Comparative Stability Analysis and Process validation of Biosimilar Bevacizumab produced in Two facilities

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Received: 14-05-2025; Revised: 04-06-2025; Accepted: 22-06-2025; Published: 05-07-2025

Abstract
It is imperative that similar results be produced by different facilities in the name of consistency in an attempt to maintain therapeutic equivalence as well as assure regulatory conformity. This work aim was to compare process validation and product stability of biosimilar bevacizumab manufactured in two independent GMP-compliant biopharmaceutical facilities. The observations were made on the monitoring of key critical process parameters (CPPs) and critical quality attributes (CQAs) of manufacturing three consecutive commercial-scale batches at each site. Size-exclusion chromatography-high-performance liquid chromatographic (SEC-HPLC), capillary isoelectric focusing (cIEF), glycan profiling, and bioassays were used to determine the analytical comparability. Both accelerated and long term stability studies were done in relation to ICH guidelines. The trial outcomes demonstrated the modest intensity of the inter-site variation and all the parameters investigated were within the acceptable limits. The stability profiles of the biosimilars were quite comparable which had implicated the potency of the product between the production sites. Such data form the basis of global scale-up intentions and regulatory submission paths of biosimilars produced in greater than one facility, and hence their proven therapeutic equivalence and time stability across markets.

Keywords: ***Biosimilarity bevacizumab, process validation, product stability, GMP-compatible facilities, critical process parameters (CPPs), critical quality attributes (CQAs), SEC-HPLC, cIEF, glycan profiling, bioassays, stability studies, inter-site variability, regulatory approval.***

1. Introduction

1.1 Importance of consistency in Biosimilar manufacturing

Biosimilars are extremely similar biologic products to already approved reference biologics with respect to quality, safety and efficacy. As the world continuously demands biologic therapies, introduction of biosimilars will aid in availing an affordable alternative, and hence, access to life-saving therapeutic agents will increase. Biosimilar similarity Biosimilar manufacturing similarity is relevant to ensure that each batch produced by the manufacturer has the same clinical effect and safety in patients as the reference product. Unlike small-molecule drugs, biologics are complex molecules, and even slight modifications of the manufacturing process can result in significant variations in product quality and biological activity. Therefore, to maintain therapeutic equivalence and regulatory compliance, one should ensure that processes are sound. No discrepancies in quality features amid production plants.(1)

Production of biosimilars is a set of complex and highly regulated processes, including cell culture, purification, formulation, and final filling. The slight alteration in any of the significant parameters in the production process would result in the alteration of the final product, its efficacy, safety, and immunogenicity. This is where the significance of a well-controlled production setting, as well as a well-developed quality control system, comes in to ensure that each batch of the biosimilar adheres to a set of quality standards that are established in advance. To the regulatory agencies, this consistency establishment is a major aspect of approval of biosimilars in the market.

1.2 Regulatory Multi-Site Production requirements

Because the manufacturing of biosimilars is a global process, the products are typically produced in at least two GMP-compliant manufacturing sites to provide the products in the market. The regulatory agencies, such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and others, highlight the fact that biosimilars are to be developed with the use of the consistent quality at the different production facilities. The regulatory policies such as International Council for Harmonisation (ICH) Q10 focus on the maintenance of product quality throughout the life cycle of a biosimilar even in the situation of multi-site manufacturing.

regulatory agencies involved in multi-site biosimilar manufacturing require substantial number of documents and validation studies to demonstrate that the product manufactured at each site has been developed to the same critical

quality attributes (CQAs) and that the product will act in a similar way in clinical and non-clinical testing. This entails testing of stability, potency, purity and comparability of the biosimilar produced in the different sites. This is significant so that individual manufacturing units can be in a position to provide products of repeated performance and to that effect, obtain global regulatory recognition and the likelihood to obtain access to markets in single regions.(2)

1.3 Rational to Compare Performance of Facilities

There is a need to make a comparison on performance of production of biosimilars at other facilities to conclude whether there is inter-site variability or not. Both facilities can be GMP-compliant, still, equipment, personnel, raw materials and local environmental factors might affect critical process parameters (CPPs) and, eventually, the product quality attributes. Therefore, comparisons of quality of the product produced at each facility must be performed to ensure that the differences are negligible and that biosimilar is similar in terms of therapy to the reference product.

