Minimizing Drug Product Losses in Small Volume Aseptic Filling

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Abstract

Cobra is an established biologics manufacturer with the capability to fill recombinant proteins, plasmid DNA and antibodies (MAbs) as well small molecule pharmaceutical APIs. Over the last 15 years we have supplied more than 400 batches to more than 100 customers located in 19 different countries.

Cobra Biologics' facility in Matfors, Sweden specializes in aseptic filling using modern, fully automated and disposable systems. Cobra's track record of successful drug product deliveries range in batch size from 3.5L to 50L or more. Historically, the filled products have been manufactured from low cost, small molecule APIs where up to 1L of product waste has been acceptable, for example from line losses and integrity testing of filters.

To better accommodate high value APIs in small volume fills, biologics such as recombinant proteins, plasmid DNA and antibodies (MAbs) required a solution. A project was initiated to minimize product losses. This was achieved by careful mapping of the fill process followed by small changes in the working procedure and the choice of disposables. This resulted in a more than 10-fold decrease in product waste.

Project Aim

- Cobra pioneers the field of disposable technology
- Customers required automatic aseptic filling of large volume of low-cost drug substance
- Manufacturing losses: ≈ 1L

- Adapted existing automatic fill/finish systems
- Adopted disposable solutions to customer-specific needs: small volume of high-cost drug substance
- Improved working procedures
- Manufacturing losses: ≤100mL

Challenges and Constraints

- Reduce system volume losses
- Minimize design changes
- Minimize re-validation works
- Minimize staff re-qualification
- System design

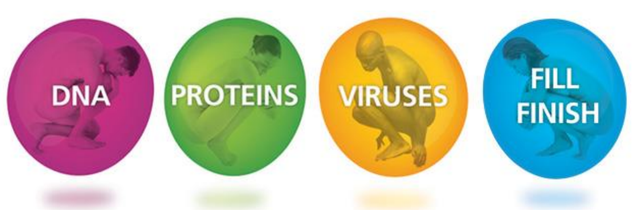
Process Steps for Improvement

Key target points during filtration:

Saturation of filter
Remaining substance in compounding bag
Loss during filtration

Key target points during filling:

Losses due to filling weight adjustment
Losses during set up of the filling tubes
Loss of fluid due to failing check weights at end of filling
Loss of fluid trapped in the tubes and bag (line losses)



Our Approach: optimize filtration and fill process

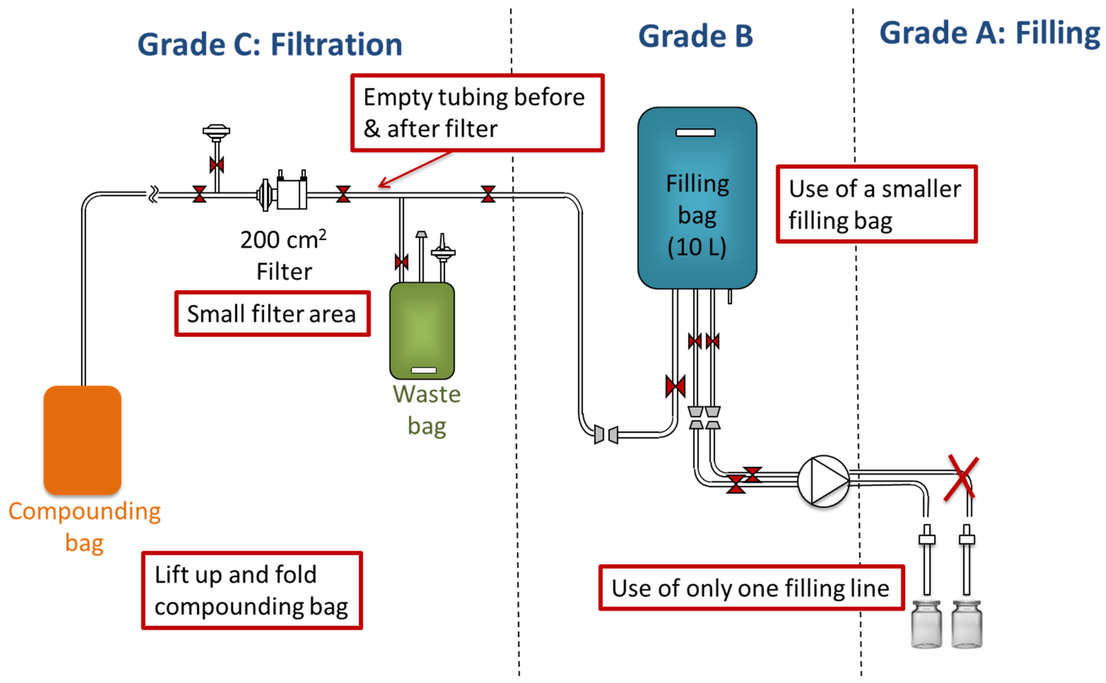


Figure 1. Strategies for minimizing losses with the existing fill set-up.

Method

Filtration of ≈1.0 to 1.5L of H_2O or buffer into ≈400 size 10mL vials with a fill volume of 3mL per vial

Results

Losses during filtration & filling process

	Run 1	Run 2	Run 3
Material	H2O	Buffer	buffer
Losses filtration step	≈ 15 g	≈ 20 g	≈ 40 g
Losses filling step	≈ 50 g	≈ 60g	≈ 35 g
Total losses	≈ 65 g	≈ 80 g	≈ 75 g

Conclusion and Outlook

Having optimized the filtration process with a reduction in downstream losses to less than 100mL, Cobra's on-going project will be to further minimize volume losses, enhancing customer product yields, by thorough review of drug product sampling and validation procedures.

Figure 2. Cobra Biologics Matfors is situated by the river Ljungan, near Sundsvall in Northern Sweden.

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