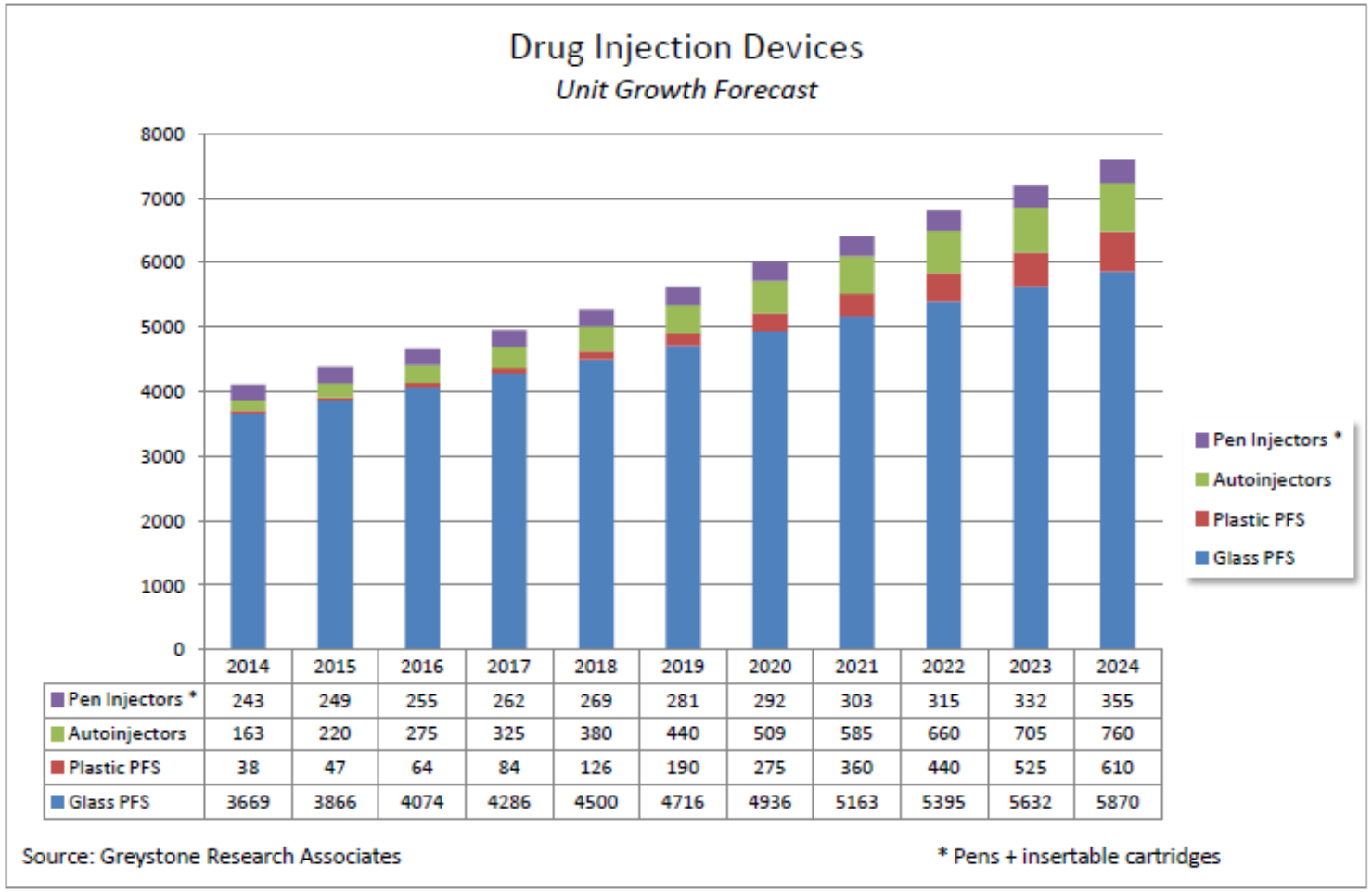
Successful Drug Delivery Requires an Integrated Approach

Tibor Hlobik, Sr. Director Product Management

Content

- Market trends and the landscape of device options.
- Primary component and container selection is critical for delivery system suitability.
- Challenges and considerations for higher dose volume drug products.
- Development activities between a Pharma company and device partner.

Global Injectable Drug Market Overview



	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Pen Injectors *	243	249	255	262	269	281	292	303	315	332	355
Autoinjectors	163	220	275	325	380	440	509	585	660	705	760
Plastic PFS	38	47	64	84	126	190	275	360	440	525	610
Glass PFS	3669	3866	4074	4286	4500	4716	4936	5163	5395	5632	5870

Source: Greystone Research Associates

* Pens + insertable cartridges

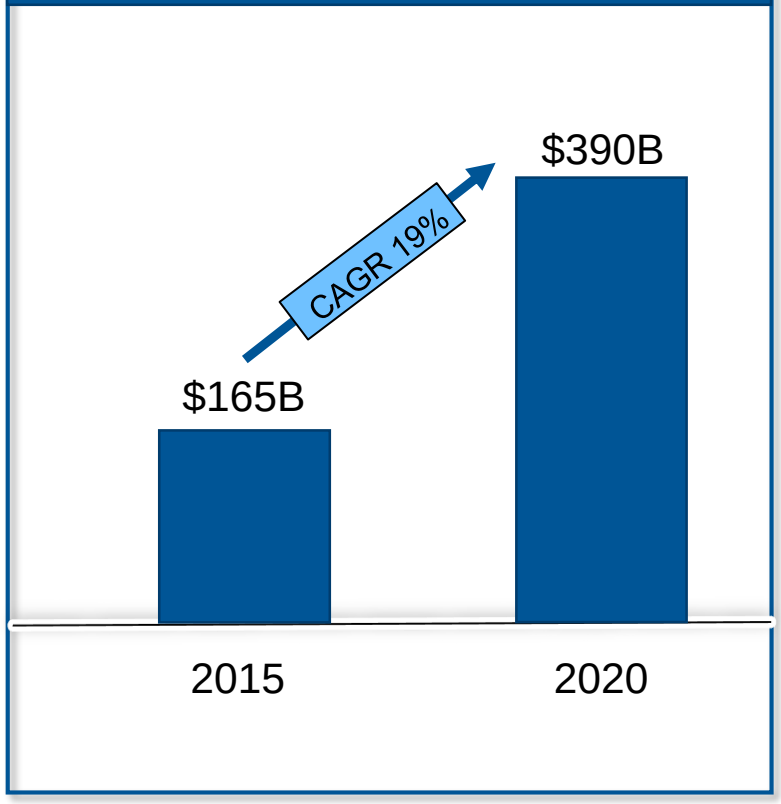
Plastic=polymer
COP/COC

Effective Drug Delivery Trends…

- Transferring responsibilities and point-of-care
  - Hospital → Clinic → Home (self administration)
  - Healthcare professional → patient or caregiver
- Increasing number of biologics
  - Increasing competition
  - Crowded therapies
  - Biosimilars
- Patient needs are more critical
  - Ease of use/usability/Convenience
  - Compliance and Adherence
- Drug complexity
  - Increased viscosity, sensitivity, concentration and dose volume

The landscape for Biologics shows significant growth compared to other segments

Sales of Biologic drugs are expected to exceed $390B in 2020, and represent 28% of all pharmaceutical sales (currently 20%)



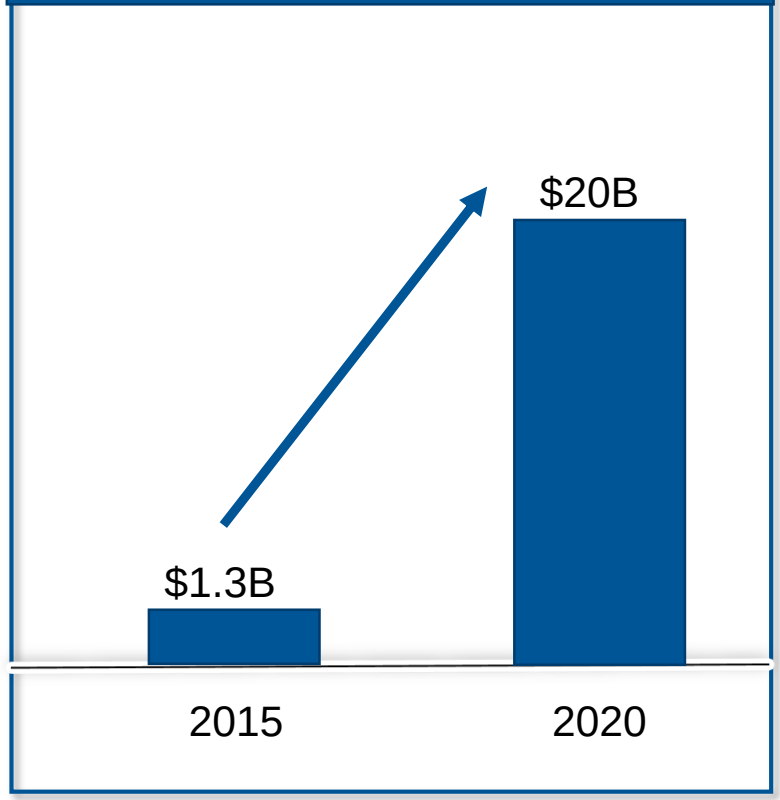
Source: IMS, March 2016. “Delivering on the promise of biosimilar medicines”

