Manufacturing Process Design: Scale-Up Studies For Success

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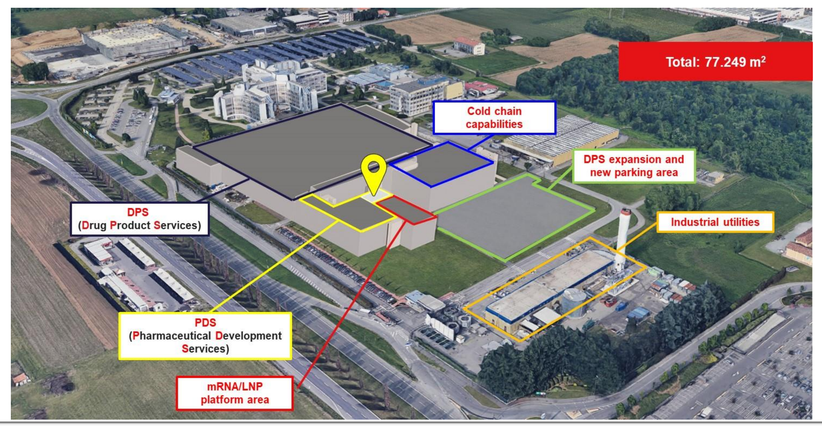
Monza Campus | Layout overview



TFS Monza PDS Formulation & Analytical Development Laboratory Services and Tailor-Made Solutions

Early Stage

- Pre-formulation studies & prototype
- Familiarization Study & Compounding Design
- Purification/Filtration Design
- Lyophilization Cycle Development & Scale-up
- Fill Volume Determination
- Spiking Study (oxidant)
- Terminal Sterilization Study
- Vials to PFS Transition Study

Middle Stage

- Product Contact Part Compatibility & In-Use Studies
- Lyophilization Cycle Robustness (DoE)
- Formulation Robustness (DoE)
- Holding Time Studies
- Freeze-thaw Studies
- Pumping Recirculation Studies
- Mixing Study

PDS FD Lab Capabilities

INTRODUCTION

The present case study provides details on activities that can be performed in the **FD Laboratory of PDS Monza** to support the **scale-up** of sterile RNA-based drug products on **GMP lines**. The main purpose of the study was to generate **sufficient process understanding** to ensure the design of a **robust process** which is feasible for **clinical and commercial manufacturing** of drug product (DP).

In particular, RNA-based DP injectable products could exhibit incompatibility with **γ-irradiated disposable** filtration assembly (widely used in GMP manufacturing) and **needle clogging** during filling activities resulting in waste of product and delays of clinical trial studies. The compatibility with gamma-irradiated and autoclaved assembly was investigated by performing a filter flush study. The high drying propensity of DP solution during filling line stoppage events was tested and verified using a full factorial design challenging different downtimes (up to 3 hours of stoppage) and the following technical alternatives: 1) Needle lumen size (2.5 mm and 3.0 mm) and needle shape (tapered, standard, and double flute beak) 2) Peristaltic pump parameters (i.e. acceleration, pump speed, anti-drip).

