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ORIGINAL RESEARCH ARTICLE

Consistency of Product Quality for SB5, an Adalimumab Biosimilar

JongAh Joanne Lee[1] · Nayoung Lee[1] · Young Jun Seo[1] · Ilkoo Kim[1]

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Abstract

Background Biologics, regardless of whether they are biosimilars or reference products, are inherently variable due to their size, complexity, and the manufacturing process involved to produce them. Since a drift or evolution of quality attributes of a biologic may impact its clinical safety or efficacy, it is critical for the manufacturer to carefully control the manufacturing process and monitor the quality attributes of a biologic.

Objective The aim of this study was to demonstrate that the quality profile of the SB5 drug product has been consistent over its production history from 2013 to 2022. SB5 is a biosimilar referencing adalimumab (Humira, trademark of AbbVie Biotechnology Ltd) and SB5 has been approved by 14 regulatory authorities including the European Commission in August 2017 (brand name Imraldi™) and the US Food and Drug Administration in July 2019 (brand name Hadlima™).

Methods A total of 93 SB5 drug product batches manufactured between 2013 and 2022 were analyzed for a series of release parameters to evaluate the consistency in their critical quality attributes including purity, charge variants, and functional activities (TNF-α binding activity and TNF-α neutralizing potency).

Results The purity, charge variants, and functional activities of all batches were consistent over time and within the stringent acceptance criteria defined by regulatory agencies to ensure the safety and efficacy of SB5.

Conclusion The data presented in this study provide evidence that the quality of SB5 has remained consistent and tightly controlled even through process changes such as manufacturing site transfers and change in formulation.

Key Points

Biologics, including both biosimilars and reference products, are heterogeneous due to their size, complexity, and the manufacturing process involved.

Control of process parameters and quality attributes is key for consistent clinical performance of a biologic.

The critical quality attributes of SB5 including purity, charge variants, and the functional activities have remained consistent between 2013 and 2022 even through process changes including manufacturing site transfers and formulation changes.

1 Introduction

Biologics have become a substantial component of pharmaceutical expenditure owing to their efficacy across numerous therapeutic areas including immunology and oncology [1–4]. Biologics spending has considerably increased over recent years. In the United States (US), the spending on biologics has increased from US$84 billion in 2014 to US$126 billion in 2018 [4, 5]. In 2019, biologics represented 43% of total US medicine spending [5, 6], and yet biologics spending is projected to grow even further, with immunology being one of the leading therapeutic areas of growth [7, 8]. Successful biosimilar uptake is therefore essential as biosimilars are expected to reduce the health care cost through price competition and to expand patient access to these effective biologic treatments.

SB5 is a biosimilar developed by Samsung Bioepis referencing adalimumab (Humira, AbbVie Inc.), one of world's leading medicines in terms of pharmaceutical spending. Biosimilars are biological products that are highly similar to an existing reference biologic, and they undergo a thorough regulatory approval process to demonstrate that there

✉ JongAh Joanne Lee
jongahj.lee@samsung.com

[1] Samsung Bioepis Co., Ltd., Incheon 21987, Republic of Korea

are no clinically meaningful differences from the reference biologic in terms of safety and efficacy. Such demonstration of biosimilarity involves rigorous analytical, nonclinical, and clinical evaluations [9–11]. As of September 2022, SB5 has been approved by 14 regulatory authorities including the European Commission (EC) (August 2017, brand name Imraldi™) and the US Food and Drug Administration (FDA) (July 2019, brand name Hadlima™) [12, 13]. Based on a robust data package including extensive analytical characterization on the physicochemical and functional level using state-of-the-art analytical techniques and comparative phase I and phase III clinical studies, SB5 has demonstrated that it is highly similar to the reference adalimumab [14–17]. Since its release in various markets, over 5 million doses of SB5 have been prescribed to patients globally [18] and the real-world evidence has demonstrated that SB5 is as safe and effective as its reference product over the areas of rheumatology, gastroenterology, and dermatology [19].

Biologics, both the reference and biosimilars, are large and complex molecules produced from living systems using a multi-step manufacturing process. Due to their size, complexity, and the manufacturing process involved, heterogeneity is a common feature of biologics [20–22]. Most biologics are mixtures of protein isoforms arising from a variety of post-translational modifications [21–24]. These modifications can be introduced by an intracellular or extracellular process during manufacturing or storage, and the resulting heterogeneity in the key physicochemical or biological characteristics of the biologic, known as the critical quality attributes, may impact the safety and efficacy of the drug.

