Shocking Data On Parcel Shipments of Protein Solutions

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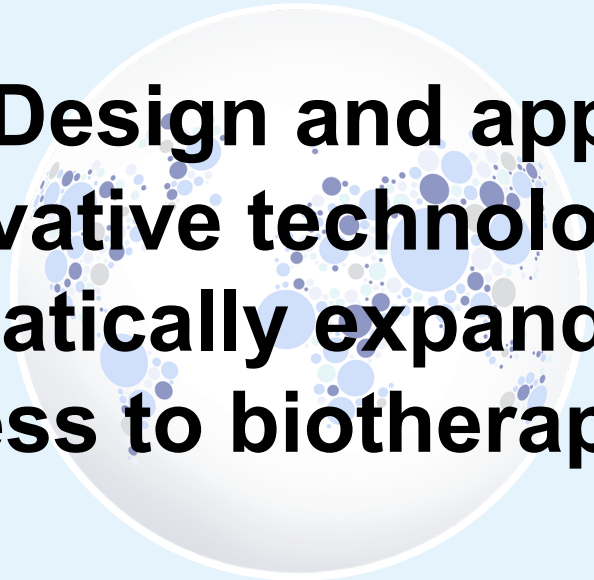
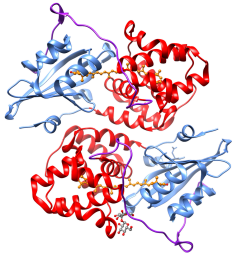
The Just Mission

There are many ways to help expand global access

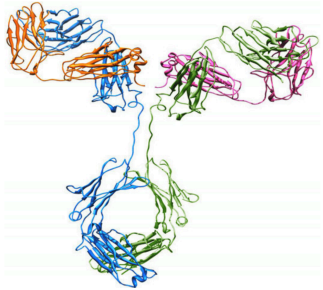


Design and apply innovative technologies to dramatically expand global access to biotherapeutics

The goal of our transportation studies



Develop a relatively quick, low-cost study for early formulation development that is predictive of transportation stability



Early formulation studies focus on storage

Conformational and colloidal stability

- Thermal analysis
- Chemical induced unfolding
- Shaking/vortexing studies
- pH jump studies
- PEG induced ppt
- K_d or B_{22} analysis
- Viscosity

Platform Storage Conditions

- Frozen
- Liquid
- Lyophilized

Quiescent storage at -70°C, -20°C, 4°C, 30°C and 40°C

Freeze/Thaw

In Use

Transportation studies tend to be excluded during IND-enabling formulation development

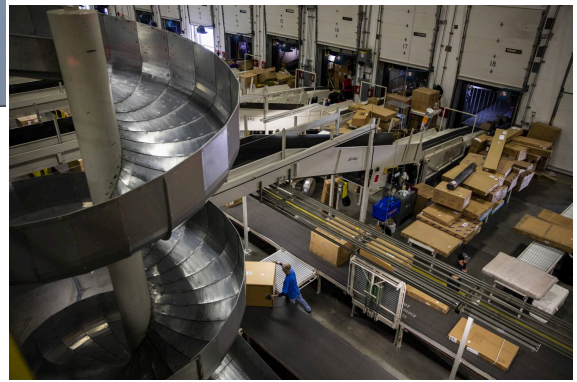
Companies are moving towards refrigerated liquid formulations for Phase 1