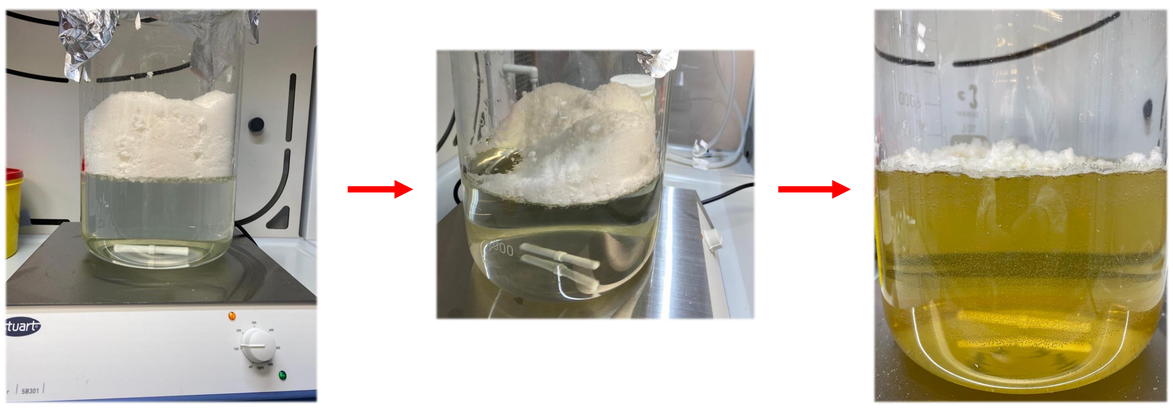
PROCESS DESIGN STUDIES: FROM COMPOUNDING TO FILTRATION STEP

DS is a **lyophilized powder**, **highly volatile** and with **a high apparent volume.** The bulk Drug Product is at high concentration of 160 mg/mL. The following studies were carried out to guarantee a **'smooth' scale-up on GMP line**

- Establish **minimum time** for DS **dissolution**
- Evaluate **homogeneity** of DP bulk solution and evaluate **pH-equilibrium**
- Evaluate **mixing time** and **speed** of DP bulk solution to obtain API homogeneity
- Evaluate any needed amount of **solution** to be **flushed** during **filtration process**
- Collect material for **bioburden analysis** method **validation**

Evaluate homogeneity of DP solution and pH-equilibrium

DS in WFI solubilized by magnetic stirring**, same equipment and conditions that will be used in GMP production**.



After complete DS dissolution (visual check) the mixing was stopped and the solution was **sampled from different positions of the vessel** and at **different time points**, to evaluate the homogeneity of the solution and pH. According to assay results, the time needed for dissolution of DS was 1 hour. This **data** can be **directly transferred into GMP manufacturing**.

Bioburden filtration and filter flush study by autoclaved filtration assembly

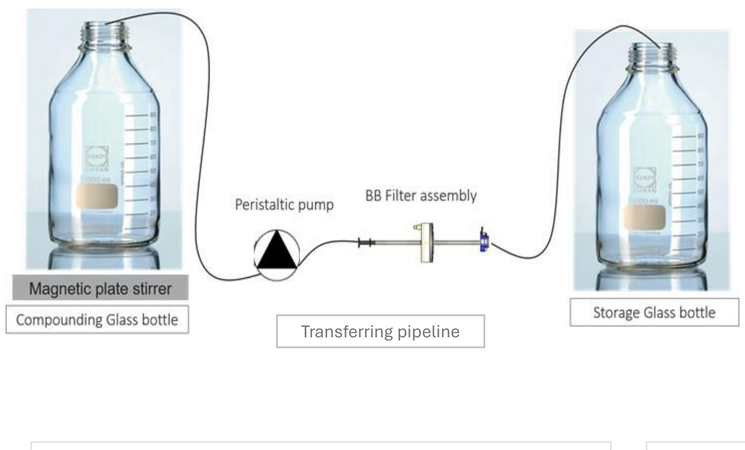
To clarify if the γ-irradiation process is the **root cause** of pH dropping during filter flush, a **comparative study** with autoclaved assemblies was performed.

As results from the execution of a feasibility study with an autoclaved filtration assembly demonstrated, there was no significant change in pH after filtration. This product will **need to be manufactured only with autoclaved assemblies**.

Bioburden filtration and filter flush study by γ-irradiated filtration assembly

Under LAF, the DP solution underwent filtration through a **γ-irradiated filtration assembly** with peristaltic pump to simulate **bioburden** reducing filtration **and sterilizing filtration** of DP.

During Bioburden filtration, a **filter flush study** was performed to evaluate the need for any discarding of DP during the filtration processes, evaluating **any loss of content** or **change in pH** in the DP solution.

