



# Small-Scale Syringe and Vial-Filling Capability for Development of Robust Filling Processes, Smooth Tech Transfers, and to Resolve Manufacturing Issues: Summary of Key Learnings

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## ABSTRACT

Filling of syringes and vials with high-viscosity monoclonal antibodies (mAbs) or small-molecule liquid formulations is a difficult task and may present several challenges. Considerable development work may be required to develop a filling process that provides a clean fill using a small-scale or at-scale filling machine. However, performing the development work using an at-scale filling machine is neither an efficient nor cost-effective long-term option due to hectic manufacturing schedules and associated resource needs. A small-scale filling line can be used to define optimal filling process parameters, support technology transfer, and develop mitigation strategies for ongoing or potential issues with minimal disruption of normal manufacturing operation. Streamlined ways of working without requiring manufacturing-scale line time is expected to result in increased efficiency and improved portfolio progression timelines. Key learnings, case studies, and recommendations for this small-scale filler are discussed.

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**F**illing of syringes and vials with high-viscosity monoclonal antibodies (mAbs) or small-molecule liquid formulations is a difficult task and may present several challenges. Challenges associated with liquid drug product filling and potential mitigation strategies are summarized in previous articles (1–3). One of the long-term strategic approaches involves the installation of small-scale filling capability to develop robust filling processes, support technology transfers, and mitigate potential manufacturing issues (1).

The filling process by a peristaltic pump-based mechanism consists of several steps, including aligning the filling needle and primary container, filling product into the containers using suitable needles, controlling product suck-back, and stoppering the containers (1). Considerable development work may be required to develop a filling process that provides a clean fill using a small-scale or at-scale filling machine. However, performing the development work using an at-scale filling machine is neither an efficient nor cost-effective long-term option due to hectic

manufacturing schedules and associated resource needs. Therefore, it is beneficial to have a suitable small-scale filling machine in an R&D facility to reduce manufacturing interruption. The small-scale filling line can be used to define optimal filling process parameters, support technology transfers, and develop mitigation strategies for potential manufacturing issues with minimal/no disruption of the at-scale manufacturing line. Streamlined ways of working without requiring at-scale line time are expected to result in increased efficiency and improved portfolio progression timelines.

Recently, GSK installed a custom-designed small-scale syringe and vial filling machine, and successfully used it to support filling of several mAb and small-molecule formulations (Figure 1). The development work performed thus far includes defining optimal filling and stoppering parameters to achieve a clean fill. The objective of this article is to summarize key learnings associated with the implementation of the small-scale filling machine and development work performed thus far as well as make recommendations for future equipment use.

## IMPLEMENTATION OF A SMALL-SCALE FILLER

### Significance of a representative small-scale machine

A small-scale filler was selected by taking several aspects into consideration. The key aspects that were considered include intended filling mechanism (e.g., peristaltic pump, rotary piston pump, or time pressure-based filling mechanism), existing internal filling machines and ability to simulate at-scale filling aspects using small-scale filler, and the small-scale filler capabilities and adaptability for future upgrades.

The impact of process parameters on filling performance reported thus far has been evaluated using a modified benchtop filling set-up/filler or a large-scale filling machine (2–6). For

**Figure 1.** Visual of a custom-designed small-scale syringe and vial filling and stoppering system.



example, Shieu *et al.* evaluated several process parameters using a modified benchtop filling unit (4–6). Parameters such as needle size, airflow around the needle tip, pump suck-back, and product viscosity were found to play a critical role in achieving clean filling. Other parameters such as pump velocity, acceleration, and fluid–needle interactions were found to have a negligible impact on filling performance. The parameters defined using such a modified benchtop unit needed to be manually translated for the large-scale filling machine, and then filling trials were performed using an at-scale machine to confirm the acceptable ranges for process parameters.

Partial or complete clogging of filling needles has been observed during large-scale manufacture of a drug product batch (2). Undesired liquid behavior (e.g., formation of product droplet at the needle tip and meniscus close to the needle tip) and rapid product drying under ambient conditions led to filling needle clogging and deflected liquid flow (2,3). The main cause for undesired liquid behavior was found to be ineffective suck-back control (2,3). Extensive experiments were performed using both manufacturing scale and benchtop equipment to optimize process parameters that would consistently produce acceptable suck-back control. Suck-back pump speed was found to be a critical pro-

cess parameter influencing this phenomenon. Decreasing the suck-back pump speed led to increased meniscus stability and prevented filling needle clogging (2,3). GSK purchased and implemented a custom-designed small-scale filling line with the goal of establishing a representative filling process that does not interfere with manufacturing scale-up scheduling (Figure 1). This system consists of a filling line surrounded by a low particulate and low bioburden closed reduced access barrier system enclosure with humidity control. Having a representative small-scale filler in the R&D space eliminated the need to use the at-scale filler for process development/optimization or for troubleshooting the manufacturing issues.