Multiple stresses occur during transportation of DP to the clinical sites

- Spring shock trucks
- Air ride trucks

- Air transport produces vibration, shock and air pressure change

- Hand delivery to the doctor, pharmacy, patient

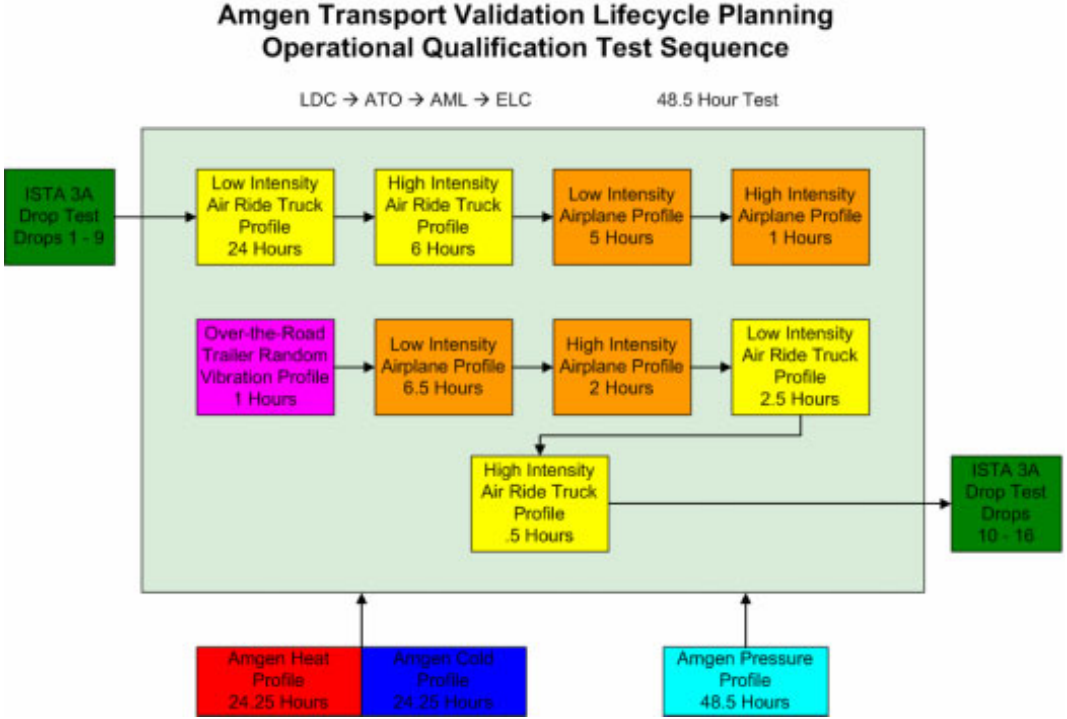


- Package sorting warehouse can produce shock exposure

http://2.bp.blogspot.com/_hh3EcdMAlg4/TRNFxs-W3dI/AAAAAAAABVE/iBc-R_dsTa8/s1600/Delivery-Truck.jpg
https://linkglobal.com/airfreight/

A well-planned transport simulation study

Vibration, shock, temperature, air pressure



A validated transportation study is necessary for commercialization, but is not always practical for early development

- Small companies won't have these facilities on site
- Speed is critical, these studies can be time consuming
- Scheduling with contractors may be logistically difficult
- For emerging companies, cost is an issue and is difficult to justify for a small number of samples

Brian Wallin, International Safe Transit Association: PreShipment Testing Newsletter, 2007, 4 Quarter