8 of top 10 drugs are Biologics, compared to 3 in 2010

		2015 sales ($B)
abbvie	Humira	14.4
GILEAD	Harvoni	13.9
AMGEN	Enbrel	9.1
janssen	Remicade	9.0
Roche	Rituxan	7.3
SANOFI	Lantus	7.1
Roche	Avastin	6.9
Roche	Herceptin	6.8
Pfizer	Prevnar	6.2
Celgene	Revlimid	5.8

Source: MedAd news annual report Aug 2016

Biosimilar products will take an increasing market share over the coming years

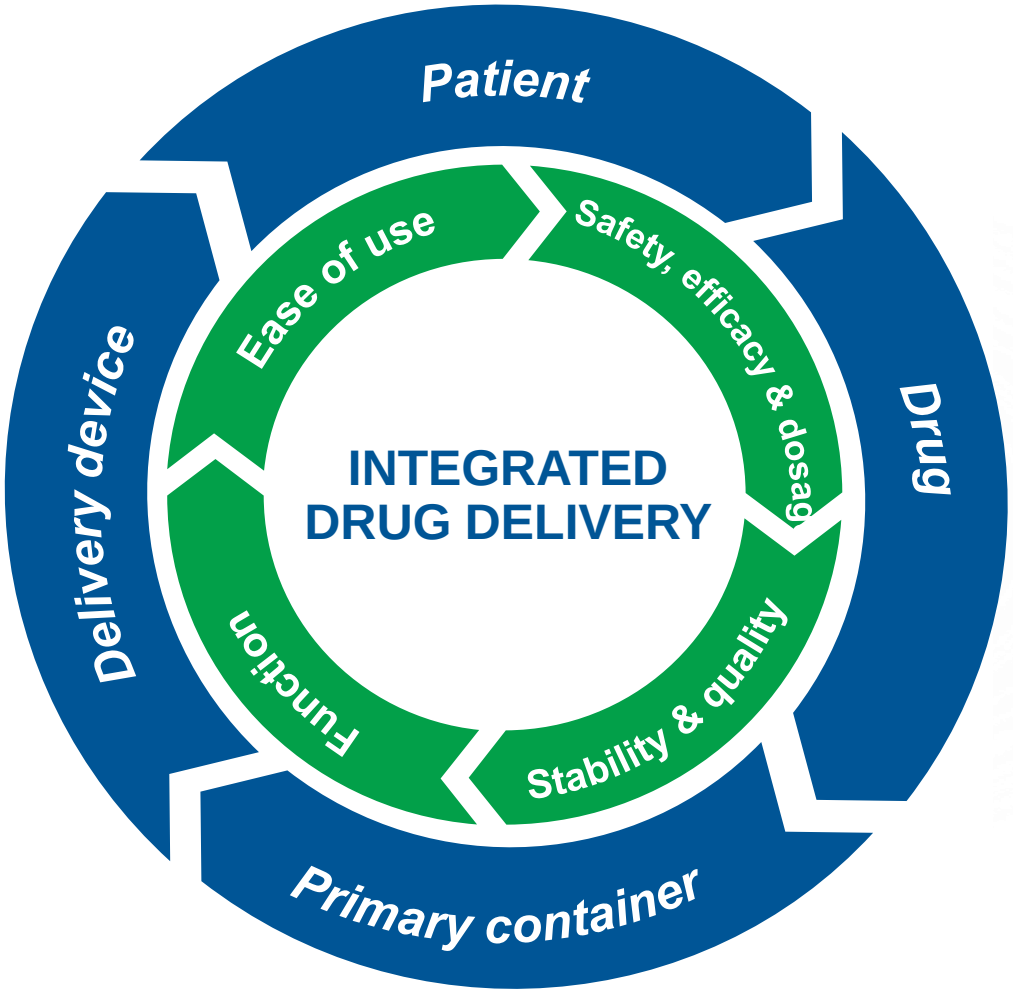


Source: IMS, March 2016. “Delivering on the promise of biosimilar medicines”

Biologics Market Trends

- **Continuing to grow faster than other segments**
  - Strong pipeline, multiple companies, advent of biosimilars, new therapies (Cell/Gene)
  - Majority of biologics require injection
- **More sophisticated biologics drugs**
  - Larger molecules = higher concentration = higher dose volume or viscosity
  - Increased sensitivity: Extractables/leachables, Silicone Oil, Particles
- **Increasing focus on Patient Outcomes and safety**
  - Adherence, Payment based on outcomes
  - Drive towards zero defects
- **Transitioning the point of care**
  - Hospitals > Clinics > Home (Trained professional > Patient)

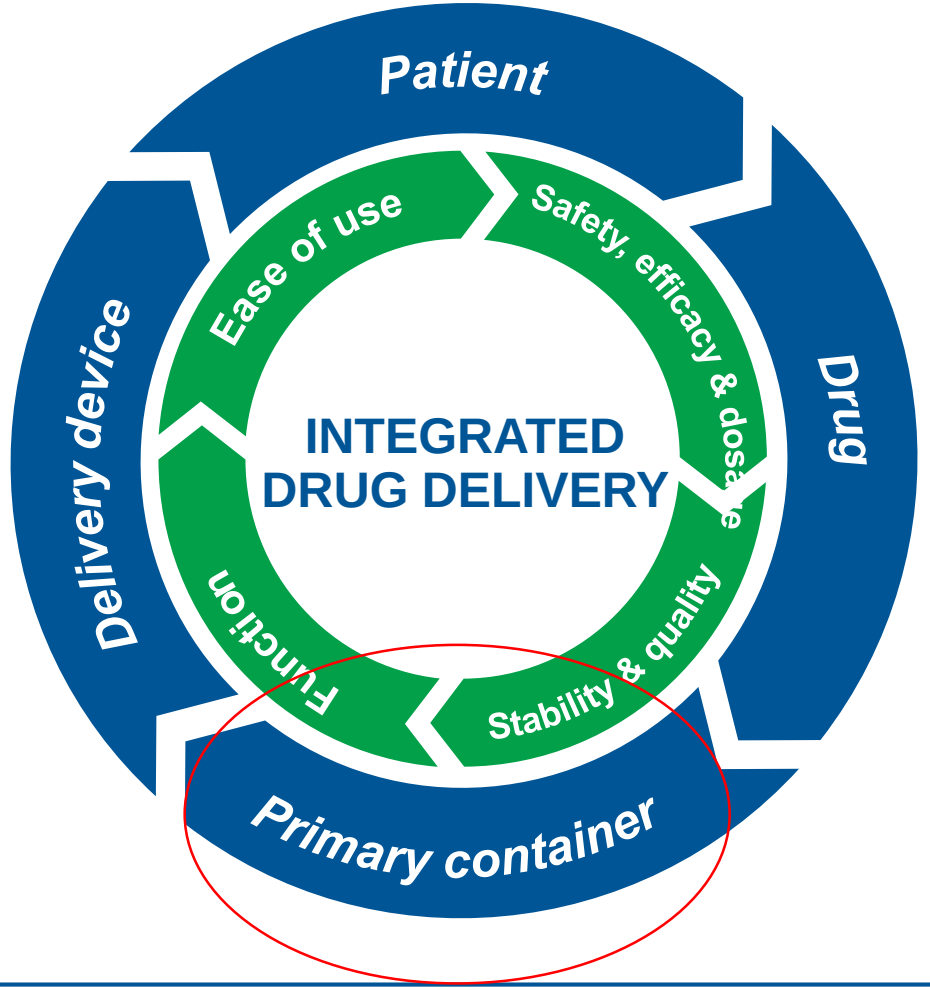
Successful Drug Delivery requires an integrated approach to 4 key elements…..



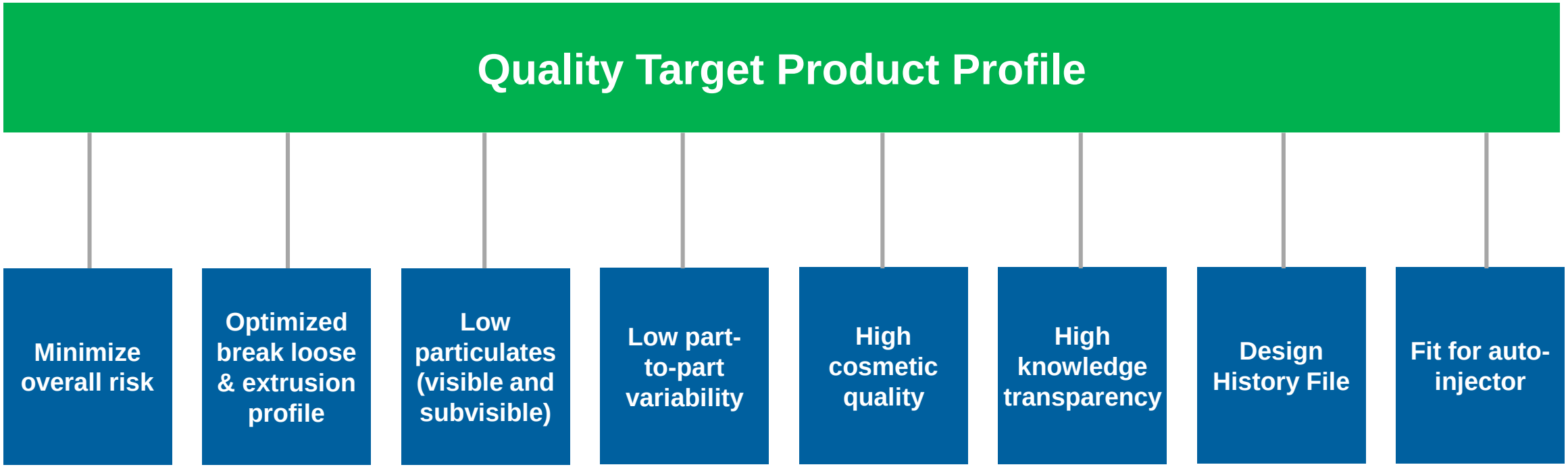
A drug can only be truly effective if……

- It is contained in a way which maintains quality and effectiveness over time
- It is prepared and administered effectively by the person(s) necessary for administration
- The drug container is combined with a device (where needed) which is easy to use, safe and effective and provides optimum performance
- The patient maintains adherence to the appropriate regimen

