// Fill & Finish of **complex biologicals** – **individualized** Processes. ///

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## Fill & Finish of complex biologicals – individualized Processes

Fill & Finish is easily the most critical step of manufacturing. This decisive step when the product is filled into primary packaging has to be adapted to product characteristics, the matrix material and the final packaging. Contamination must be controlled and care must be taken concerning correct product dosing. Biologicals are more sensitive to environmental factors and shear stress than synthetics. Thus, the requirements in regard to the dosing system are more demanding. Bausch+Ströbel works with you to find the most suitable Fill & Finish solution.

## Biologicals – the gentle giants of the pharma industry

By their very nature, biologicals such as antibody-drug-conjugates or gene therapeutics are complex molecules. Their basis – proteins and/or nucleic acids – are finely tuned to be stable in our bodies. Using them outside of their environment poses several threats to their integrity.[1] When being filled, the product is in a very delicate state. Oxygen or water molecules may chemically react with biologicals, incorrect temperatures may speed up degradation. The force of being pumped through a needle creates shear stresses on the large molecules. These and other disruptive factors have to be tightly controlled. Shear stresses originate from fluid flow and interactions of molecules at interfaces.
The magnitude and duration of shear rates depends on velocity gradients within each solution, varying significantly among manufacturing steps. The highest shear forces arise during filling.[2] These stresses can result in fragmentation and/or aggregation of the product, visible as foam.