A drift or 'evolution' [25] in the critical quality attributes of marketed biologics has been reported in a number of studies [20, 26, 27]. A drift in the product quality profile can be a result of natural variability of biologics or unintended variation owing to uncontrolled variables in the manufacturing process. Moreover, manufacturers are often motivated to make intentional changes to the process for a wide variety of reasons including process improvements, scale ups or site transfers. Some changes may be minor, but others may be major in terms of their impact and can lead to an evolution, or a sudden shift, in the quality profile [25, 28, 29]. In order to maintain consistent quality and thus consistent clinical performance of a biologic, it is important for a manufacturer to carefully control the manufacturing process and closely monitor the critical quality attributes of the drug.

Despite the frequent necessity for manufacturing process changes, robust quality systems and regulatory frameworks can ensure that the quality and clinical performance of a biologic is maintained over its lifecycle [25, 29]. In particular, equivalent safety and efficacy of a biologic before and after a process change is established based on a comparability exercise. The comparability exercise is normally based on a comprehensive analytical characterization which ensures that the pre- and post-change quality attributes are highly comparable and that any difference in the quality attributes has no adverse impact on the safety or efficacy of the drug [30–32].

Likewise, SB5 has undergone multiple process changes, some of which were minor while others were considered major, such as transfer of manufacturing sites and introduction of a new formulation. SB5, initially available only in a low concentration (40 mg/0.8 mL), has been developed for a high-concentration, citrate-free formulation (40 mg/0.4 mL). The high-concentration citrate-free formulation has been approved by the EC and the US FDA, providing added convenience for patients. Despite such process changes, the critical quality attributes of SB5 have been tightly managed through robust quality systems and rigorous comparability exercises between the pre- and post-change products in line with the regulatory guidelines. In this report, we demonstrate the consistency of product quality for 93 batches of SB5 manufactured between 2013 and 2022.

2 Materials and Methods

Representative chromatograms and raw data for the analytical methods may be found in the Electronic Supplementary Material (ESM).

2.1 Materials

A total of 93 batches of the SB5 drug product (DP) manufactured between 2013 to 2022 were used for quality analysis. These DPs were manufactured at commercial scale using drug substance (DS) manufactured from multiple sites.

2.2 Purity and Impurity

High molecular weights were measured through the size exclusion high performance liquid chromatography (SE-HPLC). A sample was injected onto a TSK-GEL G3000SW$_{XL}$ analytical column, which was connected to a Waters HPLC system; monitoring was done by ultraviolet (UV) detection ($\lambda = 280$ nm). A mobile phase consisting of 100 mM sodium phosphate and 200 mM sodium chloride, pH 6.8, was used. The flow rate was 0.5 mL/min, and monomers and impurities were detected at a UV wavelength of 280 nm. Data were acquired and processed by Empower™ software.

Purity and impurity results for %IgG and %2H1L were measured through capillary electrophoresis-sodium dodecyl sulfate (CE-SDS). CE-SDS analysis was conducted with a high-performance capillary electrophoresis system (PA 800 plus Pharmaceutical Analysis System; Beckman Coulter). The sample was electrokinetically introduced onto

a capillary (Beckman Coulter, bare fused-silica capillary, 50 µm/30.2 cm) by applying voltage at − 5 kV for 20 s and was separated in the capillary cartridge. Electrophoresis was performed at a constant voltage and monitored by UV detection ($\lambda = 220$ nm) through the capillary window and aperture. Data were acquired and processed by 32 Karat or Empower software with integration capabilities.

2.3 Charge Variants

Charge variants were measured through the imaging capillary isoelectric focusing (icIEF). The sample was mixed with pharmalyte, methyl cellulose, distilled water, pI 6.61 marker, and pI 9.5 marker. The total mixture was loaded onto an ICE3 icIEF instrument using the capillary cartridge at 4 °C. H_3PO_4 and NaOH were used as an anolyte and a catholyte, respectively. Data were acquired and processed by Chrom Perfect software.

2.4 Potency

2.4.1 TNF-α Binding Assay by Fluorescence Resonance Energy Transfer

Tumor necrosis factor (TNF)-α binding activity of adalimumab was determined by fluorescence resonance energy transfer (FRET)-based competitive inhibition binding assay. Adalimumab was labeled with fluorescent Europium chelate (PerkinElmer) and TNF-α was labeled with Cy5 fluorophore. A dilution series of unlabeled adalimumab sample (37.5–0.01 µg/mL) competed against Europium-labeled adalimumab binding to Cy5-labeled TNF-α, inhibiting the signal of fluorescence. After incubation at ambient temperature with moderate agitation, the assay plate was read by a microplate reader using time-resolved fluorimetry. Measured fluorescence was inversely proportional to the binding of unlabeled adalimumab samples. The binding activity of the adalimumab sample was calculated relative to a reference standard using Parallel Line Analysis (PLA) software (Stegmann Systems).