Why Containment Matters

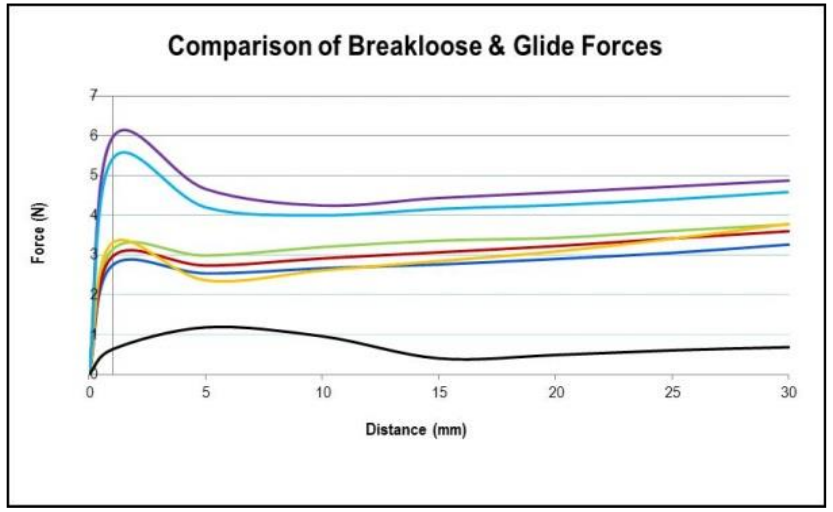


Patient Needs Drive Plunger Component Target Profile

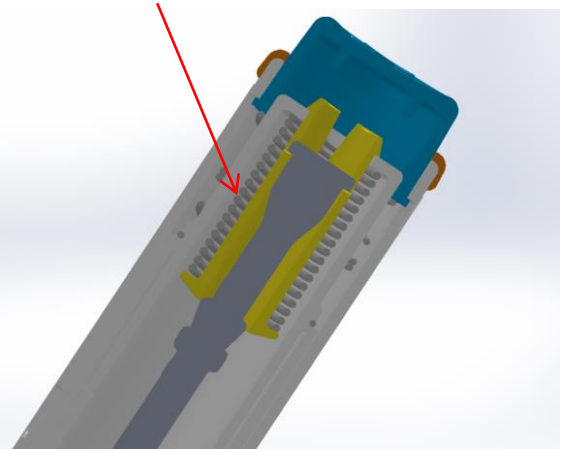


Managing Performance Risk in Autoinjectors

- If injection times vary between doses or device stall:
  - Patients may stop injection before complete
  - Patients may question quality of the product



Injector Spring Mechanism

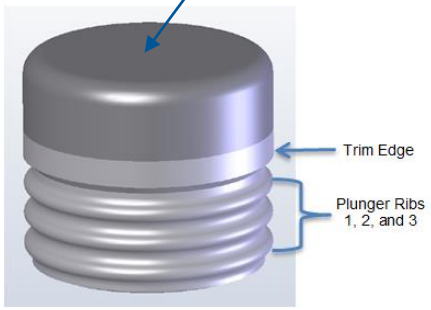


Quality by Design Fluro-laminated Film Plungers

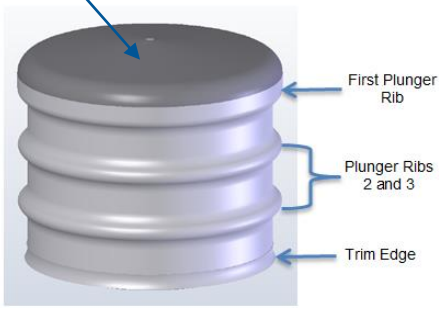
1-3mL **1mL long**

Film

Legacy Plunger



New NovaPure Plunger



Science Based Approach to Design

Design Benchmarks

2 Step Molded Styles

2 & 3 RIB

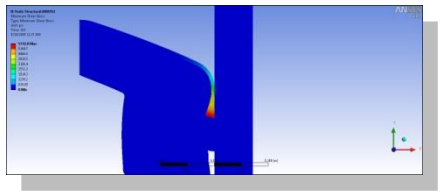
QbD Plan for Concept Development

- Defined design variables
- Established DOE
  - Correlation of key attributes
- Fabricated cavities

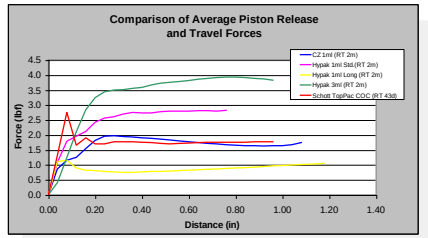
Design Characterization

- Define critical specifications

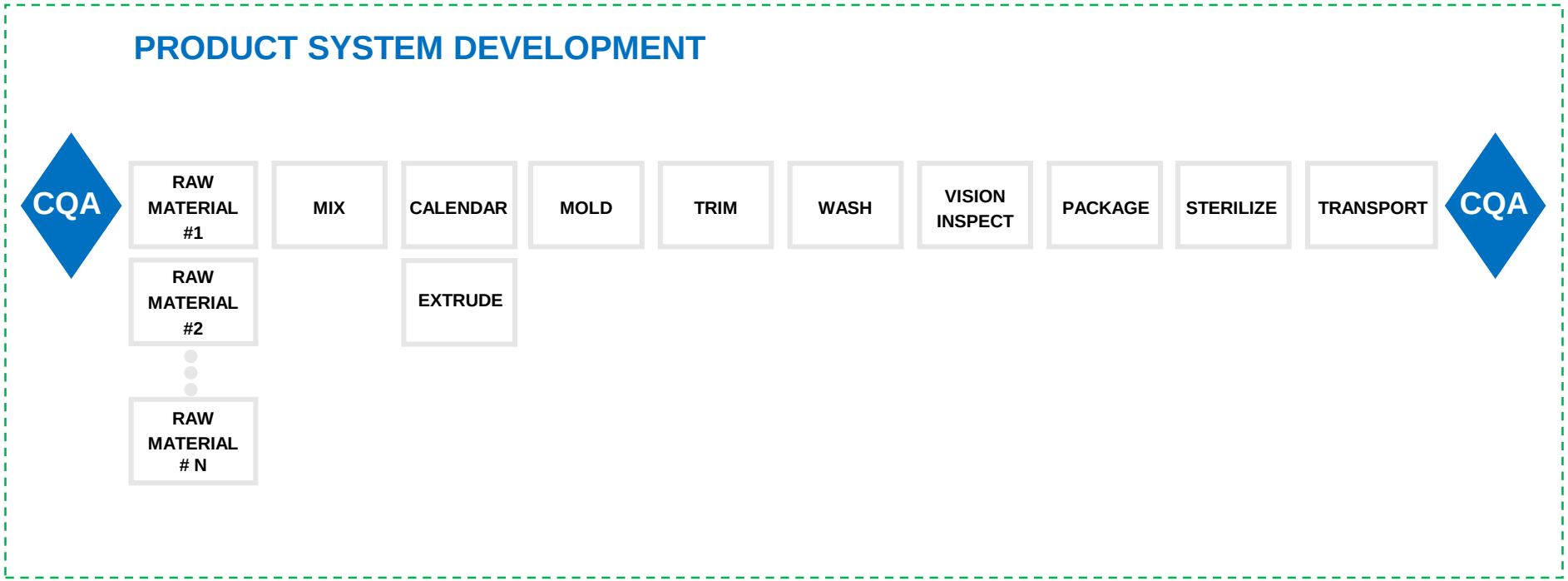
Engineering Models (FEA)



Break-Loose & Extrusion

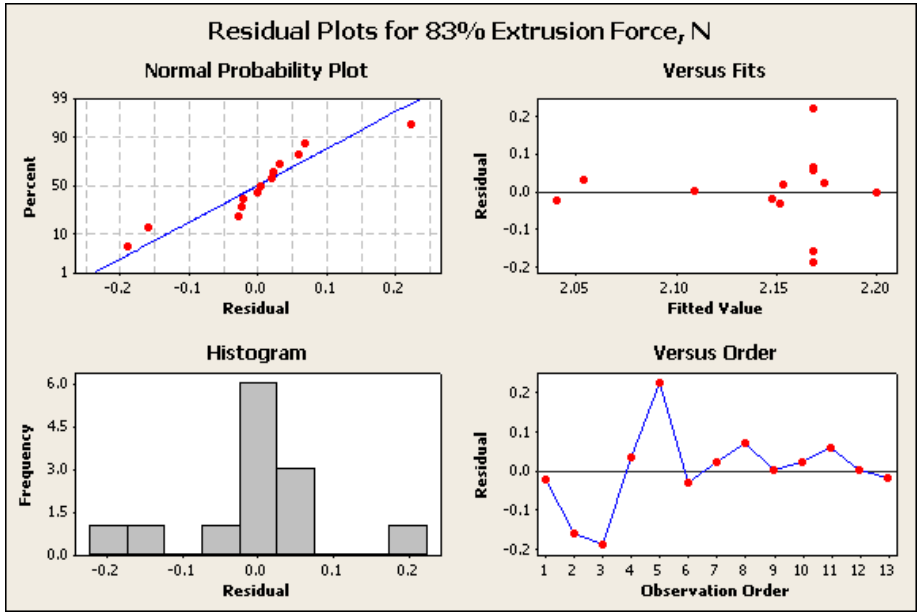


QTTP and CQA Definition are Inputs to the Process Mapping and First Phase of Development