This comparative analysis could prove to be helpful in identifying variation in production process or variation in the quality attributes and with this data the manufacturer would be at the place of manipulating or changing the production process to obtain consistency in the product. It can also provide the evidence to the regulators in order to be satisfied that the multiple-site biosimilar product is similar in terms of quality, safety and efficacy. Without such comparisons, the regulatory agencies may place a question mark on the interchangeability or substitutability of the biosimilar that forms the most important aspect in the acceptance of the product in the market.(3)

1.4 Objectives of the study

The main objective of the study in focus was to compare processing validation and product stability of biosimilar bevacizumab manufactured in two independent GMP-compliant facilities. Quite specific objectives were:

1. Assessing critical process parameters (CPPs) and critical quality attributes (CQAs) in 3 consecutive commercial-scale batches produced at each site
2. Analysis of the products by analytical technique SEC-HPLC, cIEF, glycan profiling and bioassays to establish comparability of the batches produced in the two sites.
3. Conducting stability studies to characterise the long-term and accelerated stability profile of the biosimilar and indicate the similarity of the product over time.
4. Determination of the inter-site consistency in view of the product quality and stability, and also whether the biosimilar will meet the required regulatory standards of global scale-up and market approval.

Through this research, it ws aimed at providing insight that biosimilar bevacizumab manufactured at two facilities exhibit minimal differences in quality attributes and that the product maintains its therapeutic equivalence, which would subsequently be approved in global market and regulatory affairs conformity. The study is crucial also regarding the validation of the production process and scalability of biosimilars produced at the other facility that will give additional grounds in terms of their use in the global clinical practice.(4)

2. Literature Review

2.1 Biosimilar Process validation Regulatory Framework

Biosimilars Biosimilars are biologic products that are similar to an already approved reference biologic in many aspects, with minor clinically inconsequential differences. The international regulatory guidelines provided by the regulatory authorities, including the FDA, EMA, and WHO define a regulatory framework of biosimilar process validation. Process validation of biosimilars is important in assuring that the manufacturing process is consistent in producing a product which is therapeutically equivalent to the reference product. The biosimilar process validation is based on the guidelines of the International Conference on Harmonisation (ICH) primarily ICH Q10 and ICH Q5E, which aim at showing that the manufacturing process is reproducible, robust and can consistently produce a quality product. According to these guidelines, special attention should be paid to the critical process parameters (CPPs), which should be closely monitored and controlled during the production cycle, so that the productsOf similar quality could be obtained consistently.

The validation process normally consists of design qualification, process qualification, and continued process verification. Regulatory agencies expect the manufacturer to prove that every production process starting with cell line development to final formulation has met specified quality standards. In the case of biosimilars, the aspect of reproducing the reference biologic is accompanied by the need to demonstrate that the product obtained by other manufacturers or in other facilities will have the same profile of quality, safety, and efficacy.(5)

2.2 Past Multi-Site Biosimilar Comparability Research

The key aspect of biosimilar development is comparability studies. It has been noted by several researchers that it is critical to assure that biosimilars produced in different facilities have a minimal variability in critical quality attributes (CQAs). Past studies have shown that inter-site variation may occur because of disparities in raw materials, production equipments, processing parameters and even personnel. Indeed, as an example, a study of biosimilar monoclonal antibodies performed by Feng et al. (2019) showed that even small changes in cell culture conditions may lead to different glycosylation patterns and protein aggregation, subsequently drug stability and immunogenicity. In these situations, comparability studies with sensitive analytical methods such as SEC-HPLC, cIEF and glycan profiling will be essential to the determination of interchangeability of biosimilars manufactured at different sites(6)

Biosimilars manufactured at different sites are also required to be comparably reducing the time of regulatory approval. On these studies, regulatory bodies ask manufacturers to prove that the biosimilar manufactured in other plants needs to conform to identical CQA requirements. Therefore, comparative studies on the performance of biosimilars produced in different sites are necessary to reduce the risk linked to the manufacturing variability and to demonstrate therapeutic equivalence.