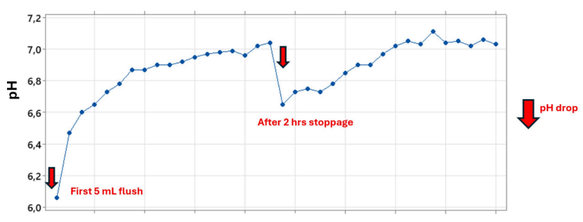


γ-irradiated filtration assembly **negatively** impacted the **pH** value, hence **product quality**.

Volatile acidic species released by the gamma irradiated assembly alter the DP up to one unit.

This would require an **initial discard** of 150 mL of **expensive** unbuffered DP solution, which impacts product quality and cost.

γ-irradiated Assembly: Filter Flush



Autoclaved Assembly: Filter Flush

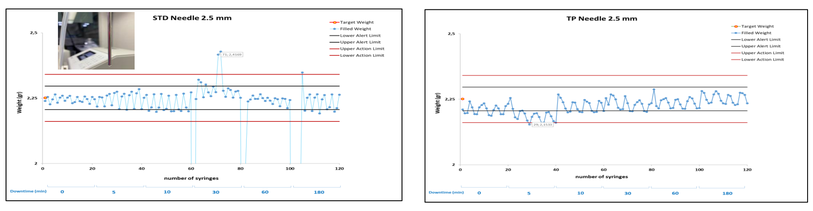
Sample	pH	Conc. mg/mL	% Label Claim
Bulk solution	7.154	160.5421	100
FF_8ml	6.603	160.0767	100
FF2_15ml	6.790	159.7048	100
FF2_43ml	6.931	159.6066	100
FF2_76ml	6.986	160.0304	100
FF2_124ml	7.081	159.9970	100
FF4_180ml	7.257	160.8368	100
FF5_2hSTOP_8ml	7.117	N/A	N/A

Well-designed and properly executed **lab-scale studies** are crucial for **early identification** of any **criticalities** that could occur during GMP sterile manufacturing,
This has a **positive impact** on our customers' **budget** as well as timelines to **safely** and **timely** bring potential drug products to our **patients**

PROCESS DESIGN STUDIES: FILLING STUDIES

Clogging of filling needles during filling operations of high concentration drug product formulations is one of the major challenges for successful large-scale manufacturing. High concentration biological-based formulations exhibit high drying propensity that could cause needle clogging during filling activities, particularly during process downtimes. Consequently, a significant variation in filling accuracy could occur resulting in high fill-weight variation and waste of expensive product. Understanding the factors that influence the propensity for filling needle clogging is essential to developing mitigation strategies for efficient large-scale manufacturing. The effect of high drying propensity, consequence of filling line stoppage events, of such RNA-based formulation was tested and verified. The formulation was at 300 mg/mL of an RNA conjugated with sugar moieties, which cause both bubble formation during filling and needle clog formation after short downtimes. The solution was characterized by a relatively high viscosity of approx. 10 cP. The DP solution was to be filled in 1.0 mL long pre-filling syringes (PFS) for which filling operations are more challenging those of vials. The following technical alternatives to prevent needle clogging were investigated.

Needle morphology & Size

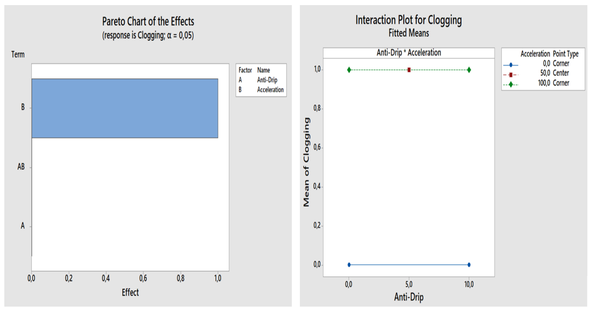


The use of standard (STD) shape needle resulted in drop formation after each dosage and needle clog after downtimes. **Tapered (TP) shape** needle resulted in the absence of both needle clogging and drop formation/drying making this shape of needle ideal for such solutions. Moreover, 3.0 mm needle size improved filling accuracy (data not shown)

