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# Fewer interventions, same sterility: isolator design data from three fill lines

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## 1 Background

Every glove-port intervention in a Grade A isolator is a planned breach of the distance between an operator and an open product. Regulators expect manufacturers to minimise them, and the revised EU GMP Annex 1 asks for interventions to be designed out where possible rather than merely validated. Yet published data on how isolator design choices change intervention rates in routine production remain scarce, and most comparisons rely on media-fill simulations rather than commercial batches.

Between 2023 and 2025 we recorded every intervention on three isolator filling lines at two sites, built over nine years to three successive designs. The lines fill similar monoclonal-antibody and peptide products in 2R to 20R vials, which allows a like-for-like comparison of design rather than of product.

## 2 Objectives

- Quantify inherent and corrective interventions per 10 000 vials on three isolator generations.
- Identify the design features that account for the largest reductions.
- Confirm that fewer interventions did not coincide with any loss of sterility assurance.

## 3 Methods

Interventions were logged electronically at the line by the operator and verified against glove-port sensor data and video. Each was classified as *inherent* (part of the normal process, such as stopper-bowl replenishment or weight checks) or *corrective* (unplanned, such as clearing a fallen vial). Rates were normalised to 10 000 filled vials per batch.

Environmental monitoring used continuous viable air sampling and settle plates at four Grade A positions per module, and sterility assurance was assessed through media fills of at least 9 000 units per line every six months. Line A (2016) uses a ten-port isolator with a manual stopper bowl; line B (2021) introduced a walking-beam infeed and an automated stopper feed; line C (2025) processes ready-to-use nested vials with a robotic de-lidder. Comparisons used a negative binomial model with line and year as factors.



**Figure 1.** Line B in its four-module configuration; the walking-beam infeed sits behind the second window from the right. 3D render.

**Line A** 2016 · 10 ports per module · manual stopper bowl
**Line B** 2021 · walking-beam infeed · automated stopper feed
**Line C** 2025 · ready-to-use nests · robotic de-lidding

## 4 Results

Over the three years the lines filled 412 batches and 31.6 million vials. Line A recorded 4.6 interventions per 10 000 vials on average, line B 1.9 and line C 0.6 (Figure 2). The difference between successive designs was significant ($p < 0.001$) and larger than the year-on-year improvement within any one line, which reflected procedural changes and growing operator experience.

Corrective interventions accounted for most of the gap. On line A, fallen or tipped vials at the infeed starwheel caused 41 % of all corrective interventions; the walking-beam infeed on line B removed this category almost entirely. Stopper-bowl replenishment was the largest inherent intervention on line A and disappeared with the automated feed on line B.

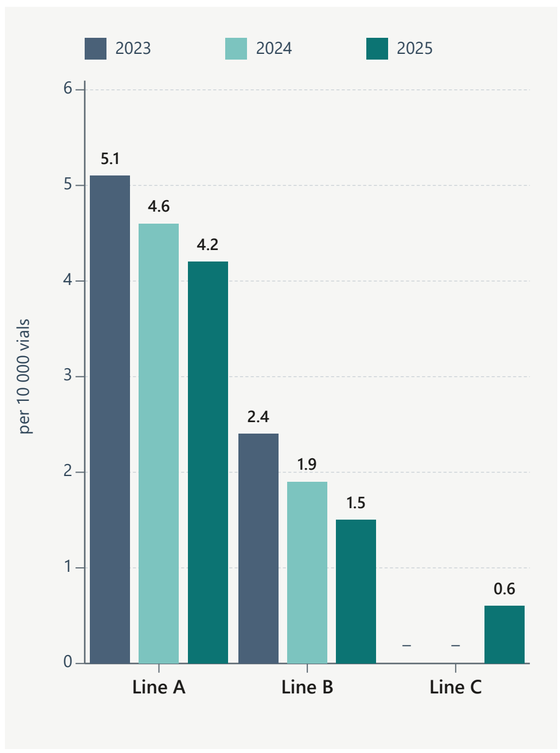



**Figure 2.** Interventions per 10 000 filled vials by line and year (inherent and corrective combined). Line C was commissioned in 2025. Bars and axes are Publisher shapes.

Within a typical 30-day campaign, interventions on line A accumulate steadily, whereas lines B and C show long stretches without any intervention at all (Figure 3). On line C, ready-to-use nests eliminated washing-tunnel jams and infeed handling, leaving weight-check adjustments as the dominant remaining intervention.

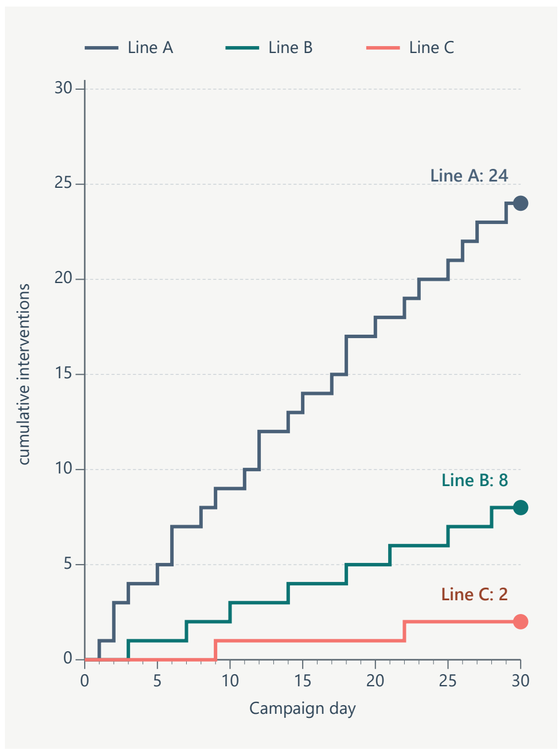



**Figure 3.** Cumulative interventions during one representative 30-day campaign per line. Step lines are open freeform shapes.

