

The Effects of Freeze-Thaw Cycling on the Stability of the Adalimumab Biosimilar SB5

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Conclusions

- SB5 was stable in the immediate pack (nude pre-filled syringe) when exposed to multiple freeze-thaw cycles.
- These results may help hospital pharmacists to assess the impact of temperature excursions during shipment or storage on the product quality of SB5.

Introduction

- Temperature excursions may occur during manufacturing, storage, distribution and clinical trials.
- Limited data are available to hospital pharmacists to support decision making following temperature excursions.

Objectives

- The purpose of this stability study was to evaluate the impact of high and low temperature conditions over a short period on the adalimumab biosimilar SB5.

Methods

Temperature exposure

- SB5 drug product (DP) was exposed to extreme temperature cycling conditions with a total of three cycles equating to 144 hours at $30 \pm 2^\circ\text{C}/65 \pm 5\%$ relative humidity and 144 hours at $-5 \pm 3^\circ\text{C}$ (Table 1).

Table 1. Short-term temperature cycling stability study design for SB5 DP

| Storage conditions | Storage time |
|--|--------------|
| Cycle 1 | |
| $30 \pm 2^\circ\text{C}/65 \pm 5\%$ RH | 48 hours |
| $-5 \pm 3^\circ\text{C}$ | 48 hours |
| Cycle 2 | |
| $30 \pm 2^\circ\text{C}/65 \pm 5\%$ RH | 48 hours |
| $-5 \pm 3^\circ\text{C}$ | 48 hours |
| Cycle 3 | |
| $30 \pm 2^\circ\text{C}/65 \pm 5\%$ RH | 48 hours |
| $-5 \pm 3^\circ\text{C}$ | 48 hours |

RH, relative humidity

Assessments

- Samples were analyzed using a variety of validated methods for appearance, pH, protein concentration, container closure integrity, impurities, charge variants, oxidation, endotoxin, particulates and biological activity.