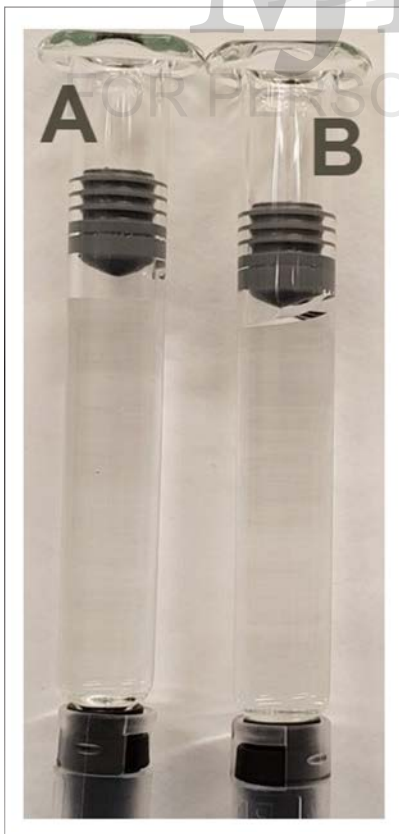
### Overcoming implementation-related challenges/approaches

The small-scale filler has been designed to simulate at-scale filling and stoppering curve parameters, which in turn has enabled easy transfer of defined process parameters to the large-scale manufacturing sites. However, design and implementation of a representative small-scale filler posed several challenges. Preparation was the key learning for the design and implementation of the small-scale equipment. Background work to ensure compatibility and consistency with existing large-scale equipment

played a crucial role in successful implementation from both mechanical and software perspectives. For example, software modifications were needed during design to ensure easy process parameter transferability to the commercial-scale machine. Engaging discussions with relevant internal stakeholders (members of drug product development teams, manufacturing operations, shipping and logistics, and site engineering) and seeking feedback played a critical role in achieving the successful implementation.

Adoption of this equipment for internal use was swift, and the equipment was successfully used thus far for leading stability batches, development work to understand design space around filling process parameters, and assessment of a new stopper design. From the data

**Figure 2.** Effect of stoppering curve parameter on stopper depth. Unacceptable (A), acceptable (B) stopper depth.



capture and transfer/storage perspective, there were a few challenges that needed to be overcome to fully implement the equipment. The small-scale filler captured a large amount of filling process-related data, which led to difficulty in organizing the data in a standardized, structured, and future-proof format. Additionally, even though the large-scale and small-scale equipment are manufactured by the same vendor, the nomenclature for the process parameters was not standardized. This problem was resolved by constructing a parameter dictionary to facilitate discussion and transfer of parameters across equipment and scale. Therefore, it is advisable to consider data capture and standardization aspects when designing and purchasing a small-scale filler.

#### PERFORMANCE OF SMALL-SCALE FILLER

After successful implementation, the small-scale filler was used for different types of studies. Types of product filled, study objectives, challenges faced, and mitigation approaches are summarized in **Table I**.

Overall, the challenges faced thus far can be categorized under three areas: integration, influential process parameters, and equipment limitations.

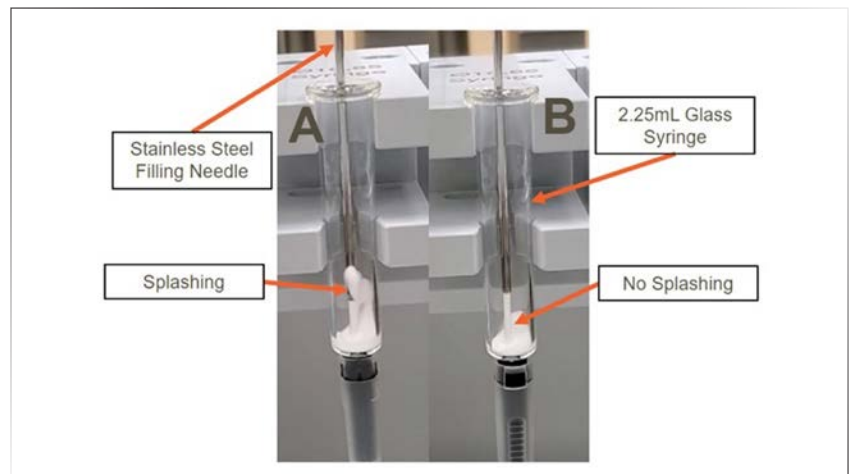
#### Integration-related challenges and solutions