Process Understanding Through DOEs

	Time	Temp	Time X Temp
Delta Force, N	0.935	0.943	0.402
17% Extr. Force, N	0.823	0.200	0.527
50% Extr Force, N	0.878	0.314	0.59
83% Extr Force, N	0.971	0.351	0.565

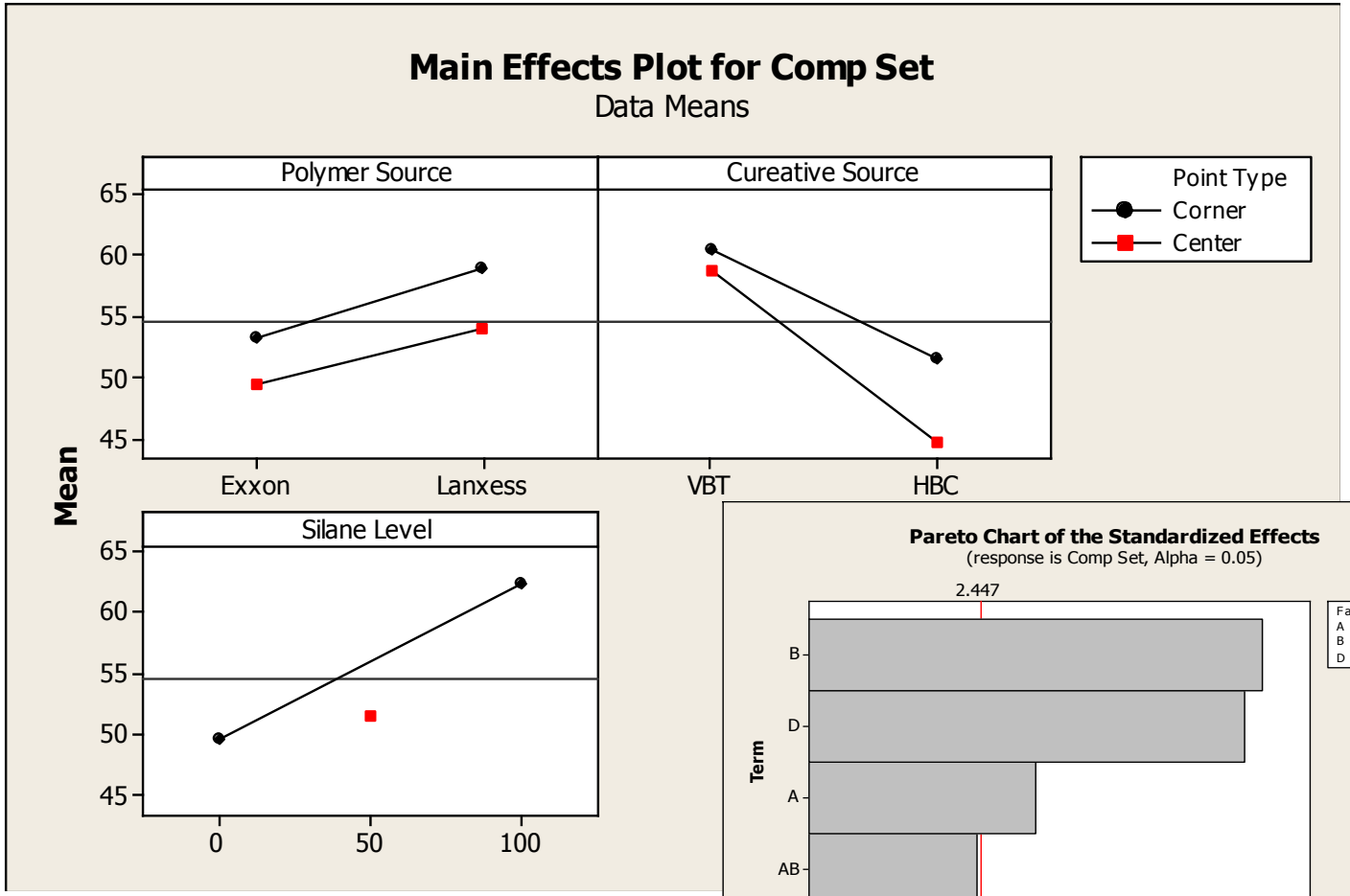


Understanding the implications of the curing process on extrusion force of a prefilled syringe plunger

Science Based Approach for Elastomer Ingredient Impact on Compression Set

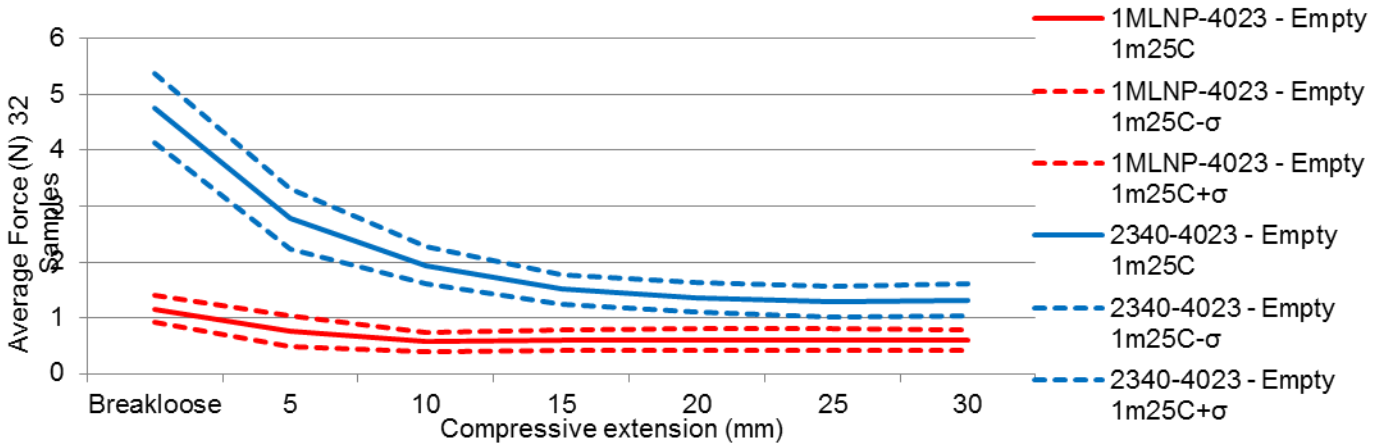
Selection of ingredients

Partial factorial design (2^4)