Recent technology made low-cost refrigerated shipping and monitoring feasible

Temperature control
- Nano Cool™ System

Monitoring
- SenseAware® device

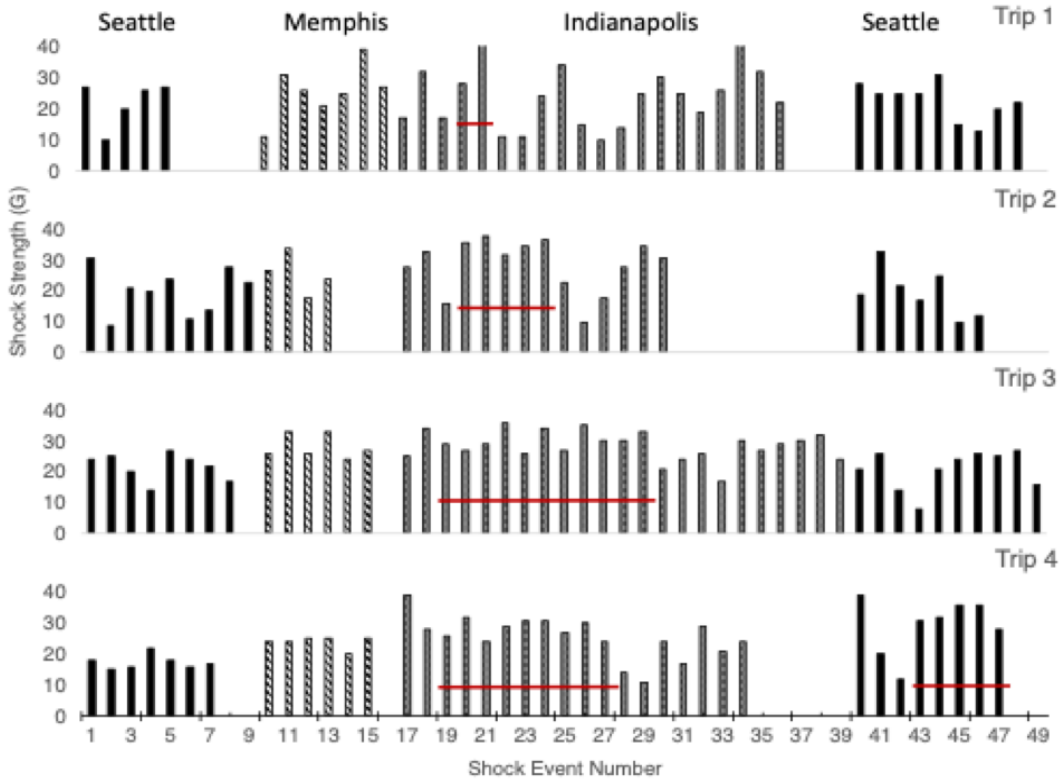
- temperature
- humidity
- barometric pressure
- g-shock
- light exposure

Combining these systems allows us to ship a small set of samples while maintaining temperature control and monitoring multiple aspects of the shipment

Monitoring results of shipments

Bumper drop test completed at mid-point of journey by Paul Harber

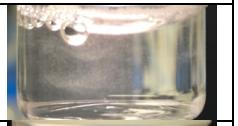
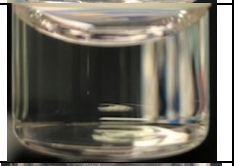
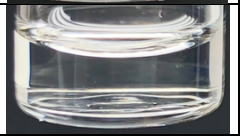
Consistent shocks occurred during each shipment



- 4 different shipments were sent to Indianapolis and back
- Samples were purposely dropped the box 10 times before shipping back to Seattle
- Likely not all drops are being captured if they are occurring too close together
- Over the 4 shipments, 40-50 shocks were registered during each trip
- Shock values range from 10g – 40g with an average of 25g
- All shocks have a gps location

Drop shocks alone show visible particles

The particles appear distinctly different from those particles observed when shipped