There were challenges to integrating a fit-for-purpose filling workflow for mAb 1, where the team was not experienced with the small-scale filler to achieve the target stopper depth (height). **Figure 2** shows unacceptable (A) and acceptable (B) stopper depth. Increased understanding of the filler capabilities and ways to optimize those capabilities allowed for the achievement of the intended goal. Also, the use of a bench-top drop shape analyzer (DSA) to determine pumping process parameters such as suck-back cycle parameters enabled rapid and successful integration of the small-scale filler for small molecule 2 (SM2).

#### Process parameters that influence filling performance

As the breadth and depth of experience with this equipment increased, there was a better understanding of the most influential process parameters for specific issues. For example, high viscosity SM1 showed that modifying the pump acceleration more effectively reduced splashing during filling than modifying overall pump speed (see **Figure 3**). The increased knowledge gained by filling different types of drug products using the small-scale filler

**Figure 3.** Effect of filling curve parameter on filling performance. Fluid behavior at suboptimal (A) and optimal (B) filling pump speed. Contact between the tip of the filling needle and product meniscus should be avoided during filling.



**Table 1.** Summary of products filled using the small-scale filler. mAb is monoclonal antibody. SM is small molecule.

Product	Product form and container	Type of study	Challenges	Mitigation approaches/take away messages
mAb1	Aqueous solution; 1-mL long syringe	Stability study	Difference in target stopper depth (height) relative to intended target stopper depth (height)	Equipment parameter stopper insertion depth was optimized to achieve the target stopper depth (height). An example of difference in stopper depth is shown in <b>Figure 2</b> .
mAb2	Aqueous solution; 1-mL long syringe	Stability study	There were no challenges as the properties (e.g., protein concentration and viscosity) were similar to that of mAb1, and the filling curve used for mAb1 was found to be optimal for mAb2	For mAb formulations with comparable properties (e.g., protein concentration and viscosity), fit-for-purpose filling process parameters could be similar.
SM1	Aqueous suspension; 1-mL and 2.25-mL long syringes	Filling cycle development	It was a high viscosity (~30 cP) suspension formulation, and such formulation was not filled with this filler before. Therefore, lack of prior process understanding posed a challenge to achieve clean filling and demanded development work.	Identification of optimal filling pump parameters through development work allowed for a successful fill (filling without splashing). An example of fluid behavior during filling is shown in <b>Figure 3</b> .
			Difficulty in achieving higher headspace required for product resuspension.	Optimization of stoppering cycle parameters (e.g., vacuum level and time) through development work allowed to achieve target headspace.
			When the peristaltic pump stops rotating after the fill cycle (after dispensing the dose of the product into the syringe), the fluid stream detaches from the needle tip and a drop of product remains hanging from the tip of the filling needle. Dripping of product droplet into the syringe occurred during withdrawal of the filling needle. Dripping of product droplet affects fill weight/volume and therefore should be avoided.	Equipment (suck-back cycle) settings were modified to initiate the suck-back of product inside the filling needle before the withdrawal of filling needle begins.
SM2	Aqueous suspension; 2R vial	Stability study	Drug particles in this suspension formulation were settling during filling.	Mixing of suspension formulation during filling ensured uniform content uniformity during filling.
	Organic solvent-based solution; 2R vial	Feasibility assessment and process understanding	Filling using a benchtop-filling setup showed fill weight target drift and increased variability due to a single-head pump design.	Mechanical similarity to manufacturing equipment provided evidence to support low risk of fill weight variability during scale up.
			It was a high-viscosity (~50 cP) organic solvent-based formulation, and such formulation requires extensive development work to define optimal filling process parameters.	Having prior knowledge regarding the suck-back meniscus stability studied using droplet shape analyzer reduced the amount of work performed with the small-scale filler to define optimal process parameters.
N/A	N/A	Assessment of feasibility for a new container closure combination	New stopper types did not sort correctly in the equipment stopper bowl due to dimensional differences.	Manual intervention required until bespoke change parts can be designed and installed. An example of stopper bowl-related issue is shown in <b>Figure 4</b> . The study also informed the requirements to adapt the commercial filling line.

