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Octoplus FF®
How to Maximize Accuracy, Product Recovery, and Flexibility

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Abstract

Single-use (SU) tools are commonly adopted for final filling drug products into their final containers due to their implementation in restricted-access barrier systems (RABS) or isolators used around the filling line. As a result, there is more focus on SU technologies and the related risks that biopharmaceutical companies must assess.

In aseptic processing, the highest quality standards are required, as well as the most suitable product design to fulfill the primary needs in fill and finish, which include precise filling accuracy, maximum product recovery, flexibility to adapt to filling lines and drug product specificities, and minimal risk of contamination.

In order to address the challenges of filling accuracy, this study compared the performances of two types of SU bags used as a "break tank." The first bag is a Flexboy® bag with a traditional 2D shape, and the second is the Octoplus FF® bag with an optimized wallet-shape bag designed for filling operations.

The performance comparison results were reported using capability analysis (Cp and Cpk) and showed that the Octoplus FF® bag performs superior to the Flexboy® bag for all volumes tested (2, 5, and 20 mL).

Introduction

In biomanufacturing processes, the last and certainly one of the most critical steps is the final filling of the drug product into its container. Within this step, filling accuracy is a key parameter that must be controlled, fully characterized, and optimized. Filling accuracy has direct consequences for the pharmaceutical company and its fill and finish department (e.g., overfilling can lead to cost increases) and for the patients (e.g., underfilling may lead to ineffective treatment or delivery of the wrong dosage).

Filling accuracy can be influenced by different parameters, including the filling machine, bag shape, tube, needles, peristaltic pump, and product to fill. In this study, we focused on the bag shape and compared two different bags: the Octoplus FF® 8 L bag, designed with an optimized wallet shape to fit the requirements of filling operations (including filling accuracy and product recovery), and the Flexboy® 5 L bag, a 2D bag with a traditional shape, mainly designed for storage applications.

Compared to the Flexboy® bag, the Octoplus FF® solution was specifically designed for precise dosing applications. It contains individual filling lines separated from each other in order to avoid flow perturbation during pumping. All the lines are fed with the same amount of liquid thanks to the flat bottom of the wallet-shaped bag, which ensures consistent and accurate dosing throughout the operation. A side-mounted inlet line is also designed according to the filling speed to fit the flow rate coming from the feed and then avoid spilling that may result in foaming (especially for highly concentrated protein-based solutions). This study highlights the impact of using an Octoplus® FF bag design on the dosing accuracy.

Materials

The test setup is shown in Figure 1.

