# Stability Evaluation of a Therapeutic Antibody Following Delivery by an Instantaneous Injection Device

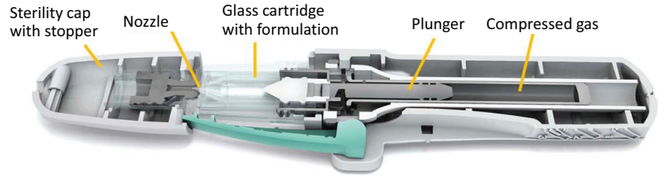
C. Howland[1], T. Petrel[1], C. Barden[1], B. Kaseman[1], A. Logan[1], H. Ziegler[1], A. Heintz[1] and B. Boyd[2]; [1]*Battelle*, [2]*Zogenix*

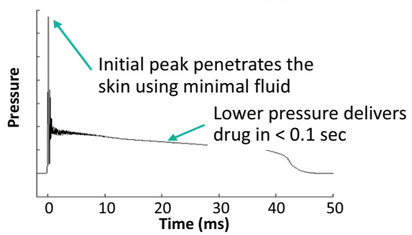
## ABSTRACT

Transitioning protein formulations to injection devices requires addressing challenges associated with delivering high concentrations of high molecular weight molecules in a manner that is easy, reliable, and minimizes risk to the patient. We are exploring adaptations to traditional, as well as new delivery devices, to enable high viscosity or high volume delivery. In addition, we are examining the impact that these devices have on protein structure.

## APPROACH

- An instantaneous injection device, DosePro® (Zogenix, Inc.), has been compared to traditional syringe delivery to determine the impact of the injection event on the stability of the anti-inflammatory biological therapeutic adalimumab (Humira®)‡.
- The DosePro (DP) device is a instantaneous injection system designed to maximize **ease of use** and patient compliance. In less than **1/10th of a second**, it can deliver 0.5 mL of a highly **viscous** payload (up to 1000 cP) targeted to the **subcutaneous** tissue without the hazards of needle handling and without the complexity of syringe injection.




- **Upon pressing the uncapped DosePro against the skin, the device drives the liquid formulation out of the integral nozzle and through the skin in < 1/10th of a second.**
- **A biphasic pressure profile is generated within the cartridge.**
  - The initial peak pressure emits a small stream of liquid formulation through the nozzle, piercing the skin.
  - This is immediately followed by a liquid stream at a lower delivery pressure, depositing the remaining liquid formulation into the subcutaneous space.

- Proteins are known to be destabilized by interfacial stress. Structural alterations in biological therapeutics can reduce efficacy and result in an adverse immune response.
- Adalimumab is a fully human recombinant immunoglobulin G1,anti-TNF-α monoclonal antibody that has demonstrated efficacy and FDA-approval for the treatment of rheumatoid arthritis. Vendor-recommended delivery is by pre-filled syringe (PFS) injection through a 27-gauge needle.
- Standard characterization techniques, such as size exclusion high performance liquid chromatography (SEC-HPLC), dynamic light scattering (DLS), and a tumor necrosis factor-alpha (TNF-α) bio-assay were used to measure the extent of adalimumab damage by each delivery method.

‡Humira is a licensed trademark of Abbvie

## RESULTS

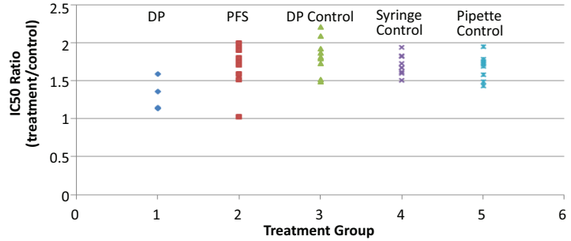
### Study Design

Adalimumab was used as received (50 mg/mL @ ~ 1 cP) in the commercial formulation and was delivered into buffer by each device to minimize the air-liquid interface. All studies were performed in triplicate.

| ID | System | Description |
|---|---|---|
| 1 | DosePro | Compressed gas delivery of adalimumab through parafilm into buffer. |
| 2 | PFS | Manual delivery of adalimumab through 30 gauge, ½ inch needle directly into buffer. |
| 3 | DosePro Control | Manual delivery of adalimumab from the DosePro subassembly into buffer. |
| 4 | PFS Control | Manual delivery of adalimumab through PFS without needle directly into buffer. |
| 5 | Pipette Control | Manual delivery of adalimumab by pipette directly into buffer. |

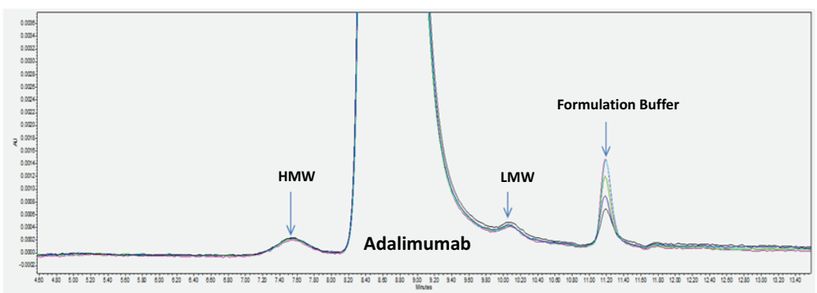
### Full Recovery of Adalimumab TNF-α Neutralization Activity Following Instantaneous DosePro Delivery

By ratio paired t-test, no statistical differences in adalimumab *in vitro* biological activity was observed across treatment groups.



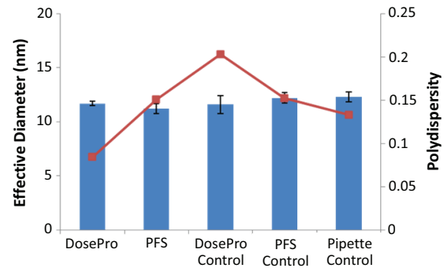

### No Change in High (HMW) and Low Molecular Weight (LMW) Adalimumab Species Was Observed Following Instantaneous DosePro Delivery

By SEC-HPLC, the major peak contributed to > 99% of the total adalimumab peak area following delivery by either PFS or DosePro device. All study conditions (ID 1-5) are shown as overlay plots.




### Adalimumab Effective Diameter and Intensity Distribution Was Largely Unchanged Following Each Treatment

Adalimumab was relatively monodisperse and centered around 13 nm for all study conditions.




### DosePro Provides Reduced Shear Residence Time for the Adalimumab Dose

Although the calculated shear rate was greater for the DosePro device, the time in shear flow for the adalimumab dose was markedly less than that of the PFS. Previous studies have suggested shear residence time to be a key element of IgG aggregation (Biddlecombe et al., 2007).

| System | Shear Rate (s-1) | Delivery Time (s) | Time in Shear (µs) |
|---|---|---|---|
| DosePro | 1.64e6 | 0.045 | 8.1 |
| PFS | 8.45e5 | 1.5 | 760 |

## CONCLUSIONS

- Adalimumab delivery by the DosePro instantaneous injection device did not yield measureable size differences indicative of aggregates or fragments.
- No statistical differences in neutralization of TNF-α cytotoxic activity was observed between DosePro and control groups.
- All results were comparable to adalimumab delivery by PFS.
- Shear flow calculations indicate near equivalency between DosePro and PFS.