## Important factors to consider during Fill & Finish

Shear stress

Sterility

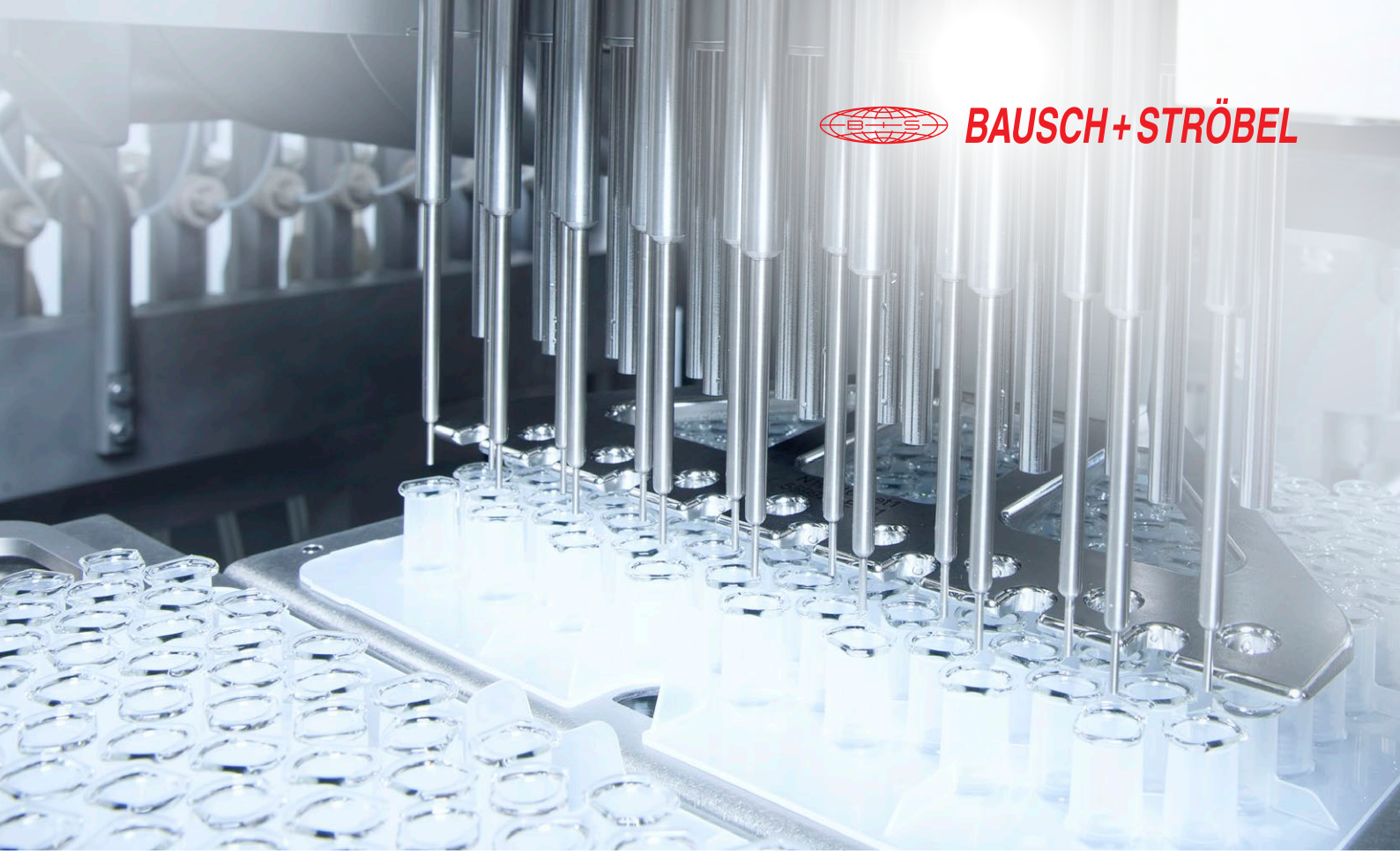
Temperature

Humidity

Oxidation /
Gas interaction

## Choosing the optimal dosing system

As well as being challenging to work with, biologicals also require speed. Biological drugs usually have to be processed within a 2–3-hour time frame due to their inability to withstand storage at room temperature. However, simply increasing the speed of the pumps comes with complications. Pumps have to be fast but gentle to protect the protein-based products from shear stress. Further critical factors are the viscosity and surface tension of the matrix material.[3] The commonly used rotary piston pump dosing systems are usually not the first choice. Time pressure and weighing dosing systems have a low shear force and allow product flow without dead space. Without any contact between the mechanical devices and the product, these pumps are in many cases a more suitable option.



## Barrier Systems

Fill & Finish stations are designed to diminish any contact between an active ingredient and the environment. This reduces the possibility of contamination and offers a controlled atmosphere for filling. Two different cleanroom technologies are available: the restricted airflow barrier system (RABS) and isolators.[4] Both systems are commonly used, but many companies are now opting for isolators, with increasing interest in closed isolators.

## Shutting out Contamination

Any contamination of biopharmaceutical products has detrimental effects on production costs, as the entire lot has to be destroyed. With ever more personalized medicines in small batch quantities, any delay due to contamination may lead to shortages for those relying on the drug. Contamination may be viable, non-viable (particular) or cross-contamination from other processed products. This is why cleaning steps must be adjusted correctly to the dosing system and primary packing, as well as the product. The future of Fill & Finish is greater flexibility. It may be necessary to dose two different drugs in one containment system with short set-up-times. Other options are disposable dosing systems and/or ready-to-use primary packaging. They require less time for sterilization and set-up but have to be replaced every time.

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## Personalized medications need personalized filling

For high value and high potency drugs, there is no “one size fits all” solution. Just as every drug has different specifications, the Fill & Finish process has to be adjusted to requirements – always in compliance with GMP-Guidelines.

## Pharma Service

As soon as a drug enters study phase II, the production of the finished product should be discussed. Bausch+Ströbel offers a service program for optimizing your drug production. Here, we will test the different filling mechanisms in trial runs and discuss suitable packaging early on. Together, we can find the filling solution that is best suited for your product.


**References:**

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[4] Denk, R. “Understanding the Impact of Annex 1 on Isolator Design,” Pharmaceutical Technology. 2020;44(11).



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# **Questions?** Let's talk!

If you would like more information about this topic please feel free to contact us.

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