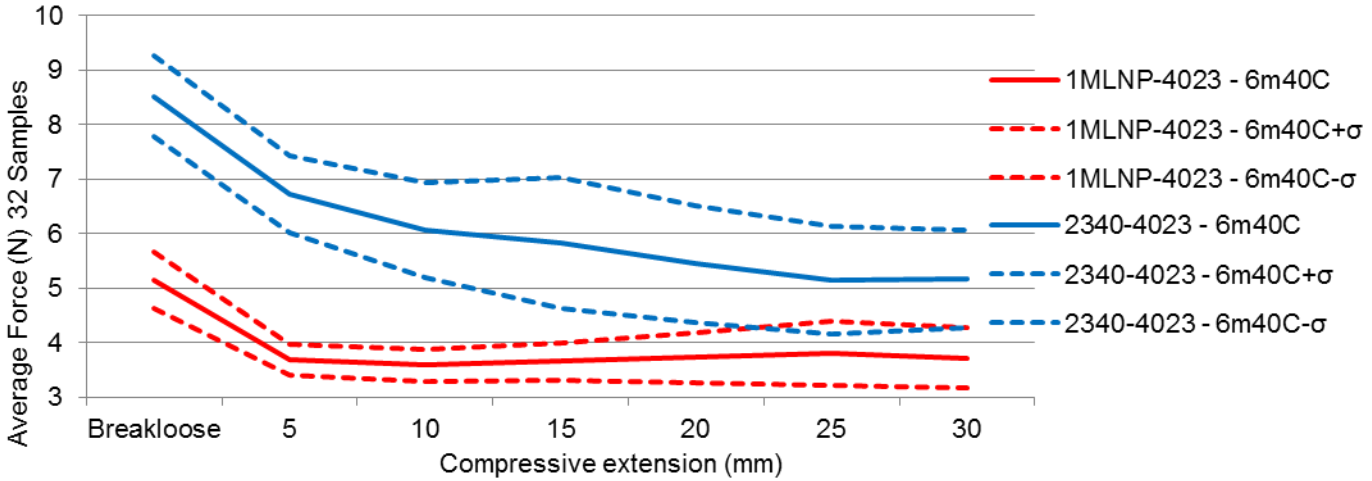


1ml long Statistical Performance Output

Empty

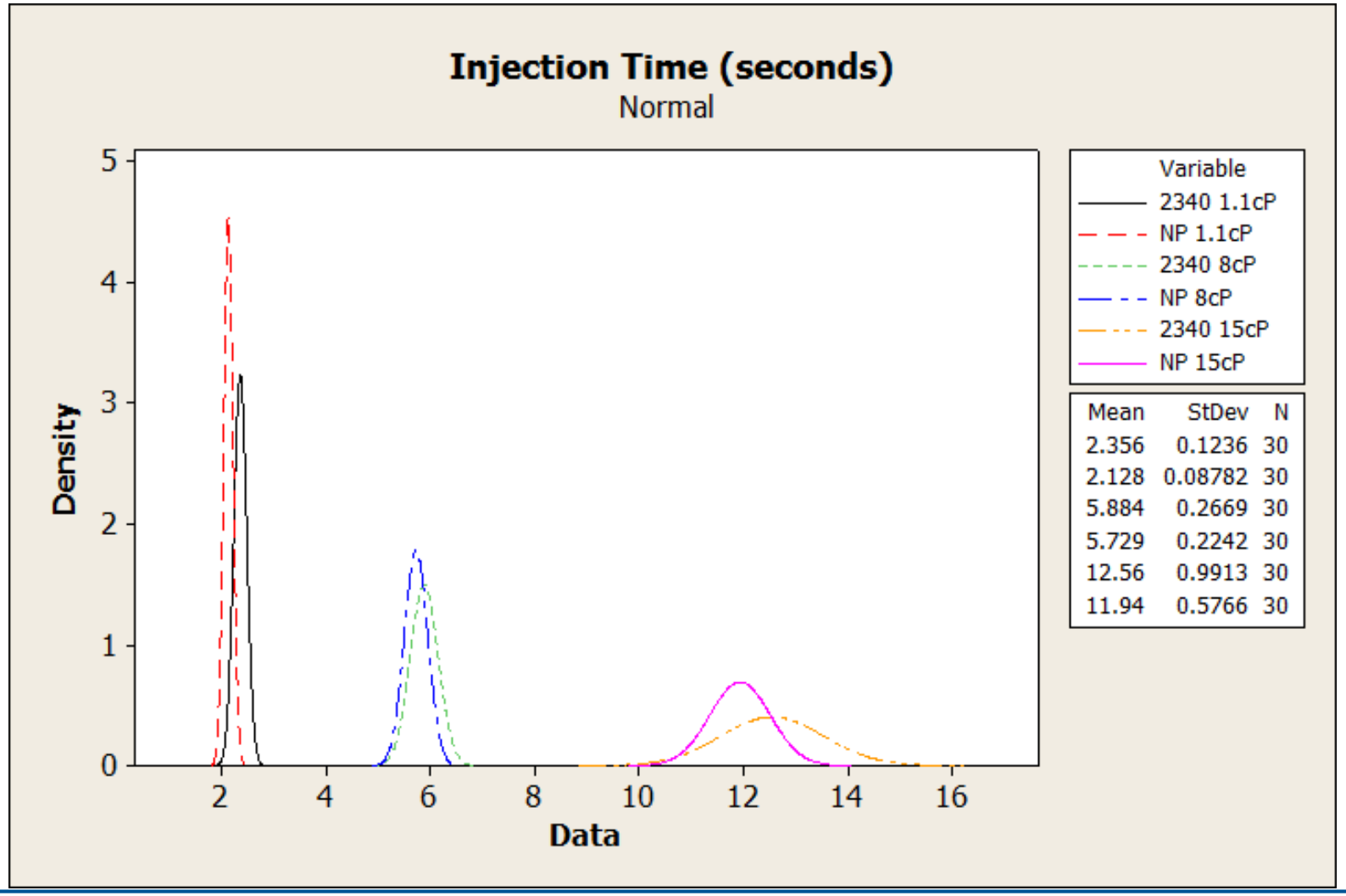


Water Filled



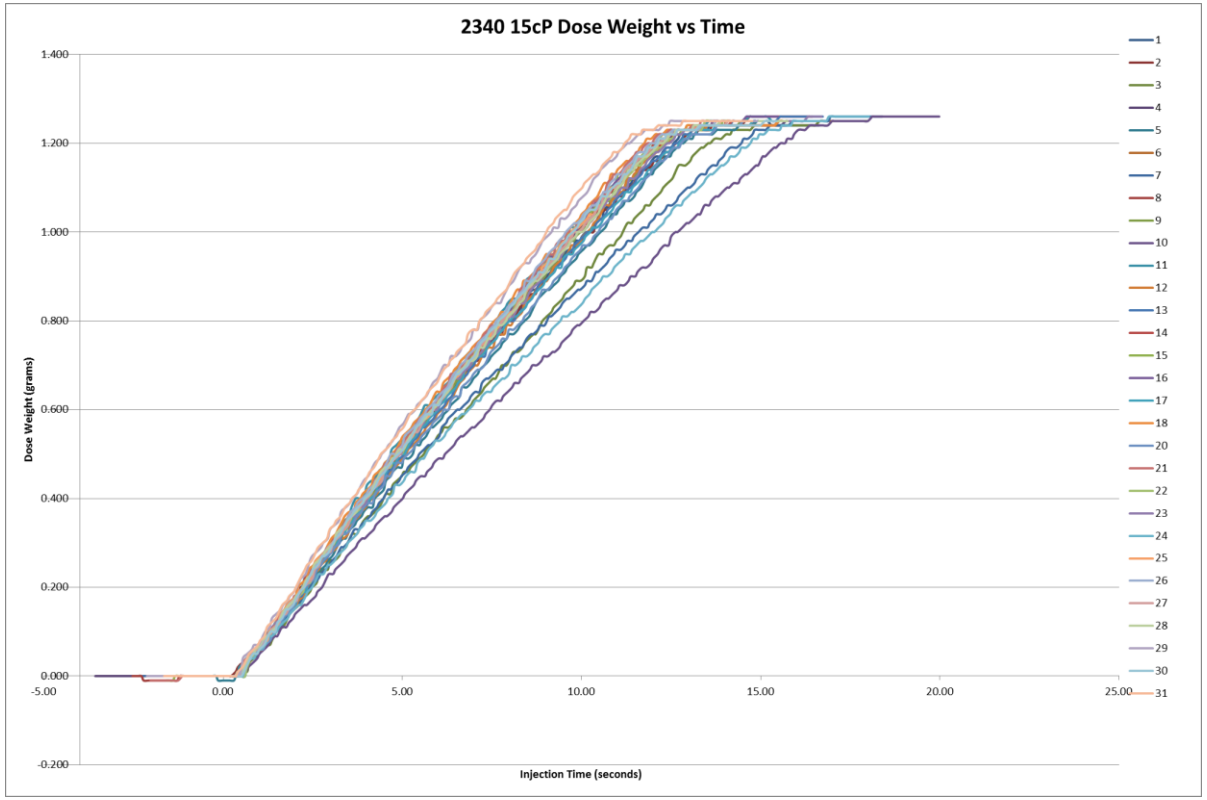
2340: legacy Plunger
NP: Qbd Plunger

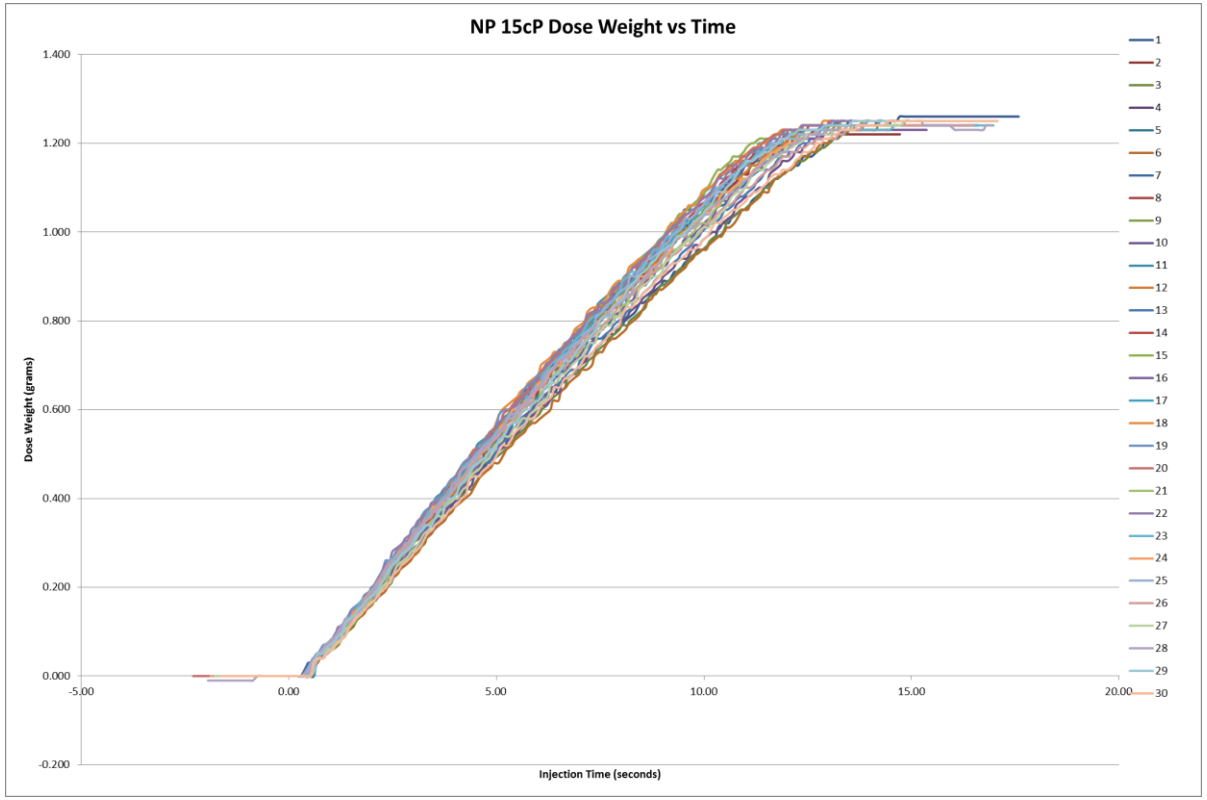
1ml long: Varied Viscosity Solutions in Autoinjector study T=0