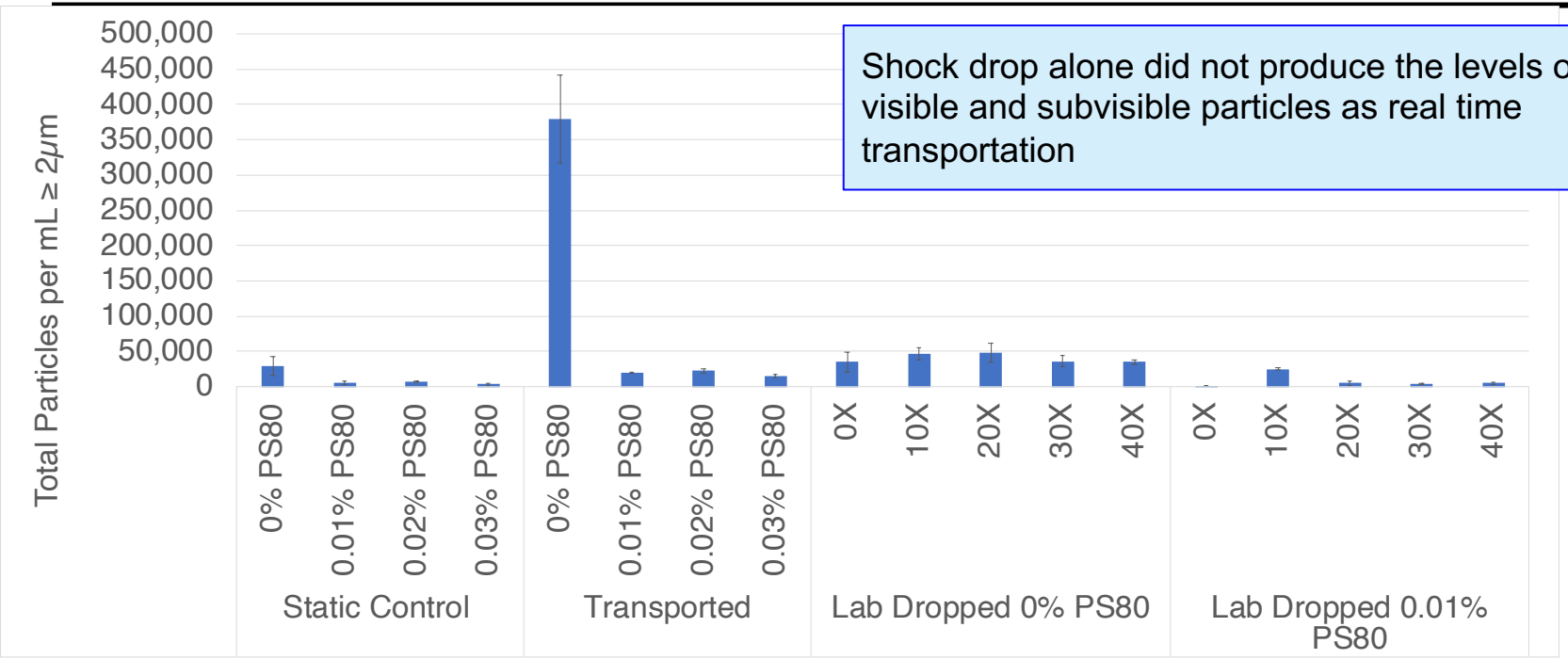
Sample Name	Shipped	Lab Dropped	Number of Particles	Picture
0% Polysorbate	+	-	TMC	
0.01% Polysorbate	+	-	0	
0% Polysorbate	-	+	TMC	
0.01% Polysorbate	-	+	0	

<u>Shipped</u>
Visible particles show a cloudy appearance

<u>Drop only (40X from18 inches)</u>
Visible particles show a more discreet appearance