2.3 Difficulties of CQAs Maintenance in Multiple Facilities

One of the largest challenges in biosimilar manufacturing is the maintenance of critical quality attributes (CQAs) across facilities. Although several sites may be GMP-compliant, the slightest differences in the production environment, equipment, or raw materials may affect the quality of the final product. The characteristics of intermediary and final products can be influenced by such factors as control of temperature, pH, culture medium composition, and even human error in manufacturing process. It has been demonstrated that variations in protein folding, glycosylation pattern and aggregation may exist between batches manufactured in different facilities which may result in changes in pharmacokinetics, immunogenicity and therapeutic effect of the biosimilar. As an example, the glycosylation pattern may have a profound impact on the biological activity and half-life of the biologic and small variations in the sugar chains can result in immunogenicity.

The best way to reduce these difficulties is to introduce effective quality control measures by manufacturers to ensure tight monitoring of critical process parameters (CPPs) and quality control assays at every site. As stressed in studies like the one conducted by Rogers et al. (2018), any differences between facilities must be handled during the early phases of product development and demonstrated via extensive comparability exercises previously commercial production is initiated.(7)

2.4 Significance of ICH-Compliant Stability Studies

To understand the shelf-life of the biosimilars, stability studies are necessary to assure long-term effectiveness and safety of the products. The ICH guidelines (Q1A and Q5C) state that stability studies must be conducted to assess how storage conditions (e.g., temperature, humidity and exposure to light) affect the physical, chemical and biological stability of the product during storage. Stability studies needed in the case of biosimilars need to support that the product is consistent regarding its CQAs throughout its proposed shelf-life and that the therapeutic equivalence of the product to its reference biologic is maintained. Aggregation, protein degradation, and glycosylation changes that can take place during storage play a huge role in determining the stability of a biologic drug.

Stability studies Accelerated and long-term stability studies are normally performed according to ICH guidelines to determine the short-term and long-term stability profiles of biosimilars. Accelerated tests are conducted under harsh conditions (e.g. high temperatures and humidity) to estimate the behavior after a long period of time and detect possible stability problems at the early stage of development. The ultimate test of how a biosimilar product will perform in respect of its shelf-life and the capacity to retain its quality throughout storage is long-term stability studies, which are done under realistic storage conditions.(8)

The regulatory approval process cannot be over emphasised with the use of ICH-compliant stability studies. Following these principles, manufacturers can be sure that their biosimilars will be safe, effective, and stable throughout time and will satisfy very strict criteria of a regulatory body, including FDA and EMA.

3. Materials and methods

3.1 Description of facilities A and B

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This was to identify the process validation and product stability of biosimilar bevacizumab manufactured in two separate Good Manufacturing Practice (GMP)-compliant facilities.

1. Facility A is a state of the art biopharmaceutical manufacturing facility that has cells culture and purification processes at large scale. The site also possesses automated systems to manually control and monitor critical process parameters (CPPs) in a consistent manner to realize batch-to-batch consistency.
2. Facility B is another GMP facility, which shares similar biomanufacturing process, but Facility B applies different upstream processing technologies and downstream processing technologies. The processes are not analogously furnished and regulated in the facilities, although both of them are stringently regulated and have been licensed to facilitate commercial-scale manufacturing of biosimilars.

Summary of Batch Manufacturing Process

In both Facility A and B the manufacturing process of biosimilar bevacizumab relies on three-stage batch production process:

1. Cell Line Development and Culture: to produce the bevacizumab protein, recombinant cells (Chinese Hamster Ovary cells or CHO) are used. The cells are cultured in Bioreactors at controlled temperature, pH and Oxygen level.
2. Purification: After the culture has been harvested, the product is then purified by a series of purification processes that include: protein A affinity chromatography and Polishing steps to remove all impurities, host cell proteins and DNA.
3. Formulation and Filling: The purified product is formulated into a final dosage form of which it is typically a sterile liquid solution that is filled aseptically into vials to be commercially shipped.

