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 reduces equipment downtime, water and cleaning-agent use, and production cost — but must be scientifically justified to protect product quality and patient safety under EU GMP (EudraLex Vol. 4, Annex 15).
- Consecutive same-product batches remove cross-contamination risk between different APIs, yet residue build-up, degradation in poorly drained areas, and microbial proliferation remain relevant quality risks.
- Benzydamine hydrochloride is a topical NSAID with analgesic and anti-inflammatory action, used for inflammatory conditions of the oral cavity and pharynx.

WHY CAMPAIGN MANUFACTURING

DOWNTIME- fewer equipment changeovers between batches.
WATER USE- less rinse water consumed per batch produced.
CLEANING AGENTS- reduced detergent & sanitizer consumption.
MANUFACTURING COST- lower cost per unit across the campaign.

QUALITY RISKS STILL MONITORED

- Residue accumulation across consecutive batches on shared equipment.
- Degradation of retained material in poorly drained, low-flow areas.
- Microbiological proliferation from omitted intermediate sanitization.

Health-based exposure limits applied per EMA/CHMP/CVMP/SWP/169430/2012.

STUDY AIM

• Evaluate carry-over levels, product quality, microbiological control and cleaning effectiveness across ten consecutive commercial-scale batches of benzydamine HCl spray 0.15% manufactured without intermediate cleaning - to scientifically justify a 10-batch campaign strategy.

MATERIALS & METHOD

CAMPAIGN DESIGN

- 10 consecutive commercial-scale batches, same equipment and approved manufacturing process.
- No intermediate cleaning/ sanitization- standardized drain-down and line-clearance after every batch.
- Full automated CIP cycle executed only after completion of batch 10.

SAMPLING & ANALYSIS

- Critical, risk-based swab locations - highest residue-retention potential.
- Surface sampling: Texwipe® 714A Alpha Swabs.
- Validated, stability-indicating RP-HPLC with UV detection at 232 nm.

MACO Derivation - PDE (Toxicology-Based)

1. No NOAEL data available → LOEL/LOAEL approach applied to the lowest therapeutic dose.
2. Lowest recommended dose 1.05 mg/day → PDE = 0.0105 mg/day.
3. MACO = 1515.94 mg per subsequent batch (415.8 kg) 3.65 ppm - set as the campaign acceptance criterion.

MACO = (PDE × batch size of next product) / max. daily dose =
(0.0105 mg × 415,800 g) / 2.88 g

MACO = 1515.94 mg; or in ppm = 1515.94 mg / 415.8 kg = 3.65 ppm

PDE, mg/day	MACO, mg/batch	PDE, mg/day
0.0105	**1515.94**	**0.0105**

Chromatographic condition	Value
Column	Lichrospher RP Select B, 125 × 4 mm, 5 µm
Flow rate	1.1 mL/min
Injection volume	20 µL
Detection	UV 232 nm
Mobile phase	DEA (0.4% v/v, pH 3.0) : MeOH : ACN = 55:20:25

EQUIPMENT TRAIN & CRITICAL SAMPLING POINTS

Risk-based swab locations target the highest residue-retention potential: transfer valves, dead-legs and the filling/nozzle path.



RESULTS AND DISCUSSION

METHOD VALIDATION

0.9999	2.5-40	<596	0.01	0.04
L1nCcHlty, R'	Range, pg/n1L	Prec1s1on. RSD	LOO. µgiml	LOQ, µg/ml

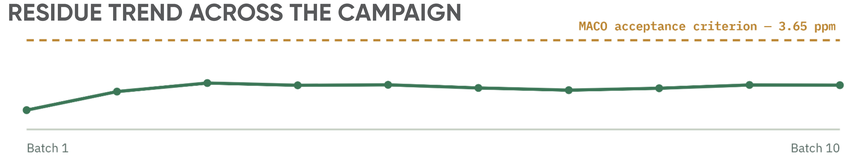
Specific, linear and precise - suitable for monitoring trace-level benzydam ine residues across the full manufactur ing campaign.

CAMPAIGN TIMELINE

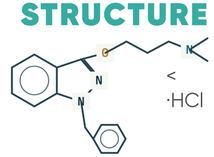


Standardized drain-down/ line-clearance after each batch; full CIP cycle only after batch 10, followed by cleaning val1dation swabbing.

RESIDUE TREND ACROSS THE CAMPAIGN



STRUCTURE



Benzydamine hydrochloride· c19H24ClN3O ·MW 345.9 g/mol

CONCLUSION

Ten consecutive batches of benzydamine HCl spray 0.15% can be manufactured without intermediate cleaning while maintaining product quality, microbiological control and GMP compliance.

- **Residues stayed below the calculated MACO — no cumulative build-up across the campaign.**
- **Post-campaign CIP cleaning validation confirmed full restoration of a validated clean state.**
- **Findings provide scientific justification for a 10-batch campaign manufacturing strategy.**

Benzydamine hydrochloride · C19H24ClN3O · MW 345.9 g/mol

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