Figure 1: *Overview of the Assembly*

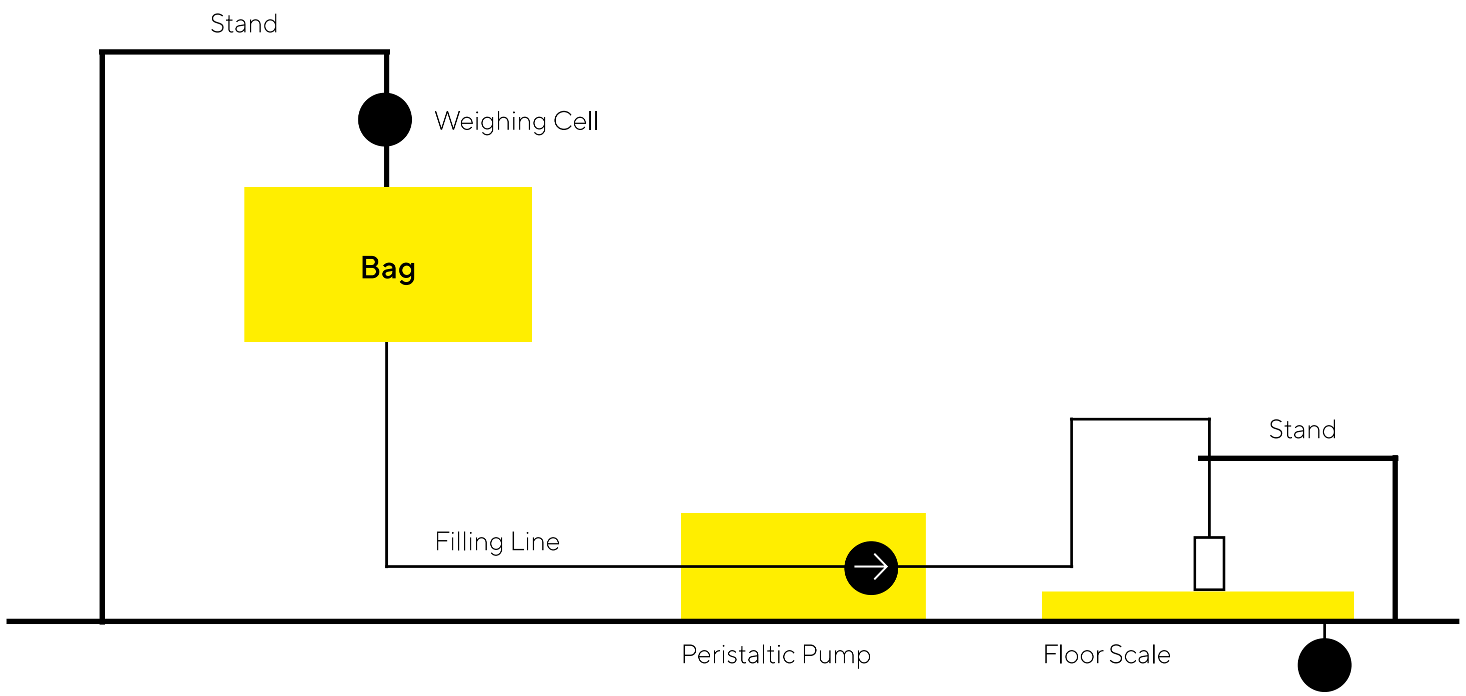


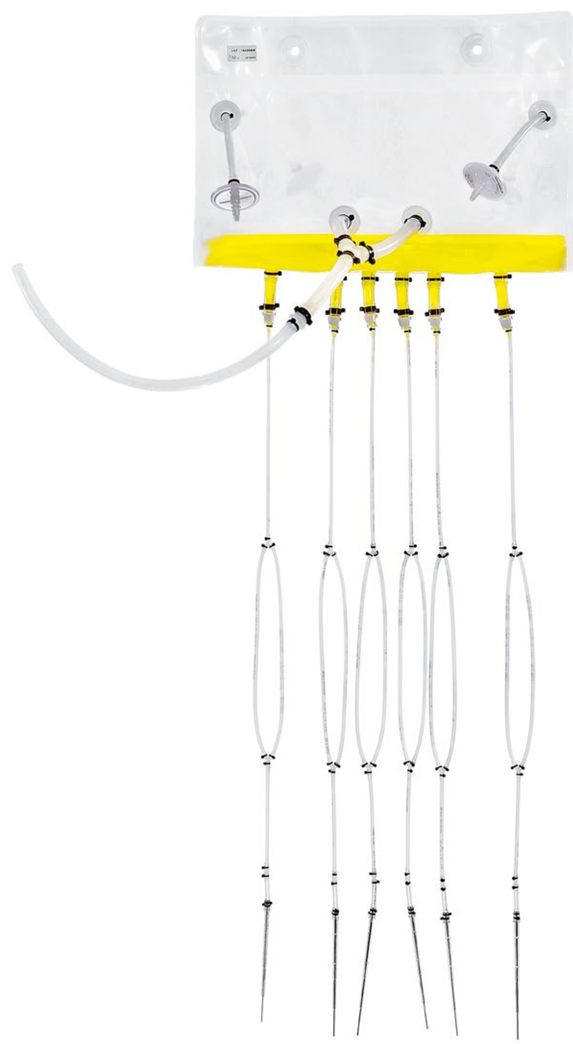
Table 1, Figure 2, and Figure 3 outline the bags used in this study.

Table 1: *Details of Bags Used*

Specifications	Octoplus FF®	Flexboy®
Design	"Wallet" shape bag	"Standard" shape bag
Material	S40 (PET/PA/EVOH/LLDPE)	S71 (EVA/EVOH/EVA)
Set	Connectors, tubes, needles, and filters	Connectors, tubes, and needles

Figure 2: *Flexboy® 5 L*

Figure 3: *Octoplus FF® 8 L*



A detailed description of the filling lines assembly is given in Tables 2-4 and shown in Figure 4. A Sartorius tubing Si (Pt) Tuflux® with a shore 60 A was used for each assembly.