Drop shocks did not fully simulate subvisible particles

Submicron particles ≥ 2µm by Flow Cam

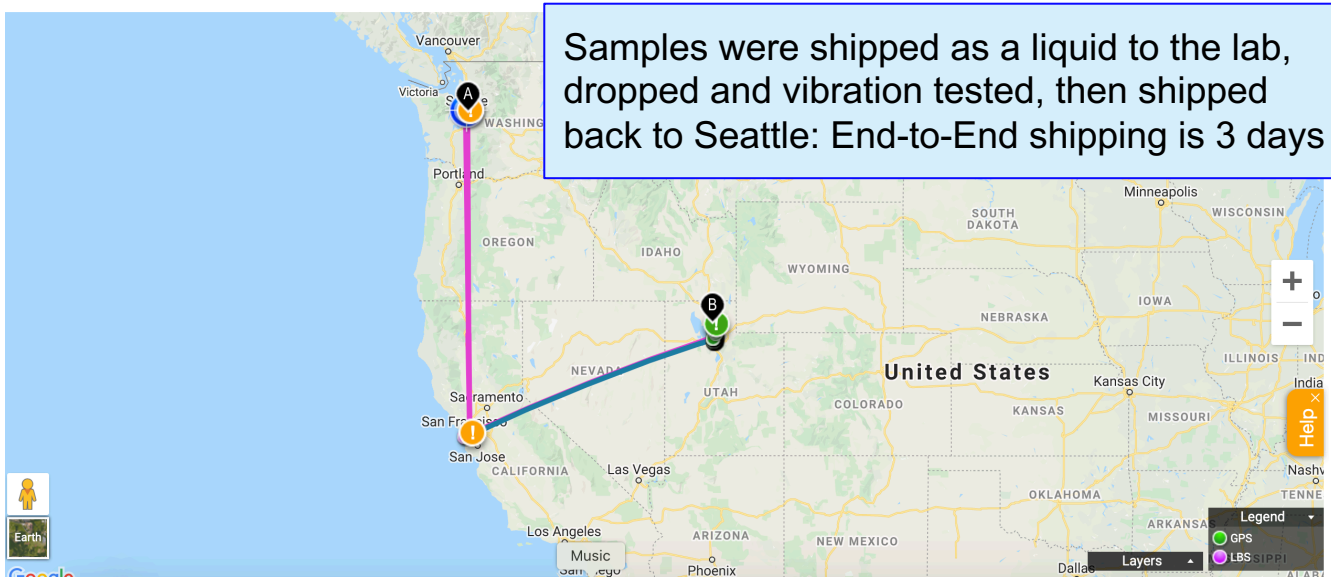


Shock drop alone did not produce the levels of visible and subvisible particles as real time transportation