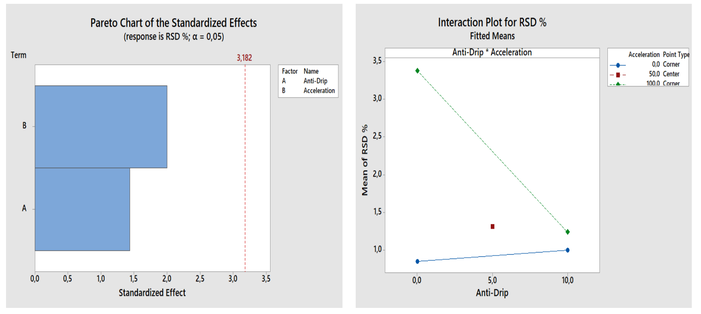
Filling Parameters Optimization: Design of Experiment (DoE)

Since standard shape needle are commonly used in our GMP lines, peristaltic pump parameters were investigated by DoE study with a full factorial design. Two different data analyses were performed, in which Needle Clogging and Filling Weight Reproducibility as responses were evaluated as final output.

Factorial Design Analysis: Needle Clogging as Response

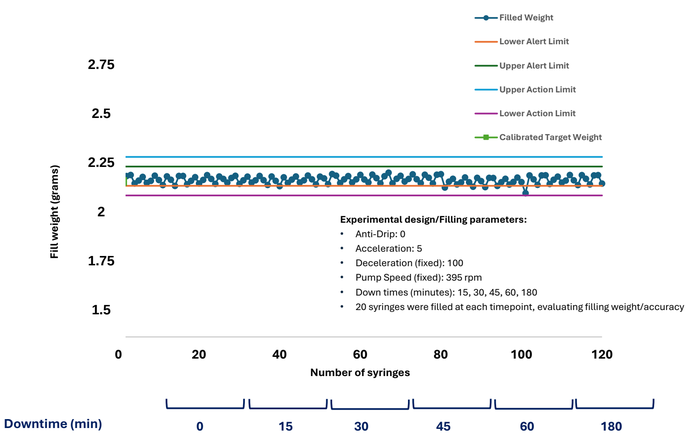


Factorial Design Analysis: Filled Weight Reproducibility as Response (RSD%)

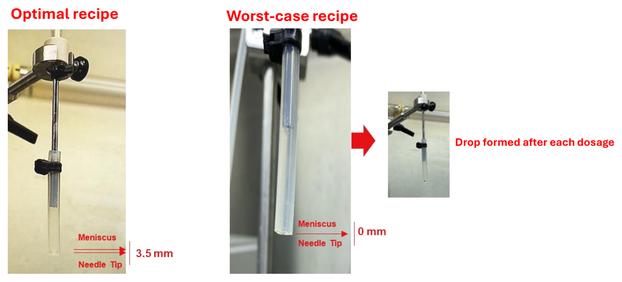


Acceleration was identified to be the key filling parameter. Low acceleration values resulted in **no needle clogging** even after hours of stoppages **while anti-drip** parameter, contrary on what stated in literature, **did not prevent needle clogging** in the tested conditions

Optimal filling recipe



Meniscus height using 'optimal' recipe and 'worst-case' recipe



CONCLUSIONS

The use of the optimized filling recipe resulted in:

- No clog formation across the duration of the study **even after 3 hours of downtime**
- No bubble formation during the dosages
- Filled weight was within the alert and action limits for all the duration of the study
- Good accuracy/reproducibility of the filled weight with calculated RSD % of 0.79%
- Meniscus height inside the needle was far from the tip of the needle and it is sufficiently stable among dosages and during filling stoppages

Understanding the factors that could impact the quality and the yield of a drug product solution ahead of large-scale manufacturing is essential to developing mitigation strategies for successful manufacturing on GMP lines manufacturing

REFERENCES

[1] Syringe Filling of a High-Concentration mAb Formulation: Experimental, Theoretical, and Computational Evaluation of Filling; Process Parameters That Influence the Propensity for Filling Needle Clogging [Journal of Pharmaceutical Sciences 108 (2019) 1130-1138