2.4.2 TNF-α Neutralization by NFκB-luc Reporter Gene Assay

Inhibitory activity of adalimumab on the soluble TNF-α signaling pathway was measured through the TNF-α neutralization assay using a 293-NF-κB-luc cell line. The 293-NF-κB-luc cell line was engineered to contain a NF-κB response element upstream to the luciferase reporter gene. Mediated by TNF-α binding to cell surface TNFR, signal cascade activating NF-κB in turn promoted the expression of the luciferase reporter gene. Serially diluted samples (500–3.9 ng/mL) were pre-incubated with TNF-α (WHO international standard for TNF-α, NIBSC) at an ambient temperature in a white 96-well plate. Following incubation, cells were transferred to wells in the assay plate, and were incubated for 24 hours. TNF-α neutralization potency was determined by a luminescent signal using the Steady-Glo Luciferase Assay System (Promega) on a microplate reader. The potency of the adalimumab sample was calculated relative to a reference standard using Parallel Line Analysis (PLA) software (Stegmann Systems).

3 Results

To demonstrate consistency in product quality of SB5, 93 DP batches manufactured between 2013 and 2022 were analyzed. These batches were filled using DS sourced from multiple sites, reflecting potential variability due to different sites, time of manufacturing, storage, and shipping conditions. The quality of the SB5 drug product is consistently maintained through control strategies including release testing, and should meet the acceptance criteria such as the specifications defined by regulatory authorities to ensure consistent safety and efficacy of the SB5 drug product. Here, the results from release tests for critical quality attributes including purity, charge variants, and functional activities are displayed in chronological order.

3.1 Purity and Impurity

Aggregates and fragments are common product-related impurities in biologics that may trigger unwanted effects on the safety, efficacy, and stability of a drug. Therefore, control of aggregates and fragments is important for maintaining the quality of therapeutic monoclonal antibodies (mAbs).

The aggregate content in SB5 was determined by SE-HPLC. SE-HPLC is a robust method for the quantitative measurement of high molecular weight species (HMWs) of mAbs [33]. As shown in Fig. 1, the HMW contents of SB5

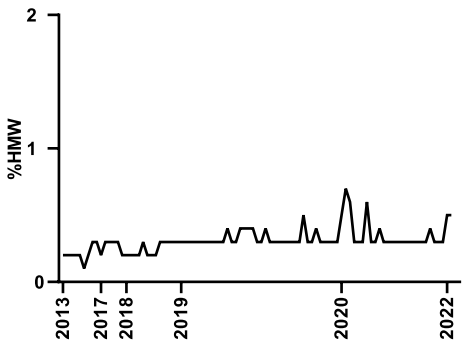

Fig. 1 High molecular weight (HMW) contents in SB5 batches determined by size exclusion chromatography

DP were consistently below 0.5% with the exception of three batches. Moreover, HMW contents in all SB5 DP batches met the acceptance criteria.

In addition, CE-SDS analysis under non-reduced conditions was performed to measure the purity/impurity levels of intact IgG and fragments. Based on the product understanding of SB5, IgG and 2H1L are controlled and tested for release. The purity level of IgG, expressed as two heavy chains and two light chains (2H2L), varied by <3.0% across all batches, ranging from a minimum of 95.2% to a maximum of 98.0% (Fig. 2a). The major impurity species in SB5 has been determined as the fragment with one missing LC (2H1L) (data not shown), and the levels of 2H1L in SB5 DP ranged between 1.8 and 3.0% (Fig. 2b). All batches met the acceptance criteria in terms of levels of IgG and 2H1L.

3.2 Charge Variants

During manufacturing, biologics are generally susceptible to enzymatic and chemical modifications, both of which may result in charge heterogeneity. Post-translational modifications such as deamidation, C-terminal lysine processing, glycosylation, and glycations can be reported as charge variants [34]. The charge heterogeneity is generally referred to as acidic or basic compared with the main species [35].