100mg/mL mAb
10mM Acetate
pH 5.2
9% Sucrose
+/- Polysorbate

Shipping study developed using a testing lab

- Sample shipped to Rocky Mountain Testing Solutions in Utah and back to Seattle



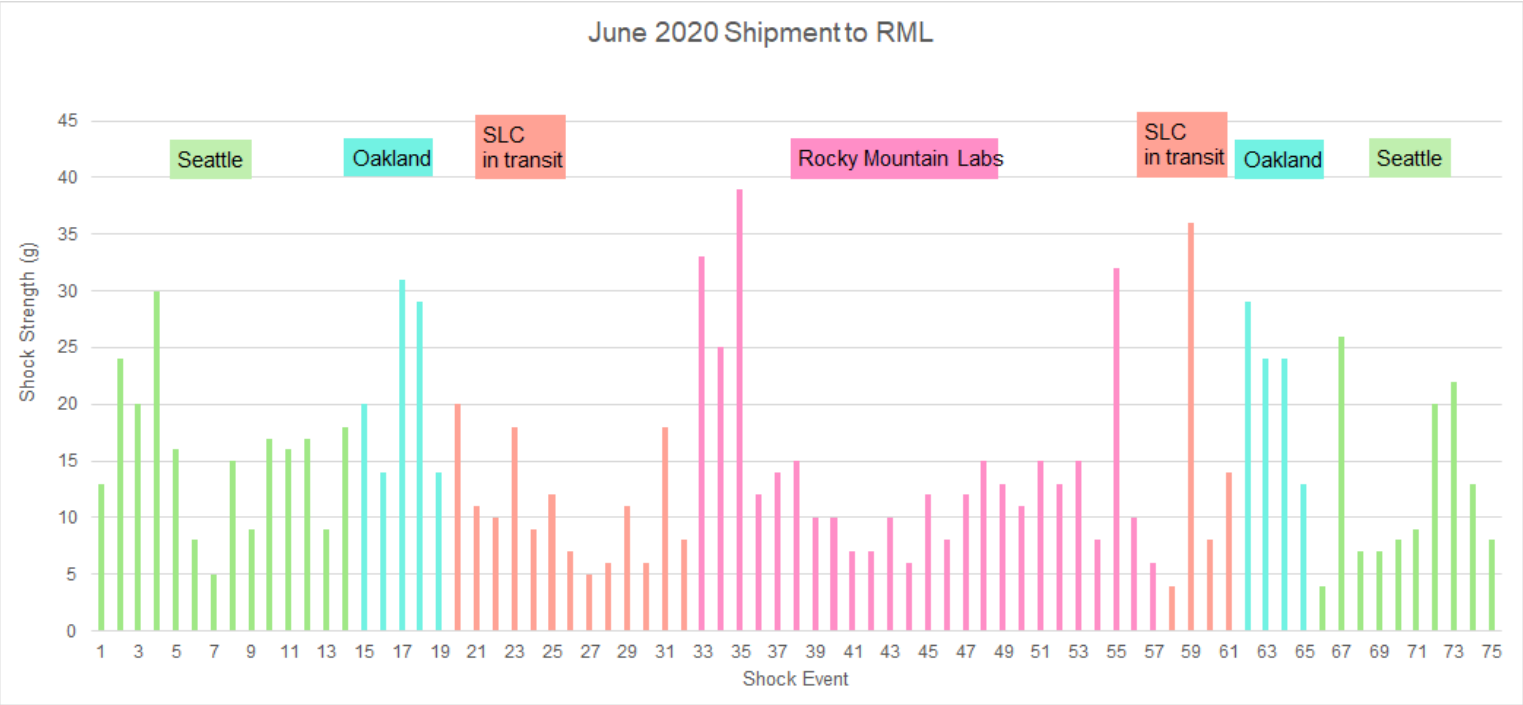
Drop and vibration performed at RMTS

- Drop Testing
  - 16 drops at 15”
- Rotary Vibration
  - Placed bottom down, 222 RPM for 20 mins. Box then rotated 90 degrees at 190 RPM for 20 mins.
- Vehicle Vibration Simulation
  - Total of 3 hours of vibration
    - 40 mins at low vibration, 15 mins at medium vibration, 5 minutes at high vibration
    - 2 hours air vibration at assurance level II
- Drop Testing
  - 5 drops at 15”, 1 drop at 30”

Photograph 4. 1st Sequence - Drop 4 - Setup.

Photograph 8. Loose Load Setup Rotated 90° Setup.

