods,

• Total and free polyribosylribitol phosphate-PRP quantification with Isoelectric Focusing-IEF, Sodium Dodecyl Sulfate–Polyacrylamide Gel Electrophoresis-SDS PAGE, Western Blotting methods,

• *In vivo* potency test,

• *In vivo* biological reactivity test,

• Physical tests: Physical controls, pH determination, total and bound protein, protein nitrogen, phenol, thimerosal, free formaldehyde, aluminium, humidity, residual humidity, phosphorus, PRP, sucrose, cresol, Tween 80, glycine, ovalbumin, o-acetyl NaCl (salt) and volume,

• Sterility test (membrane filtration method),

• Limulus Amebocyte Lysate-LAL test,

• Pyrogen test.

It is critical to prove that biopharmaceutical products are continuously produced at the desired quality and

meet the specified specifications to ensure effective and safe treatment. Therefore, all quality control analyses of the starting materials to the finished product are required as part of GMP. Which analyses are to be made for which biopharmaceutical product is determined according to the guidelines of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. With the developments in the pharmaceutical field, quality control tests will also diversify in parallel with newly developed innovative products and devices in addition to the mentioned analysis methods. For example; coulometric moisture determination with Karl Fischer method, particle size distribution and thermal analyses (Thermogravimetric Analysis-TGA, Differential Scanning Calorimetry-DSC) draws attention among the new tests that may be included in this variety.

CONCLUSION

Biosimilar products are gaining importance day by day, and there are many draft legislation and guidelines prepared by legal authorities for these products. In this direction, it will be useful to follow scientific and technological developments and current legislation during R&D, manufacturing and quality control stages.

ACKNOWLEDGEMENTS

The authors extend their thanks and appreciation to the Turkish Medicines and Medical Devices Agency, Çankaya, Turkey to provide necessary facilities for this work.

AUTHOR'S CONTRIBUTION

KORKMAZ E: writing original draft, methodology, investigation. **ÖZDEMİRHAN ME:** formal analysis, data curation, conceptualization. **ALGIN YAPAR E:** review, supervision. All authors read and approved the final manuscript for publication.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None to declare.

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