Scale-down modeling of the filling process for vaccine production

Camilla Moino [1], Bernadette Scutellà [2], Marco Bellini [2],

Erwan Bourlés [2], Gianluca Boccardo [1], Roberto Pisano [1]

[1] DISAT, Politecnico di Torino, 24 Corso Duca degli Abruzzi, Torino 10129, Italy

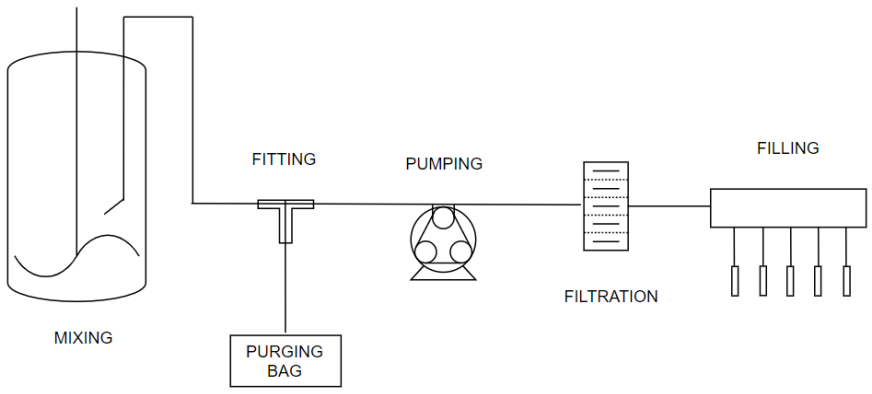
[2] GSK, 89 Rue de l'Institut, Rixensart 1330, Belgium

Introduction

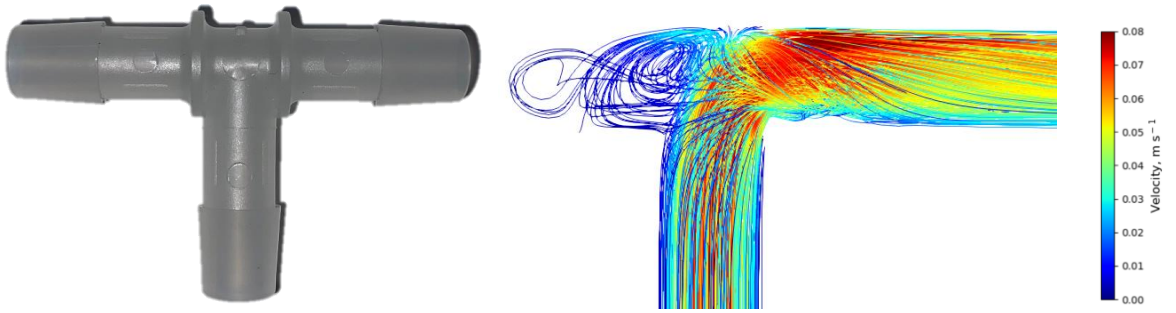
Fill-finish represents one of the final and most critical steps in the drug manufacturing process. [1] Here, bulk material is filled into smaller vials or syringes and is then ready for packing, labelling, and quality inspection prior distribution. Fill-finish poses unique challenges, including meeting the quality and stability of the target products. Protein-based products can show sensitivity to temperature changes, oxidation, light, ionic strength, and shear stress. [2] Among these, shear stress has recently gained interest because of its frequent occurrence in filling lines. Exposure of protein-based products to such stresses is believed to affect product stability by promoting unfolding and subsequent aggregation; these can alter the biological activity of the vaccine and raise the potential for side effects. [3] Several experimental studies have been conducted in recent decades to assess the impact of shear stress on model products; [4] however, the presence of additional stressors complicated the investigation and discordant findings have been reported. In such a controversial landscape, accurate modeling of shear stress in a vaccine filling line becomes necessary.

Objectives and Results

The vaccine filling process consists of several unit operations, as visible in the figure:



As a first step for further experimental investigations, Computational Fluid Dynamics is used to analyze fluid dynamics within some of these typical unit operations and to quantify the shear stress distribution. Specifically, individual fluid particles are tracked to investigate their path within the unit and detect local fields; this can be seen in the figure below, where the particle paths are followed in a typical T-fitting used for product sampling.



In this way, it is possible to obtain the shear history of each individual particle, which, together with their relative flowrate, make it possible to identify suitable equations for describing the shear stress distribution experienced by the fluid when flowing through the operational units.

In addition, traditional scale-down (and -up) approaches are tested to study the result of their application on shear stress while scaling from the commercial to the laboratory unit. Finally, suitable scale-down (and -up) approaches are proposed by using the shear stress distribution as a scaling parameter.

References

1. Kovarcik, D. P. Critical factors for fill-finish manufacturing of biologics. *BioProcess International* vol. 14 (2016). https://bioprocessintl.com/manufacturing/fill-finish/critical-factors-for-fill-finish-manufacturing-of-biologics/.
2. ICH. Guideline for Industry ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products. *Fed. Regist.* (1996). Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products | FDA.
3. Wang, W., Nema, S. & Teagarden, D. Protein aggregation-Pathways and influencing factors. *Int. J. Pharm.* **390**, 89–99 (2010).
4. Charm, S. E. & Wong, B. L. Enzyme inactivation with shearing. *Biotechnol. Bioeng.* **12**, 1103–1109 (1970).