Table 2: *Details of the Filling Line for 2 mL*

	Component Description
1	Tube ⅜"ID×⅝"OD L2.4-SI(Pt) Tuflux®-60 mm
2	Coupling Male ⅜"
3	Coupling Female ⅛"
4	Tube 1/16"ID×3/16"OD L12-SI(Pt) Tuflux®-300 mm
5	Y ⅛"×⅛"×⅛"
6	Tube 1/16"ID×3/16"OD L12-SI(Pt) Tuflux®-ROLL
7	Straight ⅛"×⅛"
8	Tube ⅛"ID×¼"OD L2-SI(Pt) Tuflux®-50 mm
9	Syntegon needle ID 1.6 mm

Table 3: *Details of the Filling Line for 5 mL*

	Component Description
1	Tube ⅜"ID×⅝"OD L2.4-SI(Pt) Tuflux®-60 mm
2	Coupling Male ⅜"
3	Coupling Female ⅛"
4	Tube 1/16"ID×3/16"OD L12-SI(Pt) Tuflux®-300 mm
5	Y ⅛"×⅛"×⅛"
6	Tube 1/16"ID×3/16"OD L12-SI(Pt) Tuflux®-ROLL
7	Straight ⅛"×⅛"
8	Tube ⅛"ID×¼"OD L2-SI(Pt) Tuflux®-50 mm
9	Syntegon needle ID 3.4 mm Basket tip

Table 4: *Details of the Filling Line for 20 mL*

	Component Description
1	Tube ⅜"ID×15/32"OD L4-SI(Pt) Tuflux®
2	Coupling Male ⅜"
3	Coupling Female ⅛"
4	Tube ¼"ID×⅜"OD-SI(Pt) Tuflux®
5	Y ¼"× ¼"× ¼"
6	Needle ID 5.5 mm

Note. All Tuflux® Silicone (Pt) are with a Shore 6 and hardness of 60.

Figure 4: *Setup of Filling Line*

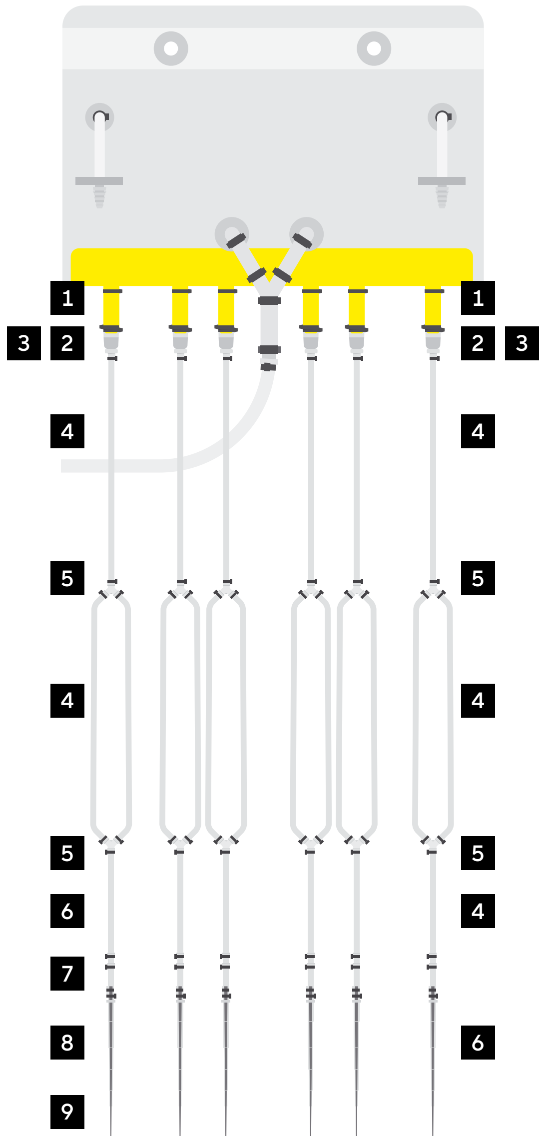


Table 5: *Overview of Components Used for the Study*

Filling Volume	Needles	Tubing	Vials
2 mL	Syntegon® ID 1.6 mm	Tuflux® SIL ID 1.6 mm	5 mL Adelphi
5 mL	Syntegon® ID 3.4 mm	Tuflux® SIL ID 1.6 mm	5 mL Adelphi
20 mL	Syntegon® ID 5.5 mm	Tuflux® SIL ID 6.4 mm	20 mL Adelphi

The same lines were used for both bags, which was necessary to observe only the influence of the bag design. Only one line is used on the bag (center line). The other outlets are closed with clamps.

