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Short communication

Evaluation of carry-over, product quality and cleaning validation following a batch campaign manufacturing of benzydamine hydrochloride spray 0.15%

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Introduction

Campaign manufacturing is widely applied in pharmaceutical production to improve operational efficiency by reducing equipment downtime, water consumption, cleaning agent usage, and manufacturing costs. However, implementation of a campaign manufacturing strategy must be scientifically justified to ensure product quality, patient safety, and compliance with EU GMP requirements throughout the manufacturing period (Eudralex Vol.4, Annex 15). When consecutive batches of the same product are manufactured on the same equipment, the classical risk of cross-contamination between different active pharmaceutical ingredients is eliminated. Nevertheless, potential accumulation of product residues, degradation of retained material in poorly drained areas, and microbiological proliferation remain relevant quality risks requiring evaluation.

Benzydamine hydrochloride is a local non-steroidal anti-inflammatory drug with analgesic and anti-inflammatory properties, commonly used for the treatment of inflammatory conditions of the oral cavity and pharynx (NCBI, 2026).

The aim of this study was to evaluate carry-over levels, product quality, microbiological control, and cleaning effectiveness during a campaign consisting of ten consecutive commercial-scale batches of benzydamine hydrochloride spray 0.15% manufactured without intermediate cleaning. The study further aimed to provide scientific justification and support implementation of a 10-batch campaign strategy, ensuring cleaning effectiveness after the tenth batch.

Materials and method

A campaign consisting of ten consecutive commercial-scale batches of benzydamine hydrochloride spray 0.15% was manufactured on the same equipment and approved manufacturing process. No intermediate cleaning or sanitization was performed between batches. Instead, a standardized drain-down and line-clearance procedure was applied after each batch, while a complete automated Clean-in-Place (CIP) cycle was executed only after completion of the tenth batch.

Critical sampling locations were identified using a risk-based approach, focusing on equipment areas with the highest potential for residue retention. Surface sampling was performed using Texwipe 714A Alpha Swabs.

Residue quantification was carried out using a validated stability-indicating RP-HPLC method with UV detection at 232 nm. Chromatographic separation

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was performed on Lichrospher RP Select B column (125 x 4, 5µm), with flow rate 1.1 mL/min, and injection volume 20 µL. The mobile phase consisted of: 55% 0.4% (v/v) Diethylamine, pH 3.0, 20% Methanol and 25% Acetonitrile.

A PDE-based toxicological assessment was performed to calculate the Maximum Allowable Carryover (MACO) value. The toxicological profile of benzydamine hydrochloride is well established and no specific hazards for human use have been identified (EMA, 2014). Since no No-Observed-Adverse-Effect Level (NOAEL) data are available, the Permitted Daily Exposure (PDE) was calculated using the lowest therapeutic dose (LOEL/LOAEL) approach. The lowest recommended daily dose of benzydamine hydrochloride 0.15% oromucosal spray is 1.05 mg/day, resulting in a PDE value of 0.0105 mg/day (Tox by design, 2024). The calculated MACO was 1515.94 mg per subsequent batch (415.8 kg), corresponding to 3.65 ppm. This toxicologically derived MACO was used as the acceptance criterion for evaluation of residue carry-over during the campaign manufacturing process.

Results and discussion

Method validation results demonstrated specificity, linearity over the concentration range of 2.5–40 µg/mL (R^2 = 0.9999), satisfactory precision (RSD below 5%), LOD of 0.01 µg/mL, and a LOQ of 0.04 µg/mL. The method proved suitable for monitoring trace levels of benzydamine residues throughout the manufacturing campaign.

Swab samples collected demonstrated that residue levels remained stable and did not exhibit progressive accumulation during manufacture of the ten consecutive batches. Residual benzydamine levels reached a steady-state condition after the initial batches and remained below the established acceptance criteria. The highest residue level detected remained below the calculated MACO value, indicating that prolonged equipment utilization did not result in significant product build-up. Finished product analysis confirmed compliance with all quality specifications for each of the ten batches, with no evidence of assay drift, active substance enrichment, or accumulation of degradation products. Microbiological monitoring demonstrated that Total Aerobic Microbial Count (TAMC) and Total Combined Yeasts and Moulds Count (TYMC) remained within established limits throughout the campaign, confirming that omission of intermediate sanitization did not adversely affect microbiological quality. Following completion of the tenth batch, cleaning validation was performed using the approved CIP procedure. Swab samples collected from predefined worst-case locations demonstrated residue levels below the established acceptance criteria. These results confirmed that the cleaning process effectively restored equipment to a validated state of cleanliness after extended campaign manufacturing.

Conclusion

This study demonstrated that ten consecutive batches of benzydamine hydrochloride spray 0.15% can be manufactured without intermediate cleaning while maintaining product quality, microbiological control, and GMP compliance. Residue levels remained below the calculated MACO limit, with no evidence of cumulative build-up throughout the campaign. Cleaning validation performed after the tenth batch confirmed the effectiveness of the CIP procedure, demonstrating that the equipment could be restored to a validated state of cleanliness following extended use. These results provide scientific justification for implementation of a 10-batch campaign manufacturing strategy.

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