2340: legacy Plunger
NP: Qbd Plunger

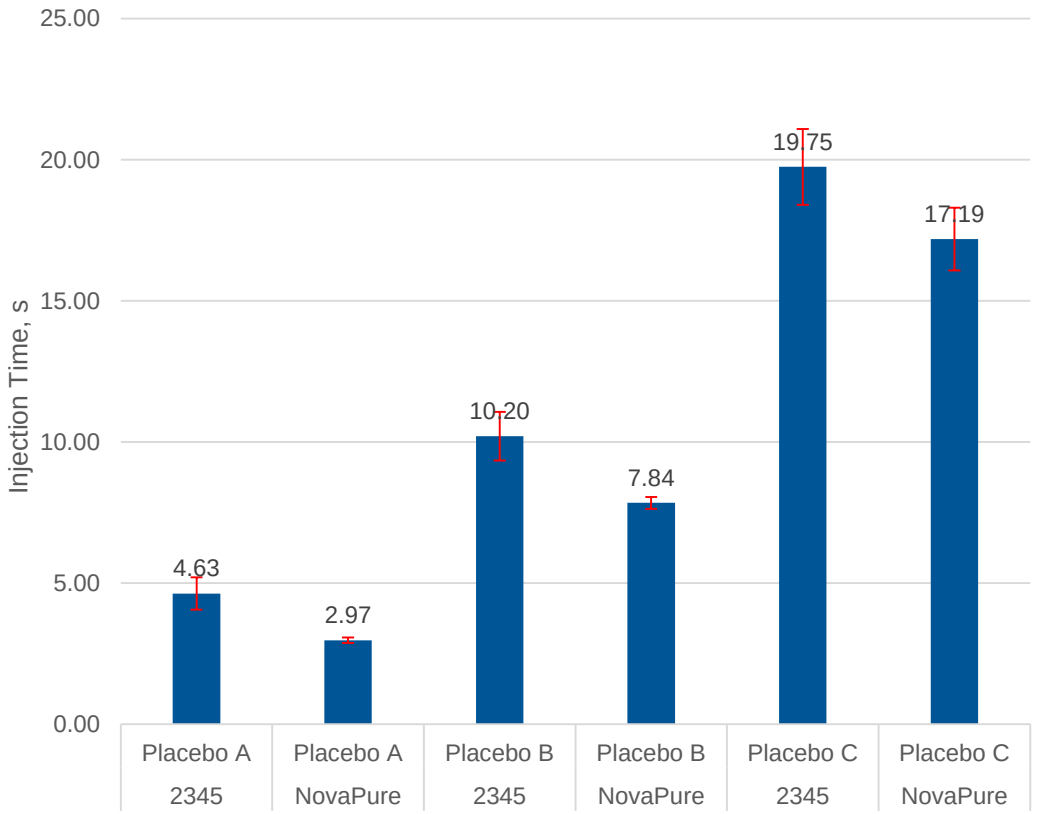
Dose Weight vs. Time Profile – 1ml long

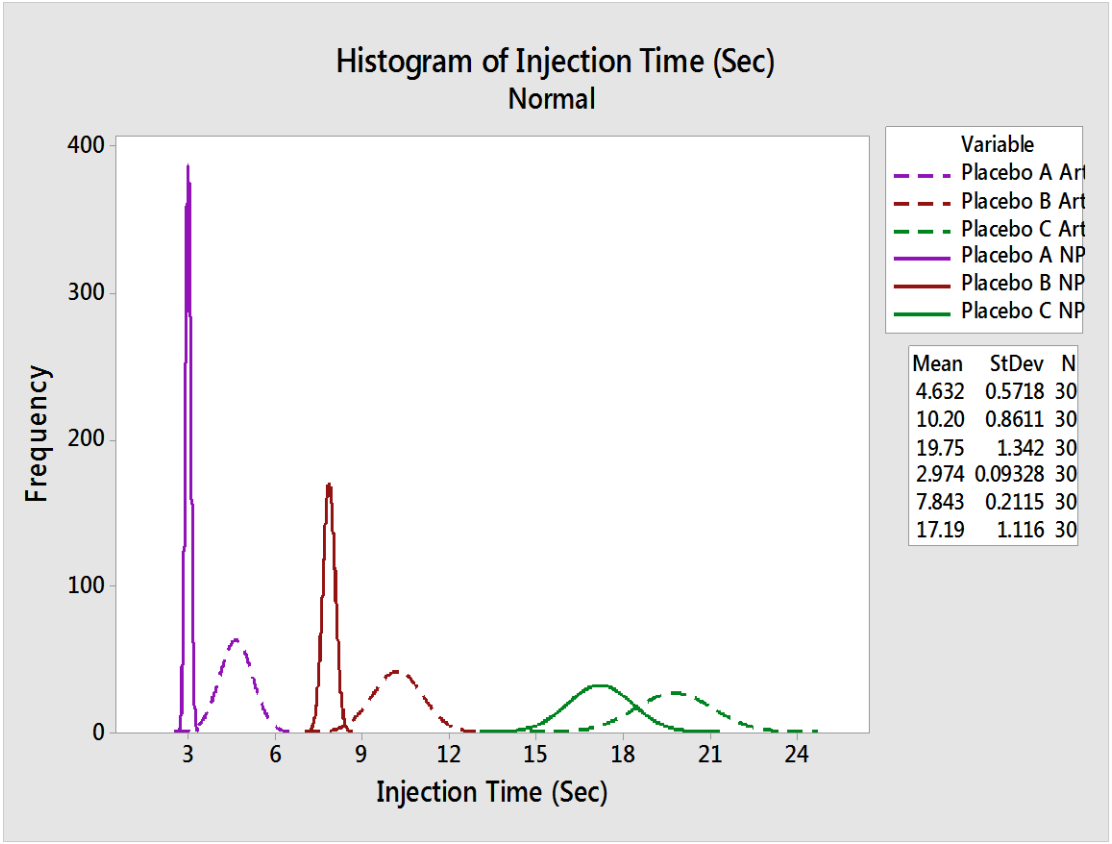




2340: legacy Plunger
NP: Qbd Plunger

Autoinjector Testing on 1-3 mL Plunger in glass syringe – Three Viscosities





- New plunger shortens the injection time.
- New plunger provides smaller variability of injection time.

2345: legacy Plunger
NP: Qbd Plunger

Cyclic Olefin Syringe Systems - In Combination with Autoinjectors

Engineered Polymer Barrel

FLUROTEC®
Barrier Laminated Elastomers

EASY LIFECYCLE MANAGEMENT
Vial / Syringe / Cartridge - Silicone Free

Managing Areas of Risk

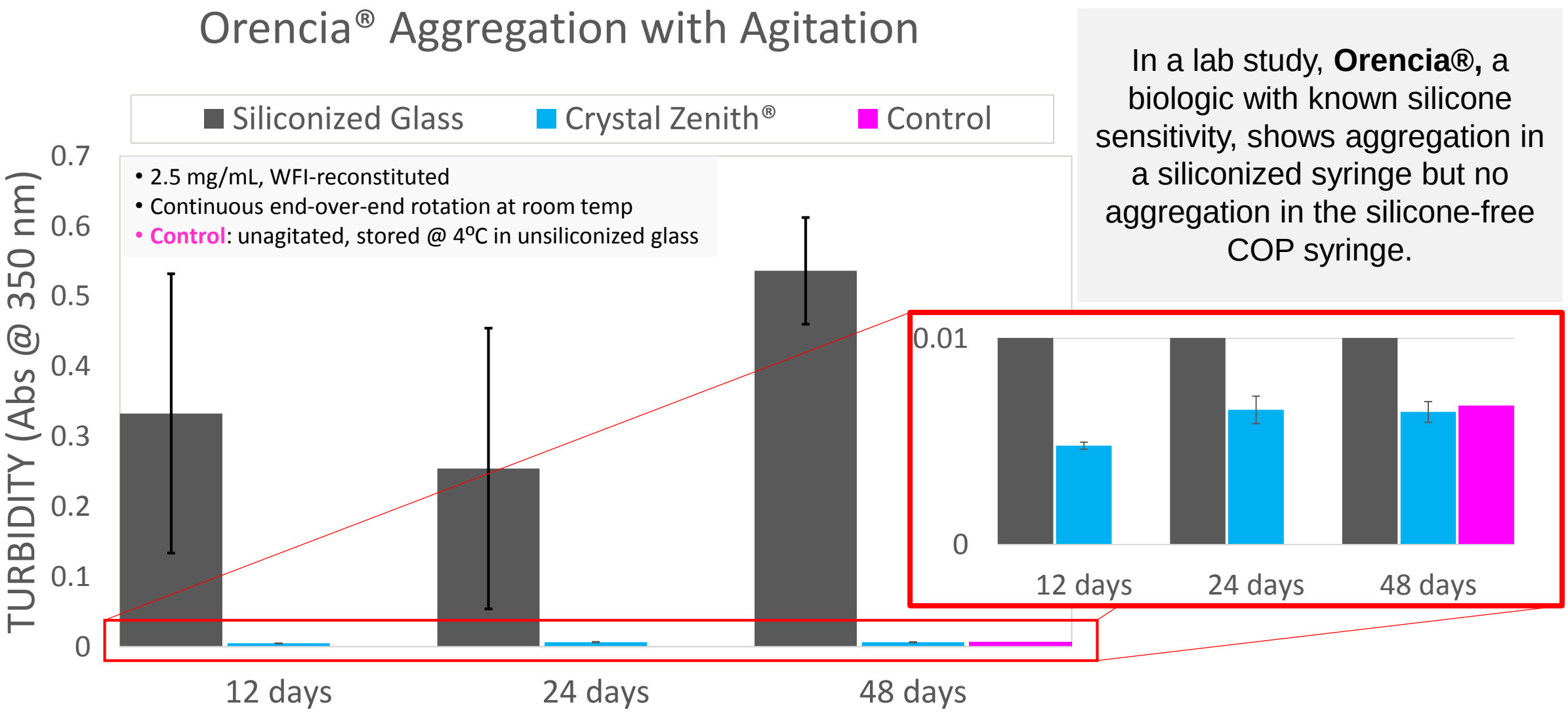
Silicone Free
to mitigate protein stability risks