Viscosity: mAb1 and mAb2: < 5 cP; SM1: ~30 cP; SM2 suspension: ~10cP; SM2 Solution: ~50 cP.

shortened the time spent and reduced the development work performed to define the optimal filling process parameters for subsequent drug products.

### Equipment limitations

Equipment limitations were realized during filling of SM1 drug product and new stopper assessment. It was not possible to achieve a higher headspace in the syringe needed for resuspension of the SM1 drug product. This limitation

was due to the design of the vacuum system associated with the small-scale filler. An alternative vacuum stoppering unit was used to achieve the target headspace. During assessment of a different stopper design, manual intervention to ensure proper sorting of the stoppers in the bowl was necessary to complete the stoppering cycle with the small-scale filler. Stopper sorting-bowl design is specific to a particular stopper design, and the initial stopper bowl was designed for the

first-intent stopper. During these studies, stoppers would get stuck at various points in the sorting process, leading to a stopper backup (see **Figure 4**). The study also informed the requirements needed to retrofit the small-scale and commercial filling lines. This allowed earlier planning to retrofit both filling lines to manufacture the product lines that needed other components (e.g., various stopper types and cartridge filling capabilities).

## RECOMMENDATIONS FOR SMALL-SCALE FILLER STUDIES

In this section, various types of filling, stoppering, and line stoppage studies that can be executed using this type of small-scale filler as well as recommendations for future study framework based on key learnings outlined previously are described below. Containers, closures, and bulk drug product (or appropriate surrogate) are needed for these evaluations.