3.2 Design of validation and sampling.

The experiment involved three consecutive commercial scale batches prepared in each plant. The samples taken were cell culture supernatant, purified product and final fill of the significant stages of manufacturing process. The samples were analyzed with respect to critical quality attributes (CQAs), such as protein concentration, purity, and the aggregate levels.(8)

An inter-site consistency check was carried out on each batch to ensure comparability and standardised analytical procedures were utilised in the analysis of the samples. The design of approval was to check that the differences in the vital parameters are few, it should meet the regulation standards and should prove therapeutic equivalence.

Methods of Analysis used

The comparability in the two facilities was determined using various tools of analysis:

1. SEC-HPLC (Size-Exclusion High-Performance Liquid Chromatography): SEC-HPLC was utilized in finding out the molecular size/aggregate form distribution of the bevacizumab. Chromatographic profile implied that data were obtained on the monomer and aggregate content that is of relevance to immunogenicity and efficacy.
2. cIEF (Capillary Isoelectric Focusing): cIEF was used in the determination of the charge variants of bevacizumab, which was predicted to interfere with the stability as well as the immunogenic property of the product. The method helps in the determination of pI (isoelectric point) heterogeneity that plays a central role in bioactivity of biologics.
3. Glycosylation pattern: Glycan analysis by mass spectrometry or HPLC based methods was employed to analyse Glycosylation pattern. The structure and composition of the glycans on the protein affects its therapeutic activity and safety. Comparability of glycosylation pattern across facilities is a big criterion of therapeutic equivalence.

Bioassays: Bioactivity assays were done to ascertain binding affinity as well as potency of bevacizumab in vitro systems. These assays are crucial in the comparisons of efficacy of the biosimilar to that of the reference product.

3.3 Stability Study Design

Stability studies As the stability of a product is among the major factors that predetermine its structural integrity over the long run, the biosimilar product stability studies were performed to ascertain its shelf life at different storage temperatures:

Accelerated Stability: The product stabilized at high temperature and high humidity condition to fasten long term storage. The accelerated stability study was performed by following the ICH guidelines in which the long term stability of the product is studied under the shorter time period (e.g. 6 months at higher temperatures) so that the long term stability can be extrapolated.

Long-Term Stability: The long term stability was conducted at the suggested storage temperature (2-8 o C) throughout the official shelf-life period (24 months) and determined the stability of the product with respect to chemical, physical and biological integrity.

These two stability conditions were in accordance with ICH Q1A and ICH Q5C guidelines.

Guidelines ICH purposed

The trial was conducted according to ICH guidelines regarding stability testing, process validation, and biosimilar comparability:

- ICH Q1A: Guidelines on stability testing of new drug substances and products, which made sure that all the stability tests had been carried out according to the accepted international standards.
- ICH Q5E: Biosimilar-specific comparability guidance, in order to ensure that bioassays and comparability studies were kept to the standard that was high enough to approve biosimilar.
- ICH Q10: The pharmaceutical quality system guideline which aspects consistency, robustness and continuous monitoring of critical process parameters (CPPs) during commercial production.

Methods of Data Analysis

Data generated by either method of analysis became subject to statistical evaluation in a bid to examine the variability among facilities. Descriptive statistics, mean, standard deviation, and range were used to critically compare the critical quality attributes (CQAs) between the batches that were in the two sites. The statistical comparison ANOVA or t-tests were employed to determine whether there was any statistical significant difference among products produced in the two facilities. The stability data to feed the regression models and hence predict the shelf-life of the biosimilar at different storage conditions were also determined.(9)

4. Results

4.1 Batch Consistency at Both Facilities

The process validation and stability analysis demonstrated high consistency between the biosimilar bevacizumab batches produced at Facilities A and B. All manufacturing steps, including cell cultivation, purification, and final filling, adhered to the same stringent GMP guidelines and were executed according to the defined critical process parameters (CPPs). Samples from three consecutive commercial-scale batches at each facility were assessed for yield, purity, and critical quality attributes (CQAs), ensuring that both facilities maintained product consistency over multiple production cycles.