Barrier-Coated Elastomers
to mitigate protein stability risks

Engineered Polymer
to mitigate breakage risks (device malfunction, fill / finish interventions, product exposure / loss)

Full Commercial Portfolio
for easy lifecycle management and speed to market

Silicone Free for Optimum Biologics Compatibility

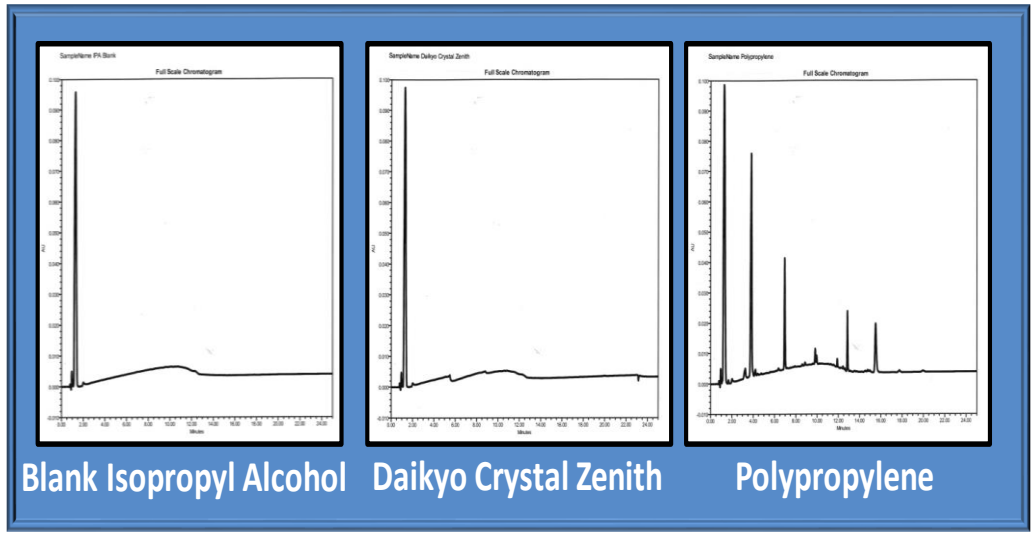


In a lab study, **Orencia®,** a biologic with known silicone sensitivity, shows aggregation in a siliconized syringe but no aggregation in the silicone-free COP syringe.

Waxman L and Vilivalam V, Evaluation of end-over-end rotation/agitation of protein solutions in prefilled syringes made from glass or plastic as a preliminary indicator of protein aggregation, Protein Stability Conference, Breckenridge, Colorado, US, 2011

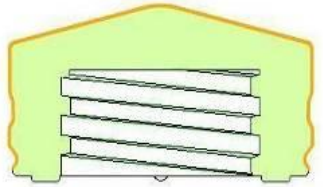
Significant Reduction in Occurrence of Inorganic and Organic Leachables

Container System

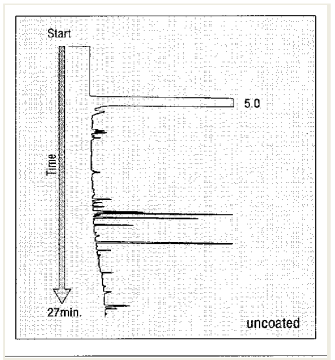


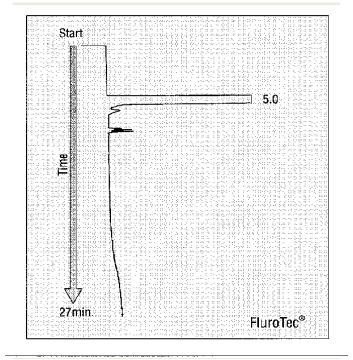
Elastomer Closures

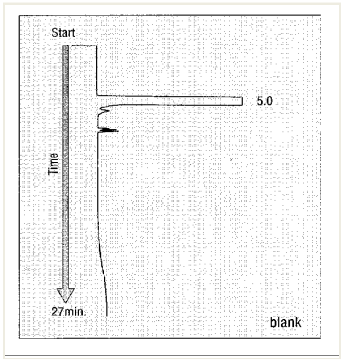
Piston for CZ Syringes fully laminated with Daikyo Flurotec



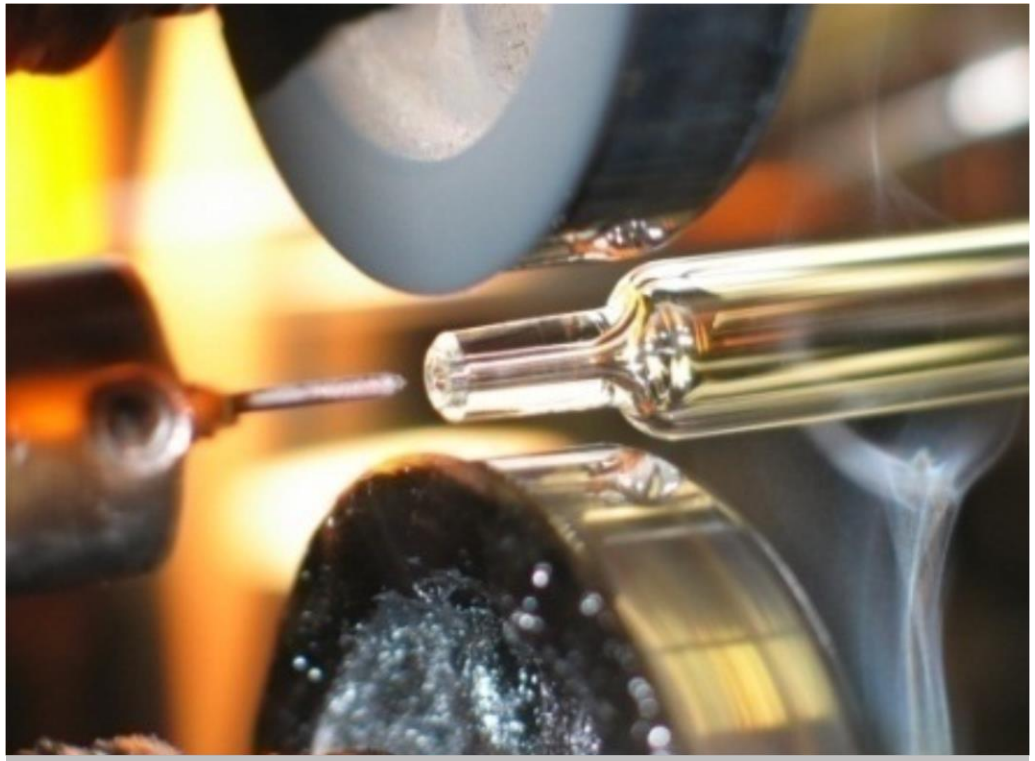
Migration of organic components into n-heptane monitored by GC





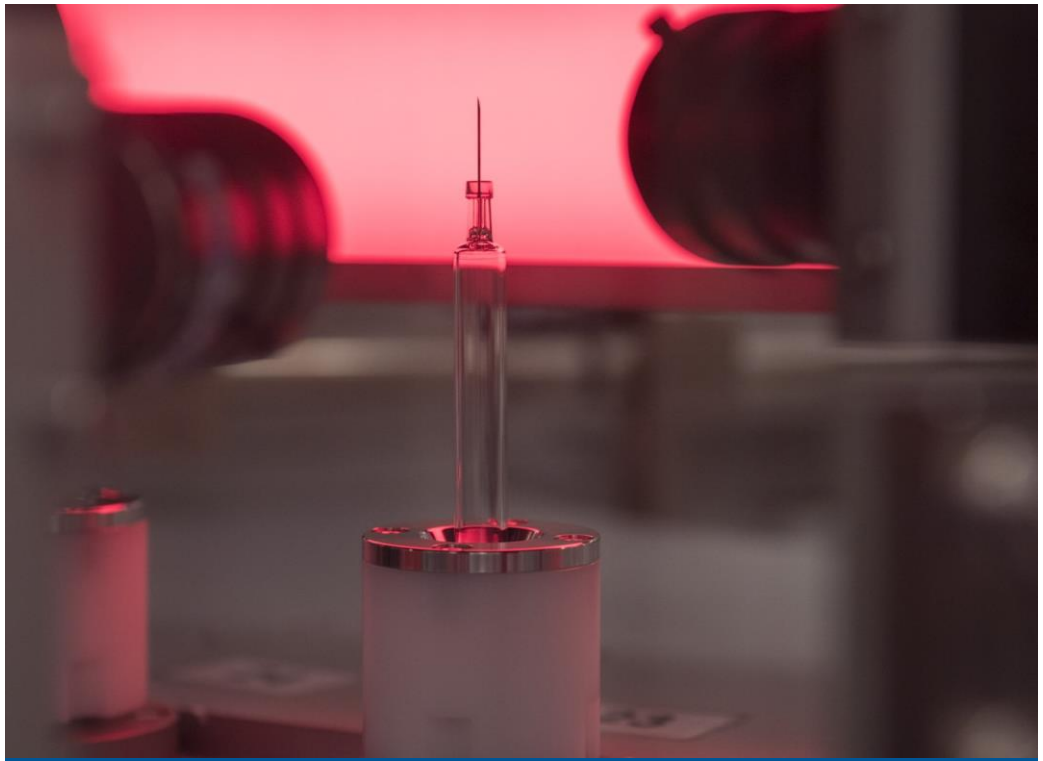


Glass versus Engineered Polymers: Fundamentally Different Manufacturing Processes