The acidic and basic variants of SB5 are mainly composed of sialic acid and lysine variant forms, respectively. Although these charge variants were found to have no impact on biological activities [14], levels of charge variants were controlled in respect of manufacturing consistency. The charge variants were monitored by icIEF, where the different charged species are separated according to their isoelectric points (pIs). As shown Fig. 3a, all tested batches showed levels of the main species ranging from 62 to 67% and met the acceptance criteria. The levels of acidic and basic variants ranged from 20 to 28% (Fig. 3b) and from 8 to 11% (Fig. 3c), respectively. The charge variants were consistently within the acceptance criteria for all batches.

3.3 Biological Activities

Adalimumab exerts its therapeutic effect primarily by binding and neutralizing soluble TNF-α, thereby blocking the downstream signaling of TNFR1 [36]. Considering the primary mechanism of action of adalimumab, the TNF-α binding activity and neutralizing potency of SB5 were measured through FRET and NF-κB reporter gene assays, respectively.

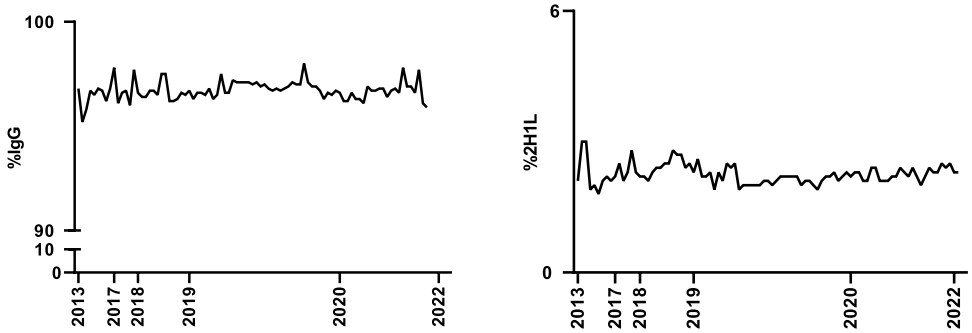

Fig. 2 Purity and impurity levels in SB5 batches analyzed by non-reduced capillary electrophoreses-sodium dodecyl sulfate (CE-SDS). **a** Purity levels of IgG and **b** impurity levels of 2H1L

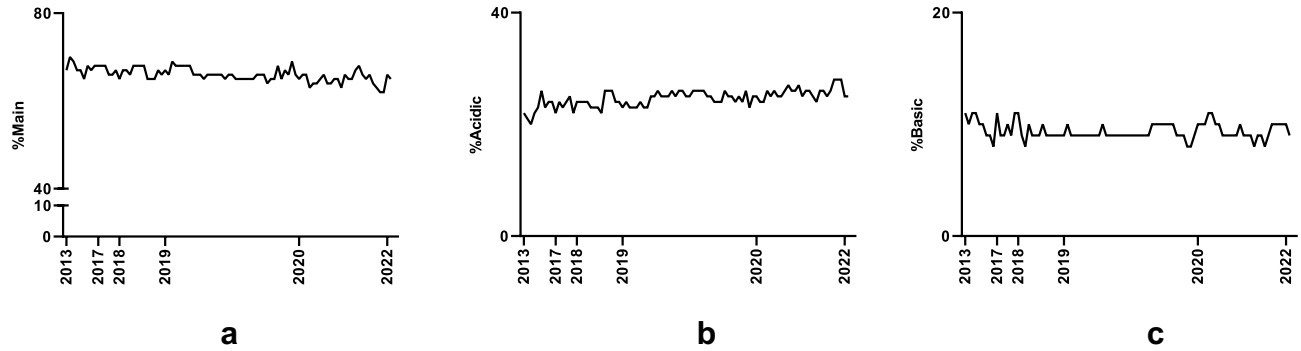

Fig. 3 Charge variant levels in SB5 batches analyzed by imaging capillary isoelectric focusing (icIEF). **a** %Main, **b** %Acidic and **c** %Basic

Figure 4 shows the TNF-α binding activity and TNF-α neutralizing potency for SB5 DP ranged from 86 to 108% (mean 99%, SD 4%) and from 88 to 119% (mean 98%, SD 4%), respectively. In terms of biological activities, all batches were manufactured consistently within the acceptance criteria.

4 Discussion

Unlike small molecule drugs, biologics are inherently variable owing to the heterogenous post-translational modifications which depend on the cellular process and manufacturing process such as culture, purification, and storage [21, 29, 37]. Even subtle changes in the process parameters can alter the quality profile of a biologic; however, manufacturers are often challenged with the need to introduce manufacturing changes during a product's lifecycle such as to meet increased demand or to improve their process for better efficiency and quality [28].