Similar shock patterns observed in shipments to Utah and Indiana

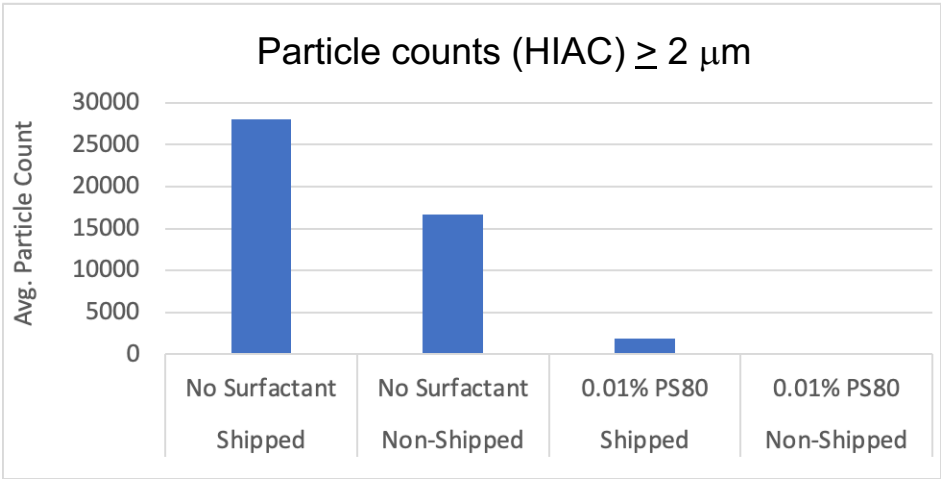


Results similar to prior observations

mAb was at 100 mg/mL in acetate/sucrose/+/- surfactant/ pH 5.2

NO Surfactant

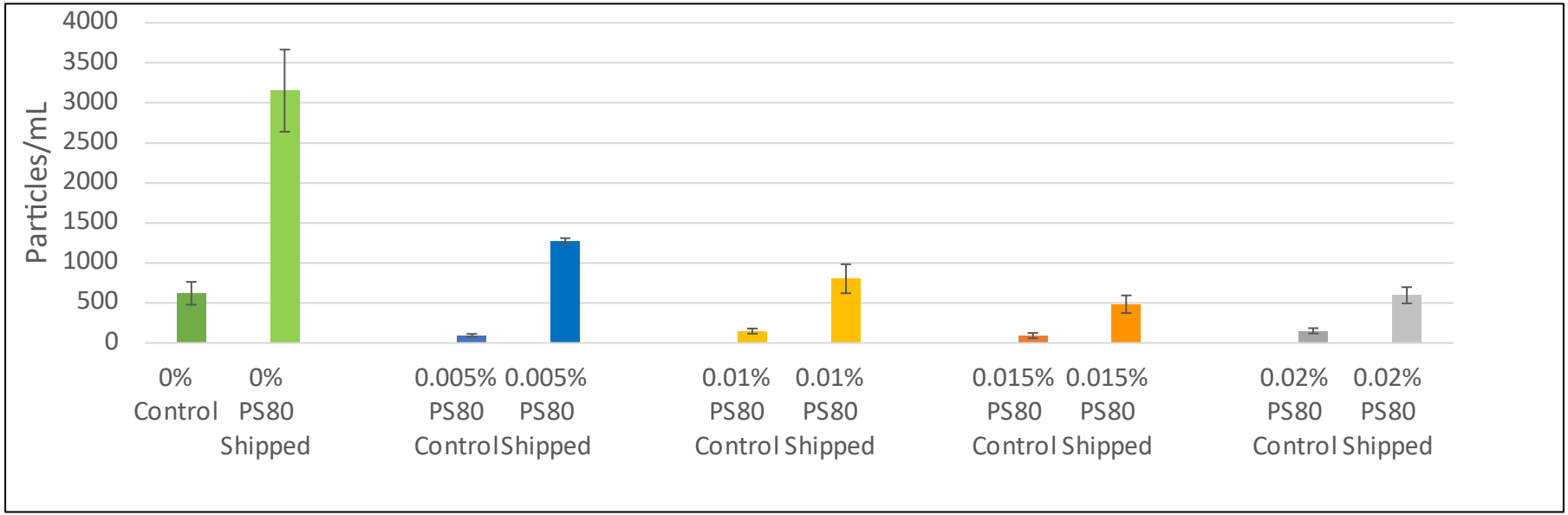
0.01% PS80



- Without polysorbate this mAb particulates under static conditions

Shipping study can be used for defining the amount of polysorbate in a formulation

Particles greater than **2µm** before and after shipping



Conclusions

- Early readout of transportation induced degradation would be helpful for determining an appropriate formulation
- Shipping using domestic shipping routes show particle formation in samples without polysorbate and a severe reduction in particle formation in the presence of polysorbate
- Monitoring of real time transportation along 2 different routes showed consistent shock events between 10g and 40g occurring in domestic travel
- Lab drops (up to 40) did not fully replicate real time transportation particle levels suggesting that a combination of shock and vibration is needed for evaluation of transport stress
- Domestic shipping studies appear to be an adequate quick, low cost read out of transportation stress allowing us to set polysorbate levels during early formulation development

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