Additional equipment used in the study is described below. Scales and peristaltic pumps, which could cause variation in the accuracy testing process, were calibrated and metrological controlled.

- The peristaltic pump (Flexicon PF6) was used to fill the samples
- Various Sartorius precision scales (CPA2245) were also used to weigh the samples before and after filling
- A scale (Meilen) was used to control the weight of the assembly during the whole experiment in order to perform the different filling steps by volume range
- An oven (Heraeus UT6) was used to dry the samples after each filling step

Methods

Equipment was assembled and process designed to mimic a small-scale fill-and-finish machine.

Bags were filled to 5 L with water. Dosage accuracy trials were performed with Octoplus FF® bag et Flexboy® bag using a peristaltic pump. A total of 150 vials were filled during the experimentation for each volume and each bag.

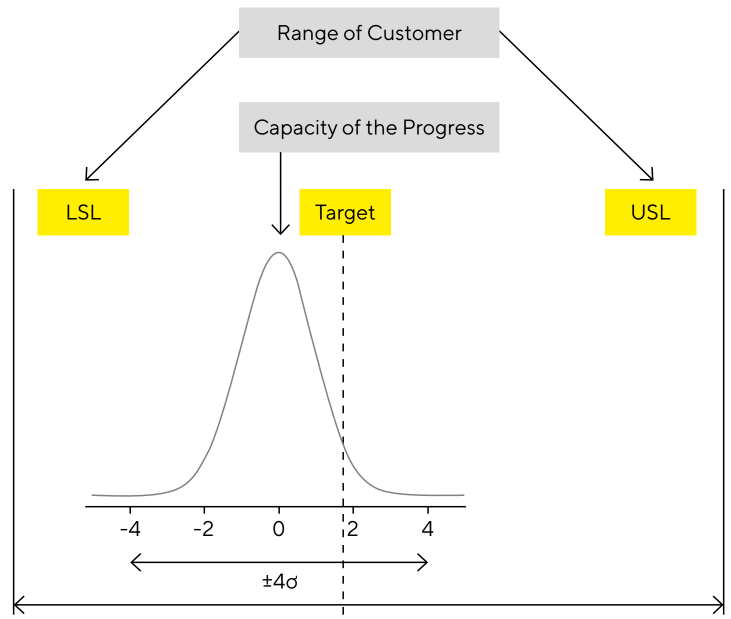
A process capability test (Figure 5) was chosen to give a comprehensive comparison between the process where every element of the setup can bring variability, including single-use bags chosen, specificity of the design (length and type of tubing, needles, etc.), installation (type of pumps, scales, etc.), and the specification from customer (range of the volume in each vial).

Capability analysis is performed through 2 factors:
Cp (comparing the process variation to the tolerance width) and Cpk (evaluating the centering and the variation of the process compared to the applicable specification).

Cp factor is the relationship between:
- Scattering between limits of the process USL and LSL
- Scattering of the process with ±6σ standard deviation

Cpk factor is the relationship between:
- Distance between the average of the process and limits (USL and LSL)
- Scattering of the process (with a threshold of 1.66 usually used for comparison of a critical process where 99.99% of results are considered) from the standard deviation of each data group

Figure 5: *Capability Analysis Definition*



Results

Dosing accuracy is specified by the capability of each test to be superior to the threshold defined (1.66). Results are summarized in Table 6.

Figures 6-8 show the scattering of each point between limits and around the defined target.