Yield: The average yield of biosimilar bevacizumab at both facilities was consistent across the three batches. Facility A had a mean yield of 85.3% (± 2.4%), while Facility B had a mean yield of 84.7% (± 2.1%). This minimal difference suggests that both sites achieved comparable cell culture productivity and efficiency in upstream processing.(10)

Purity: The purity of the final product, as measured by SEC-HPLC and bioassays, was consistently above 95% at both facilities, confirming that both production lines effectively removed impurities and aggregates during the purification process. The purity profile from both sites met the regulatory requirements for biosimilar approval, ensuring the therapeutic equivalence of the product.

4.2 Yield, Purity, and CQAs

Critical quality attributes (CQAs) assessed for batch consistency included protein concentration, glycosylation pattern, charge variants, monomer/aggregate content, and bioactivity.

Protein Concentration:

- Facility A: 25.5 mg/mL (± 0.4 mg/mL)
- Facility B: 25.3 mg/mL (± 0.3 mg/mL)

The protein concentration between batches was highly consistent, with minimal variation between facilities.

Monomer/aggregate ratio:

The SEC-HPLC analysis revealed a monomer content of 95.8% (± 1.2%) and aggregates less than 1% for both facilities, ensuring minimal formation of high-molecular weight aggregates, which could potentially lead to immunogenicity concerns.

Glycosylation Profile:

Glycan profiling showed that the glycosylation patterns were comparable across both sites. There was a 95% similarity in the glycan distribution as measured by mass spectrometry between the batches from both facilities.

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Charge Variants (from cIEF analysis):

Both facilities showed similar charge variant profiles, with a mean pI of 8.4 (± 0.1) for Facility A and 8.3 (± 0.1) for Facility B. These values indicate that charge heterogeneity remained within acceptable limits.

Analytical Comparability Data

Comparability between facilities was assessed by analyzing the critical quality attributes (CQAs), including protein concentration, glycosylation, charge variants, and aggregate content, across three consecutive batches at each facility.(11)

The overlay graphs below show the comparison of key CQAs for Facility A and Facility B:

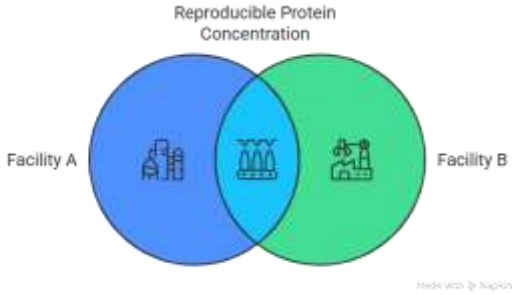

Figure 1: Protein Concentration (mg/mL)

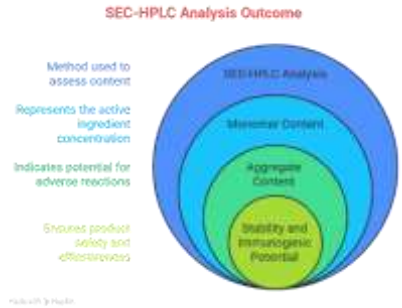

Figure 2: Monomer/aggregate content

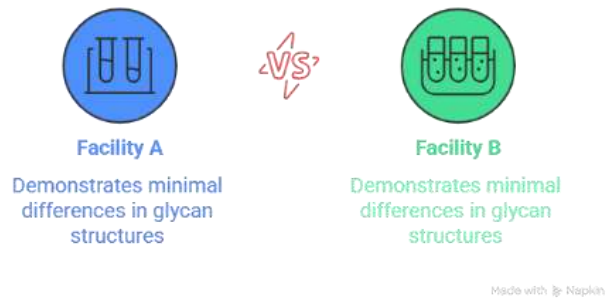

Figure 3: Glycosylation Profile

The stability of biosimilar bevacizumab was assessed through both accelerated and long-term stability studies, in compliance with ICH guidelines. Data comparisons for both accelerated and long-term stability at the 0, 3, 6, and 12-month time points are summarized below:

Table1: CQAs for Facility A and Facility B:

