On the use of Computational Fluid Dynamics to assist modeling of pharmaceutical filling lines

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Fill-finish of protein-based parenteral formulations represents a crucial step in the pharmaceutical industry that necessitates careful monitoring of product stability down the line. Mixing, pumping, filtering, and filling are the most important steps which expose the parenteral product to various stressing conditions, including interfacial stress and shear stress. The combination of these elements is widely believed and proven to influence product stability, but the defined roles of these players in the product damage process have not yet been identified. The present work addresses a current industrial problem, by focusing on the analysis of shear stress on protein-based therapeutics flowing in filling lines by means of Computational Fluid Dynamics (CFD) simulations. The purpose of this work is not to pinpoint the mechanism triggering the damage of the product, but it represents the first step towards wider experimental investigations and introduces new strategies to quantify the average shear stress. First, an extended summary of existing literature that explores the experimental impact of shear stress in pharmaceutical operations is provided. Next, flow standard in tubing, fittings, sterilizing filtration, and pumping are analyzed. For each unit operation a specific path was followed to achieve a computational replica of the real geometry; standard flow conditions were then tested and the relevant shear stress exposures were investigated and further compared.

The field of scale-down approaches, used to scale the commercial process down to the laboratory level, is also explored. Since quality control is critical in the pharmaceutical realm, it is essential that the scale-down approach preserves the same stress exposure as the commercial scale, which in the present work is considered to be that resulting from shear effects. Therefore, innovative approaches for scaling down the commercial process are proposed and numerically validated. The numerical work presented in this project helps to shed light in a field that has seen some confusion in the literature. Shear stress indeed contributes synergistically to product damage when combined with interfacial stress. Knowing the extent of shear is therefore the first step toward addressing the industrial problem and is precisely the goal and outcome of this project.

Given a line component and its operating conditions, the proposed workflows allow estimation of the mean shear stress and fluid dynamics analysis. In the future, a coupling of CFD with experiments could facilitate even more targeted controls on product stability.