Figure 6: *2 mL Flexboy® Versus 2 mL Octoplus FF®*

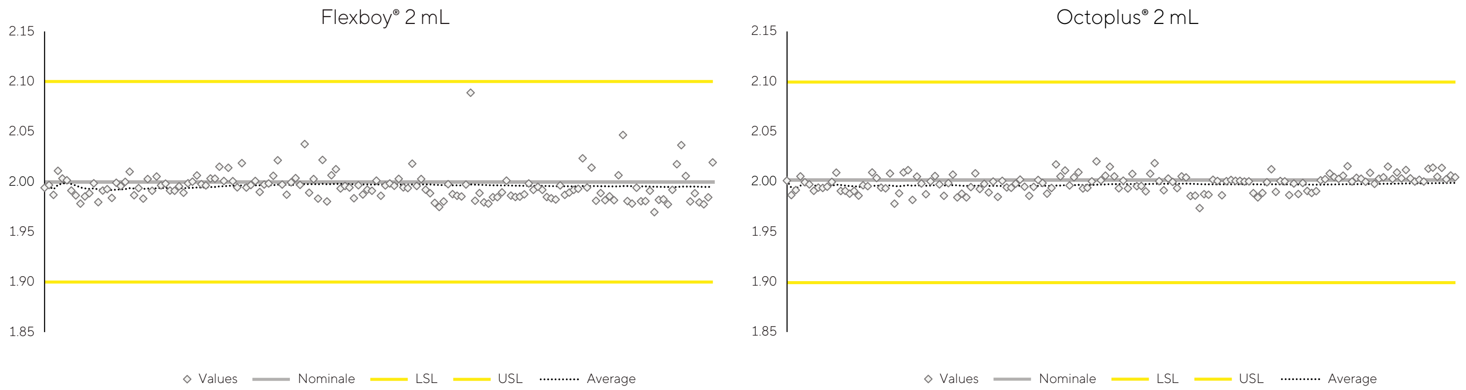


Figure 7: *5 mL Flexboy® Versus 5 mL Octoplus FF®*

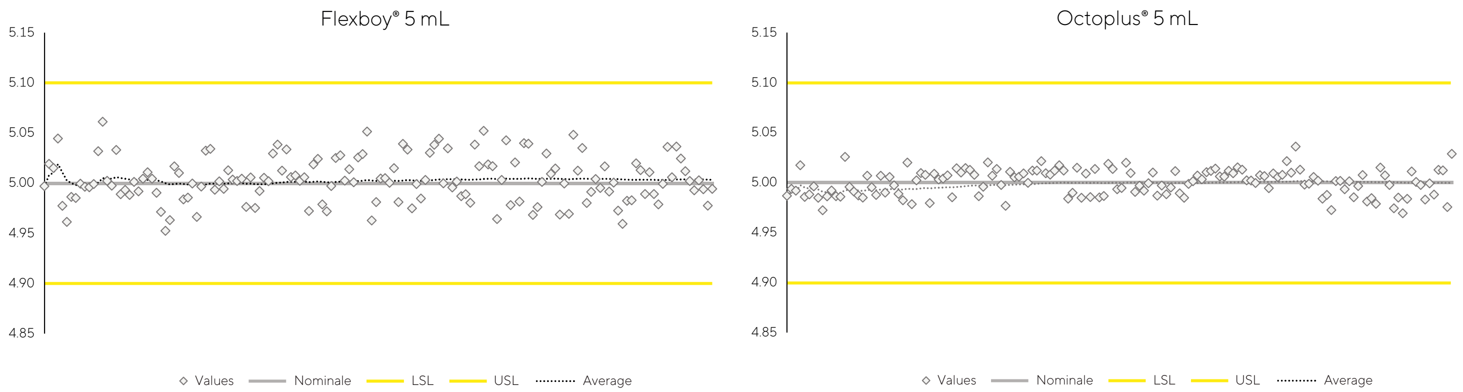


Figure 8: *20 mL Flexboy® Versus 20 mL Octoplus FF®*

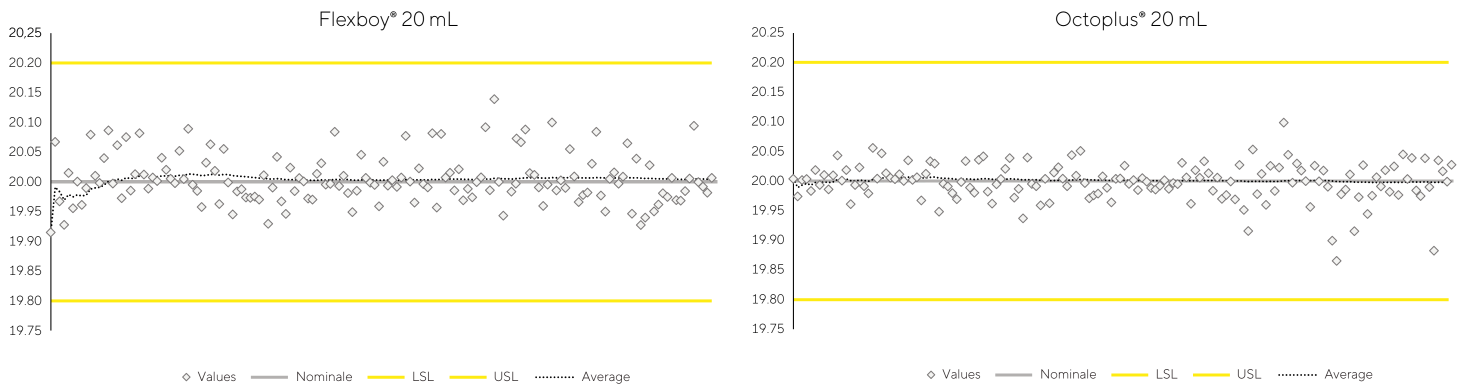


Table 6: *Results of Cp/Cpk Analysis*

Bags	Flexboy®	Octoplus®	Flexboy®	Octoplus®	Flexboy®	Octoplus®
Target	2.00 mL	2.00 mL	5.00 mL	5.00 mL	20.00 mL	20.00 mL
Average	1.995 mL	1.999 mL	5.003 mL	5.000 mL	20.005 mL	19.998 mL
Standard Deviation	0.015	0.009	0.022	0.013	0.044	0.022
Cp (≥ 1.66)	2.278	3.826	1.489	2.577	1.513	3.044
Cpk (≥ 1.66)	2.165	3.781	1.438	2.575	1.478	3.018

For 2 mL vials, both assemblies reached a Cp and Cpk superior to 1.66 (Table 6). However, Flexboy® bags showed lower Cp/Cpk values than Octoplus® FF due to visible scattering into the limits (Figure 6).

For 5 mL and 20 mL vials, Flexboy® bags did not reach the defined capability threshold, whereas Octoplus FF® has a Cp and Cpk superior to the threshold (Table 6), also shown in scatter plots for each volume (Figures 7 and 8).

When the Cp/Cpk values are below the threshold, accuracy is not compliant with the target. For 5 mL and 20 mL dosages, the results obtained for the Flexboy® bag show that the standard shape of this bag has a negative influence on the dosing accuracy. This observation could be due to multiple factors, some of which are listed below:

