

# COMPARISON OF ROBOTIC AND MANUAL RECONSTITUTION: STABILITY ASSESSMENT OF PROTEIN DRUGS IN HOSPITAL COMPOUNDING

I. CEDERWALL<sup>A</sup>, C. SABATÉ MARTÍNEZ<sup>B</sup>, U. ELOFSSON<sup>A</sup>, A. MILLQVIST FUREBY<sup>A,E</sup>, R. BAGHDARSARIAN NAMAGERDI<sup>C</sup>, B. FURTMANN<sup>D</sup>, C. SCHOENAU<sup>D</sup>, M. WAHLGREN<sup>E</sup> AND M. PAULSSON<sup>B\*</sup>

<sup>A</sup>RISE Research Institute of Sweden, Stockholm, Sweden, <sup>B</sup>Department of Women's and Children's Health, Uppsala University, Akademiska sjukhuset, SE-751 85 Uppsala, Sweden, <sup>C</sup>Hospital Pharmacy Compounding unit, Uppsala, Sweden, <sup>D</sup>Sanofi-Aventis Deutschland GmbH, Biologics Drug Product Development & Manufacturing, Industriepark Hoechst, K703, Brünigstr. 50, 65926 Frankfurt am Main, Germany, <sup>E</sup>Department of Food Technology, Lund University, P.O. Box 124, 22100 Lund, Sweden. \*mattias.paulsson@uu.se



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## Background and Importance

- Protein drugs are widely used in hospitals for treating cancer and immune diseases
- Manual reconstitution introduces risks of human error, variability, and handling stress on proteins<sup>1</sup>
- Silicone oil can be introduced from syringes or closed system transfer device

Automated reconstitution offers improved safety, and reduced workload. Studies suggest that robotic compounding provides comparable/improved quality compared to manual preparation<sup>2</sup>

### Why is this important for hospital pharmacists?


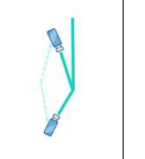
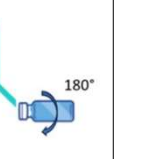

- ✓ Reduces risk of protein degradation
- ✓ Supports better patient safety

## Aim and Objectives

**Aim:** To evaluate automated vs. manual reconstitution of protein drugs and assess their impact on drug stability

**Objectives:** Compare **five reconstitution methods** (manual vs. four robotic programs)

## Materials and Methods

Fast program	Slow program	Wave program	Manual reconstitution
			
10 horizontal shaking movements Used for drugs that are difficult to dissolve	3 or 10 vertical shaking movements Used for drug that are sensitive to create foam	43 turns creating a wave movement along the vial walls Developed to avoid foaming and to completely wet the vial wall	Swirling movement Performed according to Summary of Product Characteristics (SmPC) Used as a control reference

### Protein drugs tested (supplied by EFPIA partners):

- A (Nanobody, liquid)
- B (Bispecific antibody, lyophilized)
- C (Nanobody, lyophilized)
- D (Bispecific antibody, lyophilized)

### Reconstitution methods compared:

- ✓ **Manual reconstitution** (Uppsala, Barcelona)
- ✓ **Robotic** Grifols Kiro Oncology (Fast, Slow3/10, Wave)

### Analyses performed:

- > Visual inspection for foaming & air bubbles
- > Dynamic Light Scattering (DLS) for nanometer particle distribution
- > Flow Imaging Microscopy for subvisible particles
- > Size-Exclusion Chromatography for aggregate formation and monomer loss

## References and Acknowledgements

- Cappelletto et al. J Pharm Sci 2024 DOI 10.1016/j.xphs.2024.05.027
- Geersing et al. 2023 J Pharm Sci DOI 10.1016/j.xphs.2023.10.015
- Eshraghi et al. Int J Pharm 2022 DOI 10.1016/j.ijpharm.2022.122210

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## Results

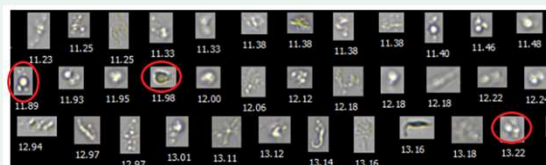


Fig. 1 Flowcam particle images of protein D fast program. Protein-D complexes in red circles. Area based diameter (µm) in white.

### Particle Formation:

- No clear advantage of one robotic method over another.
- Protein characteristics (formulation, vial design) mattered more than the reconstitution method

### Stability:

- No major impact on protein aggregate formation and monomer loss was seen across different methods
- Wave-based reconstitution showed slightly gentler handling

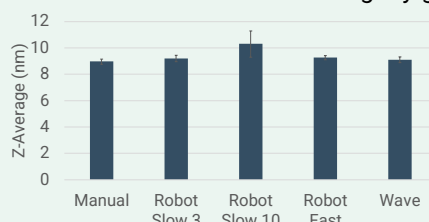


Fig. 2 DLS Z-average of Protein D reconstituted using different protocols. n=3

For challenging drug formulations, where lyophilizates form a gel-like cake on the vial wall, verifying dissolution without visual inspection is challenging. Fully automated robotic systems may struggle with these formulations

## Conclusion and Relevance

- ✓ Automated reconstitution is a viable alternative to manual preparation in hospital settings
- ✓ Protein formulation and vial design impact stability more than reconstitution method. The volume of the injection solution relative to the container may cause sloshing, leading to air entrainment and potential hydrodynamic stress on the drug solution previously seen in syringes<sup>3</sup>
- ✓ Silicone oil can be introduced from siliconized rubber membranes during IV preparation. Keeping vials upright minimizes this risk manually but is not feasible in robotic systems. However, this contribution may be negligible compared to the syringe plunger and CSTD

What does this mean for hospital pharmacists?

- ◆ Robotics may improve safety and efficiency in aseptic drug preparation
- ◆ Possibility to choose reconstitution methods based on protein formulation factors
- ◆ Further optimization and training are required for robotic systems in hospital pharmacies