Results

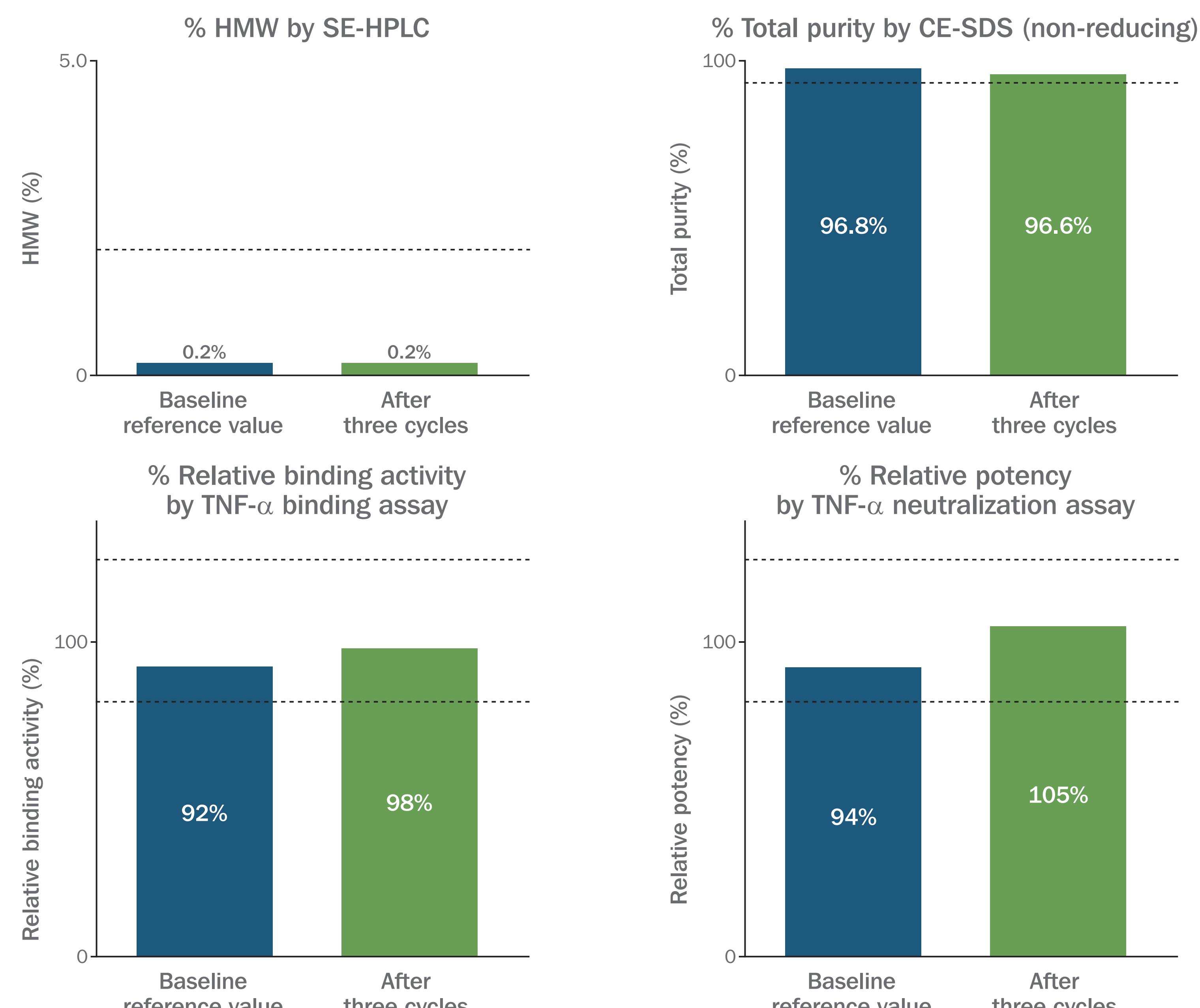
Critical quality attributes

- There were no apparent changes in critical quality attributes between baseline and following three temperature cycles (Figure 1).
- All results met the stability acceptance criteria for the four critical quality attributes.

Other

- Table 2 shows appearance, including colour, clarity, visible particle, pH, protein concentration, oxidation level, charge variant, endotoxin, container closure integrity and particulates, after three temperature cycles versus baseline.
 - The results showed no apparent changes and/or met the stability acceptance criteria for each product quality attribute over the three temperature cycles.

Figure 1. Short-term temperature cycling result of SB5 DP across four critical quality attributes



----- Stability acceptance criteria.
CE-SDS: capillary electrophoresis-sodium dodecyl sulfate; HMW: high-molecular-weight species; SE-HPLC, size exclusion-high performance liquid chromatography; TNF- α , tumour necrosis factor- α

Table 2. Test results of SB5 drug product at baseline and following three temperature cycles

| Category | Test item | Baseline reference value | Temperature cycle 3 |
|-----------------------|---|---------------------------------|--|
| General test | Appearance: Colour | Colourless | $B8 \leq \text{Sample} < B7$ |
| | Appearance: Clarity | 18 NTU | 17 NTU |
| | Appearance: Visual particulates | Practically free from particles | Practically free from particles |
| | pH | 5.3 | 5.3 |
| Quantity test | Protein concentration (A_{280}) (mg/mL) | 51.6 | 49.7 |
| Purity and impurities | SE-HPLC % HMW impurities | 0.2 | 0.2 |
| | CE-SDS (non-reducing) % Total purity | 96.8 | 96.6 |
| | icIEF % Single highest impurity | 2.1 | 2.0 |
| | icIEF % Isoelectric point of main peak | 8.6 | 8.6 |
| | icIEF % Acidic | 21.8 | 25.0 |
| | icIEF % Main | 67.1 | 64.5 |
| | icIEF % Basic | 11.2 | 10.5 |
| Biological activity | Competitive binding assay to TNF- α by FRET % Binding activity relative to reference standard | 92 | 98 |
| | TNF- α neutralization assay by NF- κ B reporter gene % Potency relative to reference standard | 94 | 105 |
| Safety | Particulates ^a Particle $\geq 10 \mu\text{m}$: particles/syringe | 1521 | 1494 |
| | Particle $\geq 25 \mu\text{m}$: particles/syringe | 15 | 18 |
| | Endotoxin (EU/mL) | <5 | <5 |
| | Container closure integrity NS | | All sample syringes tested negative for visible signs of dye incursion |
| Additional tests | CEX-HPLC % Acidic | 23.5 | 24.0 |
| | % Main | 67.2 | 65.2 |
| | % Basic | 9.3 | 10.9 |
| | Oxidation % Heavy chain Met34 | 0.6 | 0.6 |
| | % Heavy chain Met83 | 0.3 | 0.4 |
| | % Heavy chain Met256 | 5.8 | 4.7 |
| | % Heavy chain Met432 | ND | ND |
| | % Light chain Met4 | 0.2 | 0.5 |
| | Particulates Particle $\geq 2 \mu\text{m}$: particles/syringe | 12217 | 13111 |
| | Particle $\geq 5 \mu\text{m}$: particles/syringe | 6257 | 6882 |
| | Particle $\geq 8 \mu\text{m}$: particles/syringe | 2476 | 2579 |

^aThe acceptance criteria of particulate matter are 'Particle $\geq 10 \mu\text{m}$: $\leq 6000/\text{syringe}$ ' and 'Particle $\geq 25 \mu\text{m}$: $\leq 600/\text{syringe}$ ' according to Ph. Eur. 2.9.19-/USP 788-
CE-SDS, capillary electrophoresis-sodium dodecyl sulfate; CEX-HPLC, cation exchange-high performance liquid chromatography; DP, drug product; EU/mL, endotoxin units per milliliter; FRET, fluorescence resonance energy transfer; HMW, high-molecular-weight species; HPLC, high performance liquid chromatography; icIEF, imaged capillary isoelectric focusing; ND, not detected; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NS, not scheduled; NTU, nephelometric turbidity unit; SE-HPLC, size exclusion-high performance liquid chromatography; TNF- α , tumour necrosis factor- α

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