Due to the inherent variability of biologics and their potential to drift, or even evolve as a result of manufacturing changes, healthcare and scientific communities have expressed concerns that the product quality of the reference biologic and the biosimilar may eventually diverge, resulting in two distinct group of biologics with different clinical performance [25, 38]. In this respect, it is important that biologics manufacturers demonstrate the consistency in product quality throughout the product's lifecycle despite multiple manufacturing changes such as process improvements, scale ups or site transfers. Especially for biosimilars, this would help the healthcare community to overcome the challenges and barriers to biosimilar adoption [39] and accept biosimilars with more assurance of their safety and efficacy, eventually facilitating better accessibility of these drugs to those patients in need.

In this report, we demonstrate that the critical quality attributes including purity, charge variants, and functional activities have remained consistent for 93 batches of SB5 manufactured and released between 2013 and 2022 despite process changes including manufacturing site transfers and change in formulation. Aggregate and fragments can affect the safety and efficacy of a biologic product; therefore, the purity and impurity of SB5 are controlled during release. As presented in this report, the level of HMW species remained consistently low in SB5. In addition, the levels of IgG and 2H1L by non-reducing CE-SDS was consistent in SB5. Post-translational modifications such as deamidation can yield charge heterogeneity. Although some charge variants may not influence biological activity [14], others may impact the biological activity of a mAb [40]. Results demonstrated that the levels of acidic, main, and basic variants measured by icIEF remained consistent in SB5. TNF-α binding activity and TNF-α neutralizing potency, which have direct effect on the efficacy as the main mechanism of action of adalimumab, were consistent in SB5.

Purity, charge variants, TNF-α binding activity, and TNF-α neutralizing potency are quality controlled during the release of SB5 DP based on regulatory-approved specifications. The critical process parameters are controlled tightly during manufacture to ensure the adherence of the quality attributes to their release specifications. Based on the comprehensive product and process understanding of SB5, a range of process parameters are classified as critical process parameters depending on their impact on the critical quality attributes and are closely monitored. In addition, extensive comparability exercises are performed in accordance with regulatory guidelines [30–32] when manufacturing changes are introduced. The comparability of quality attributes between pre- and post-change processes is evaluated using more stringent acceptance ranges compared with the release specifications to deliver consistent product quality over the lifecycle of SB5.

Collectively, the results presented in this report should help healthcare providers and other stakeholders to understand biosimilars with more confidence in the consistency of the product quality and clinical performance in terms of its safety and efficacy.

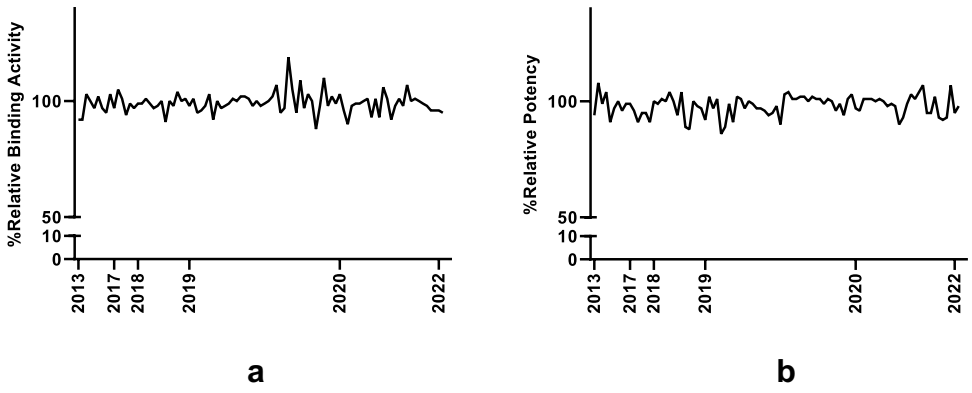

Fig. 4 Biological activities in SB5 batches determined **a** by fluorescence resonance energy transfer (FRET)-based competitive inhibition binding assay and **b** cell-based NFκB-luc reporter gene assay

5 Conclusion

The results demonstrate that the quality of SB5 has been consistent and tightly controlled over a decade of product manufacturing despite multiple process changes that it has undergone, including manufacturing site transfers and change in formulation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40259-023-00581-x.

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Declarations

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Conflicts of interest Authors are employees of Samsung Bioepis Co., Ltd.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability statement The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Authors' contributions The main text of the paper was written by JongAh Joanne Lee and Nayoung Lee. All authors contributed to collection and analysis of data. All authors reviewed and approved the final manuscript.

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