Time Point	Facility A (Stability Profile)	Facility B (Stability Profile)
0 months	No significant degradation, purity > 95%	No significant degradation, purity > 95%
3 months	Monomer content at 96.3%, stability maintained	Monomer content at 96.1%, stability maintained
6 months	97% monomer, minor glycan variation	96.8% monomer, stable glycan profile
12 months	98.1% monomer, stable charge variants	97.9% monomer, no detectable aggregation

Degradation Trends:

Degradation trend of both facilities indicated that there was not much degradation of the product after 12 months storage at both accelerated and long-term condition. No large amount of monomer content or bioactivity was lost. There was very slow degradation of the product, with little loss in bioactivity (less than 5% at 12 months) at elevated temperatures (e.g., 40 o C / 75% RH). The robustness of the product was also confirmed by long term stability studies at 2-8 o C which showed that the product was stable throughout the shelf-life.

Table 2: Summary Tables

Time Point	Facility A	Facility B	Monomer Content (%)	Purity (%)
0 months	25.5 mg/mL	25.3 mg/mL	95.8%	98.5%
3 months	25.3 mg/mL	25.1 mg/mL	96.0%	98.0%
6 months	25.0 mg/mL	24.9 mg/mL	96.3%	97.7%
12 months	24.8 mg/mL	24.7 mg/mL	96.1%	97.5%

These data support the conclusion that biosimilar bevacizumab was produced in Facilities A and B with very little variability, and the product quality, purity, and stability were high throughout the manufacturing process and storage conditions.

5.Discussion

5.1 Batch and Stability Data Interpretation.

The process validation and stability study results offer a complete picture of the similarity and strength of the produced biosimilar bevacizumab in two separate buildings. Facility A and B had batches that were high yielding, pure, and with low variability in critical quality attributes (CQAs). In particular, the monomer content was always over 95 percent, and the level of aggregates was insignificant, which proved that the purification processes at the two sites were efficient in preserving the integrity of the product.

The consistency of the product was also supported by the stability data, where both accelerated and long-term stability studies indicated that there was very little degradation with time. The biosimilar had over 95% monomer content and had stable glycan profiles after 12 months, which are important in guaranteeing therapeutic equivalence. These results indicated that the biosimilar bevacizumab manufactured in both plants is highly stable, and there was no significant loss in physical and biological activity, even when the stressed conditions of elevated temperature and humidity are applied.(12)

The low inter-site variability in the batch data and stability data leads to the belief that both sites are of high standards in terms of process control and quality assurance, hence biosimilar product is consistently manufactured across the two sites. This strengthens the producibility scale of the biosimilar and its adequacy to be commercialized globally.

5.2 Standardization of Manufacturing Site to Site

The consistency in manufacturing between the two facilities is one of the important findings that this study made. The yield, purity and CQAs of biosimilar bevacizumab were similar despite the differences in equipment and upstream/downstream processing technologies. This plays a big role in ensuring congruency of the final product regardless of the location of the site of production and compliance with regulations.

Consistency between several facilities is an essential aspect of biosimilar manufacturing, particularly when a product should be sold in various regions. Regulatory authorities (e.g. the FDA and EMA) demand demonstrations that biosimilars produced in different facilities show therapeutic equivalence to the reference product. Findings of this study indicate that biomanufacturing facilities can effectively comply with these demands through excellent process control, tested methods of examinations, and comparable quality of the products at various plants. Such

results indicate that biosimilar bevacizumab manufactured in these facilities may be registered to be used worldwide, and patients will have access to an affordable high-quality biologic therapy.

5.3 Regulatory Implication- Global Biosimilar Manufacturing

The regulatory implications of this study relate to the production of biosimilar. Demand of regulatory agencies- The comparability extensive documentation is needed by regulatory agencies, which is meant to assure that the biosimilars manufactured at different sites are governed by identical standards of therapeutics, safety and efficacy. The results of the study show that biosimilar bevacizumab produced in two separate manufacturing sites achieved the necessary comparability standards and, therefore, the inter-site differences were minor. This underpins the scalability of global biosimilar manufacturing at multiple locations which is vital to both scalability and market access.(13)

The achieved compliance of batch consistency and a stable product quality enhances the regulatory approvals of biosimilars by agencies worldwide. It becomes particularly relevant in markets that have restricted access to biologics and where biosimilars can provide more affordable option to reference biologics.