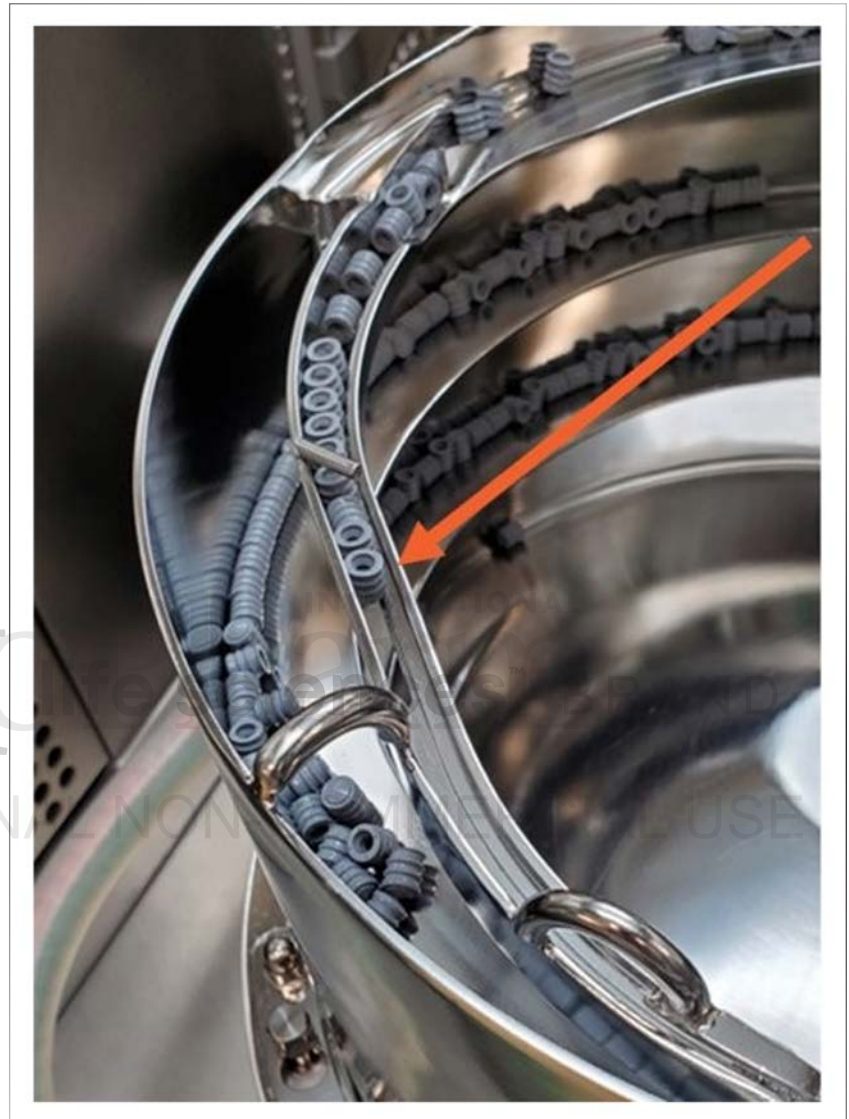
### Process parameter development

Filling and stoppering process parameters for new products can be developed using the small-scale equipment. Typically, for any product that is new to the small-scale filling line, a fit-for-purpose check is recommended to determine if a previously developed “first intent” filling and stoppering cycle is acceptable. If the first intent process parameters are not optimal or require modification, it is recommended that additional filling and stoppering studies be performed using the small-scale filler to define acceptable ranges for the process parameters. The number of studies that might be needed can be influenced by product properties (e.g., viscosity, solid content, surface tension, and drying behavior), drug product design (container/closure combination), and product lifecycle stage (clinical development, process characterization, or targeted investigation). Several factors can influence the intended study design and scope, and the resulting needs of any future studies should also be considered.

### Development stability

Filling for product quality and stability assessment can be executed using previously developed filling cycles or filling cycles that have been deemed fit for large-scale manufacturing. Previously developed filling curves can be verified as a replacement for full development if appropriate for initial filling of a product. Stopper height and fill target in-process controls (IPCs) can be used to confirm

**Figure 4.** Example of stopper backup due to difference in the stopper type, which requires frequent manual intervention to ensure smooth movement of stoppers. Stuck stopper is shown with an arrow.



that the process parameters are appropriate for studies such as development stability or device testing. Stability fills for new products potentially require filling process parameter development prior to a stability fill.

### Stoppage strategy

Filling line stoppages are an inherent part of large-scale manufacturing of drug product batches due to various reasons, such as IPC fill weight checks. An IPC weight check can lead to multi-

ple stoppages, and the number of stoppages depends on the frequency of fill weight checks. Additional stoppages can be caused by potential manufacturing interventions due to planned events or unexpected issues. Repeated occurrences of product layering on the inner surface of the stainless-steel filling needle during the suck-back cycle and drying of the deposited product during line stoppage has been shown to cause considerable product buildup inside the needles (2,5). Undesired product buildup

inside the needle has caused narrowing of the fluid stream during filling. Suck-back can also be disabled to investigate behavior on equipment that does not have this capability. The impact of frequency and duration of line stoppages on product buildup and fluid flow behavior can be studied using the small-scale filler. Filling line stoppage studies enable definition of optimal-filling line stoppage duration, frequency, and filling needle priming strategy. The filling line stoppage studies are performed with filling and stoppering parameters that have been previously developed or confirmed to provide a clean fill. Product buildup inside the filling needle and liquid behavior (e.g., deflected liquid flow and splashing) can be examined through imaging and image analysis. Fill weight measurements are performed as part of the line stoppage studies. The number of dispenses/injections to waste tub (needle priming) needed to clear the potential product build up inside the filling needle can be determined as part of the line stoppage studies.

### Proven acceptable ranges

Proven acceptable ranges for filling and stoppering cycles can be defined using the small-scale filler. For example, acceptable ranges for filling and stoppering cycle parameters (e.g., filling pump speed, suck-back pump speed, suck-back volume, vacuum level, and vacuum time) can be defined. However, confirmation of ranges or further minimal optimization may be needed with the large-scale manufacturing equipment. These studies consist of modifying parameters outside of nominal values and observing filling behavior to determine critical process parameters as well as their acceptable ranges.

### CONCLUSION

Successful filling and stoppering of biopharmaceutical and small-molecule drug products during large-scale manufacturing is dependent upon a well-defined process. Such a process

is developed using a thorough understanding of the process parameters and failure modes. A small-scale filling machine that simulates the large-scale filling conditions has played a critical role in understanding and defining this process. Implementation of representative small-scale filling equipment has enabled development of robust processes, accelerated development timelines, and provided new avenues for completing specific studies within the drug product development space (e.g., resolving manufacturing issues and evaluating a new stopper). Various mAb as well as small-molecule drug products have been successfully filled using this equipment for various purposes. Key learnings around integration, influential process parameters, and equipment limitations have improved understanding with the equipment and enabled the identification of avenues for improvements.

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