**Table 1.** Interventions and sterility outcomes, 2023–2025.

| Line | Year | Batches | Vials (M) | Interventions per 10 000 vials | | | EM action | Media fills | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Inh. | Corr. | Total | | Units | Pos. |
| **A** | 2016 | 168 | 11.9 | 2.1 | 2.5 | **4.6** | 3 | 27 600 | 0 |
| **B** | 2021 | 171 | 13.8 | 1.1 | 0.8 | **1.9** | 2 | 22 400 | 0 |
| **C** | 2025 | 73 | 5.9 | 0.5 | 0.1 | **0.6** | 0 | 11 800 | 0 |
| **All** | | **412** | **31.6** | **1.4** | **1.3** | **2.7** | **5** | **61 800** | **0** |

Inh. = inherent, Corr. = corrective, EM action = environmental excursions above the action level, Pos. = positive media-fill units. Totals weighted by vials filled.

No media fill on any line produced a contaminated unit (0 of 61 800 units), and the rate of environmental excursions above the action level was low and statistically indistinguishable between lines (Table 1). Glove breaches found by integrity testing fell from seven on line A to one on line C, in proportion to the number of glove manipulations (Figure 4).

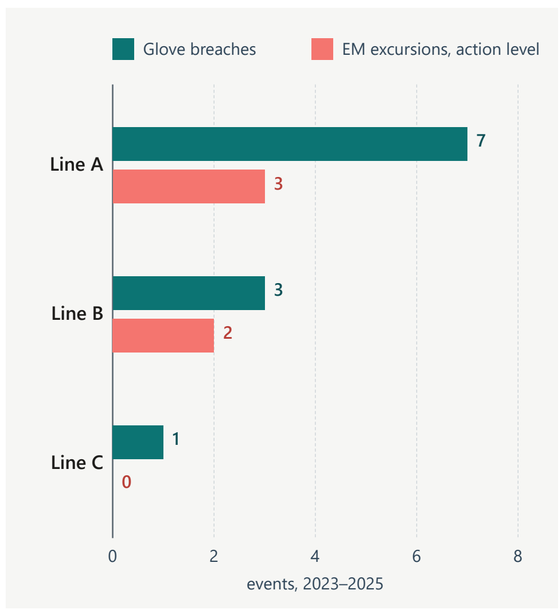



**Figure 4.** Glove breaches found by integrity testing and environmental excursions above the action level, per line, over the three years.

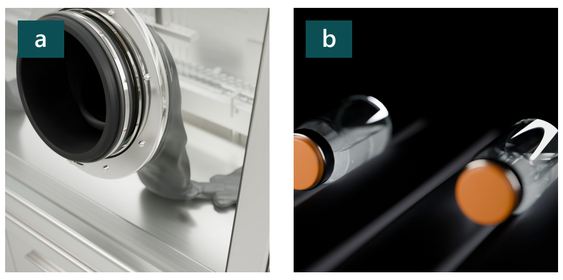



**Figure 5.** (a) Glove port with bayonet latch: every manipulation is logged by its sensor. (b) Backlit camera inspection of filled vials, where corrective rejects are counted. 3D renders.

## 5 Discussion

Our data support the intuitive view that the safest intervention is the one that never happens. The largest gains came not from additional monitoring but from mechanical design: an infeed that cannot tip vials, a stopper feed that does not need an operator, and components that arrive sterile in nests. Each change reduced the number of times a gloved hand entered the critical zone, and none of them required a change to the decontamination cycle or the monitoring programme.

Because sterility outcomes were already excellent on line A, the study cannot show that fewer interventions reduce contamination risk; it shows that the reduction came without any detectable loss. We therefore treat intervention rate as a leading indicator of aseptic risk and now report it monthly alongside environmental data. Limitations include the single company, the non-randomised comparison of designs commissioned years apart, and product mixes that were similar but not identical.

## 6 Conclusions

- Successive isolator designs cut interventions from 4.6 to 0.6 per 10 000 vials.
- Infeed handling and stopper feeding explained most of the reduction.
- Sterility assurance was unchanged: no positive media-fill unit on any line.
- Intervention rate is a practical leading indicator and belongs in routine trending.

KEY NUMBERS

**−87 %**

interventions per 10 000 vials, line A (2016) to line C (2025)

**0 of 61 800**

media-fill units contaminated, all lines, 2023–2025

**41 %**

of corrective interventions on line A were tipped vials at the infeed

**7 → 1**

glove breaches found by integrity testing, line A to line C

## 7 References

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Poster PDF and data tables

Sample poster with invented data, people and institutions, produced for ToupieSoft. The QR-style block is decorative and encodes nothing.