- Hydrostatic pressure on each line can influence accuracy due to the position of each line through the bottom of the bag. Figure 3 shows the rake shape for Octoplus FF® compared to the single drain line in the Flexboy® involving a distribution line for multiple pumps (Figure 2).
- The variable height of the solution at the side of the bag due to the bag shape (Flexboy® is bottle-shaped, whereas the Octoplus FF® is flat-bottomed) could have a negative influence.
- The length and configuration of the filling line with tubing and needles characteristics
- Configuration of the assembly (bag positioning, filling machine, pumps, etc.)

Conclusion

This study demonstrated that the design of the "break tank" bag influences the dosing accuracy of a filling process using a peristaltic dosing pump. The Octoplus FF® bag performed better than the Flexboy® bag when the capability values (Cp and Cpk) were compared. This is likely due to the specific wallet shape of the Octoplus FF®, emphasized by the position of the line through the bottom of the bag and the configuration of the SU assembly.

The Octoplus FF® bag is easy to install, and proper deployment of the bag will result in no folds (where the product could be trapped). Moreover, it maximizes product recovery and eases draining thanks to its optimized bag design and thanks to his side vent filters (optional). It also accommodates production scale and drug product specificities, facilitating scale-up from clinical to commercial, with fast tracked validation work and highly characterized materials.

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