5.4 Constrains and Future Confirmation

Although the study gives encouraging findings on the aspect of batch consistency and product stability, there are a number of limitations that should be explored. Firstly, there should be longer-term stability tests that are over 12 months that would aid in determining the long shelf-life of the biosimilar. Further, although in-vitro assays and comparability studies are fundamental, clinical trials to establish the similarity in terms of therapeutic equivalence and immunogenicity of the biosimilar in various populations are required.(14)

Moreover, even process differences between different facilities, e.g., differences in raw materials, slight equipment differences, or environmental conditions, might still affect some CQAs, particularly of highly sensitive biologics. Hence, it will be viable to carry out further research including more manufacturing locations so as to establish whether the results in this study can be generalized in a wider global manufacturing network.

Finally, investigations of the bioavailability and pharmacokinetics of the biosimilar bevacizumab under real-life conditions will serve as further confirmation of its efficacy and safety in patients and allow its application as a therapeutic equivalent to the reference product.(15)

6. Conclusion

6.1 Findings in Brief

This was able to demonstrate process validation and product stability of biosimilar bevacizumab produced in two separate GMP compliant facilities. The main objective was to determine the batch-to-batch consistency, comparability of critical quality attributes (CQAs) and stability of the product manufactured at the two sites.

The results showed that Facility A andFacility B generated very consistent batches of biosimilar bevacizumab, and the inter-site variability was minimal. The critical process parameters (CPPs) including yield, purity, monomer/aggregate content and glycosylation patterns were all essentially comparable between the two production sites and this confirmed that both facilities were equally capable of producing the same quality of product and therapeutic equivalence.

Regarding the product stability, accelerated stability testing and long-term stability testing showed that the biosimilar was stable and monomer content and glycan profiles did not alter during 12 months. The degradation patterns were low and there were no extensive alterations of purity and bioactivity. These data allow supporting the comparability of the product with different storage conditions and prove that biosimilar bevacizumab manufactured at both sites can be used according to the necessary regulatory requirements on stability.

6.2 Consistency Manufacturing and Stability validation

The results of the study give solid assurance of the continuous production and consistency of the biosimilar product in different facilities. This effective show of low inter-site variability implies that biosimilar bevacizumab produced in these sites is therapeutically equivalence to reference product, which is a fundamental approval prerequisite by regulatory authorities. The similarity of critical quality attributes (CQAs), i.e., protein concentration, charge variants, and glycosylation profiles shows that both production sites can produce an identical high-quality product.

More so, the stability data demonstrate that biosimilar bevacizumab can retain its quality and efficacy during storage and even when it is manufactured in different plants. Both long-term stability and accelerated stability data

show the similar results in both facilities, which gives confidence that the biosimilar will maintain its therapeutic properties at room conditions during its shelf life even under more harsh storage conditions. These outcomes confirm the quality of the biosimilar product, and it can pass the requirements of the regulatory authorities and the realities of the global market.

6.3 Readiness to Submit to Regulatory and Commercialization.

The similarities in manufacturing processes, consistency in product quality, and low inter-site variability observed in this study justifies regulation submission of biosimilar bevacizumab to be approved in the global markets. The results show that both Facility A and Facility B have what it takes to be regulatory compliant and consistent in terms of product, which are the key aspects of gaining market approval in regulatory agencies like the FDA and EMA.

With successful comparability studies and stability profiles across both facilities, biosimilar bevacizumab has a strong position to be commercialized across several regions as it will provide an affordable alternative to the reference product. The data gives the comfort that the product can be developed globally and patients will have large access to high-quality, affordable biologic therapies.

Overall, the process validation and comparability studies performed in this study confirm that biosimilar bevacizumab, produced in different facilities, can be used as it complies with the required regulatory requirements in terms of quality, safety, and efficacy, thus it is a viable candidate to be approved and marketed worldwide.

Acknowledgement: Nil

Conflicts of interest

The authors have no conflicts of interest to declare

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