TUBULAR GLASS

Larger dimensional tolerances
Complex needle attachment
*(**tungsten** pin for forming and **glue** for fixation)*



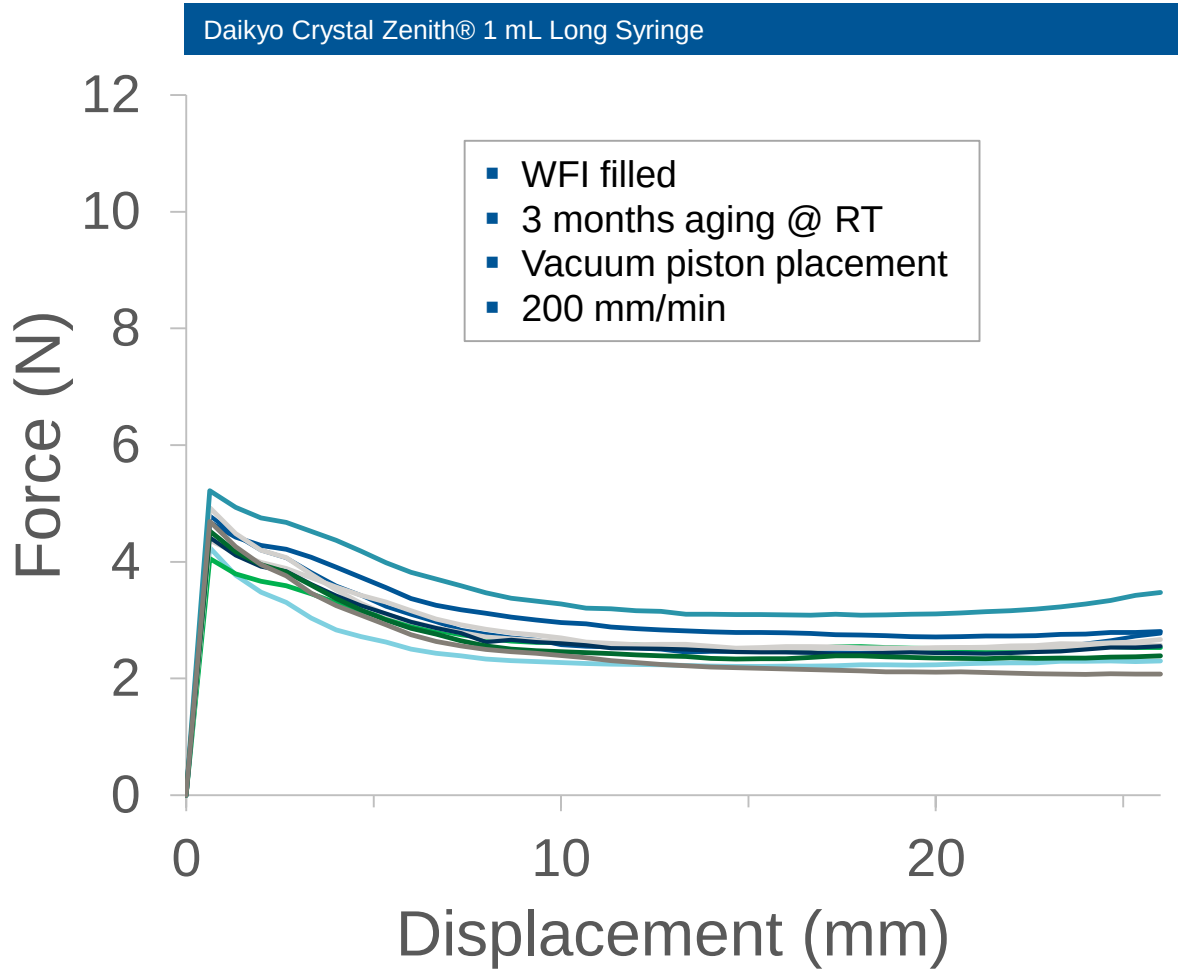
ENGINEERED POLYMERS

Tighter dimensional tolerances, **zero draft**
Clean, simple and **secure** needle attachment
(free of tungsten and glue)

Silicone-Free Syringe System

Lubricity without silicone oil

The FluroTec® laminate film on the plunger acts as a dry lubricant which, in combination with the smooth polymer surface, gives **consistent break loose and extrusion forces**.

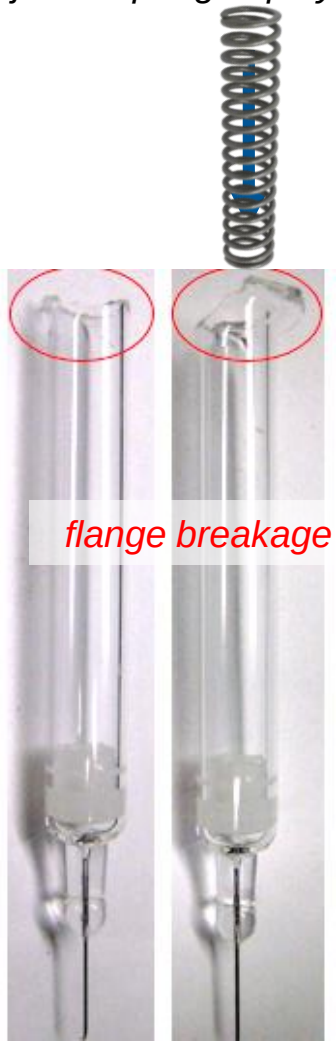


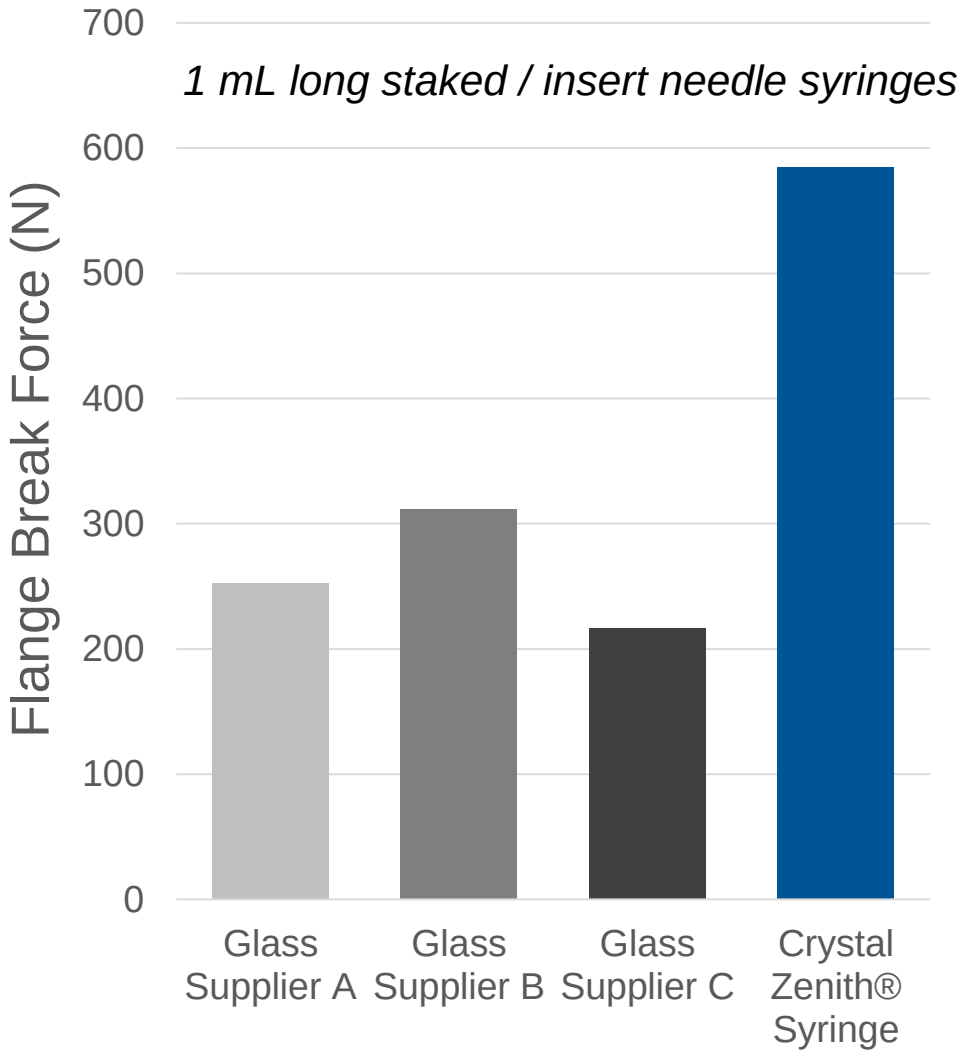
Engineered Polymers: Improved Flange Strength

Syringe flanges can be susceptible to breakage inside autoinjectors when high forces are exerted by firing springs or with viscous drugs.

Polymer syringes have **up to 2.5X increase in flange strength** versus glass.

Autoinjector spring deployment

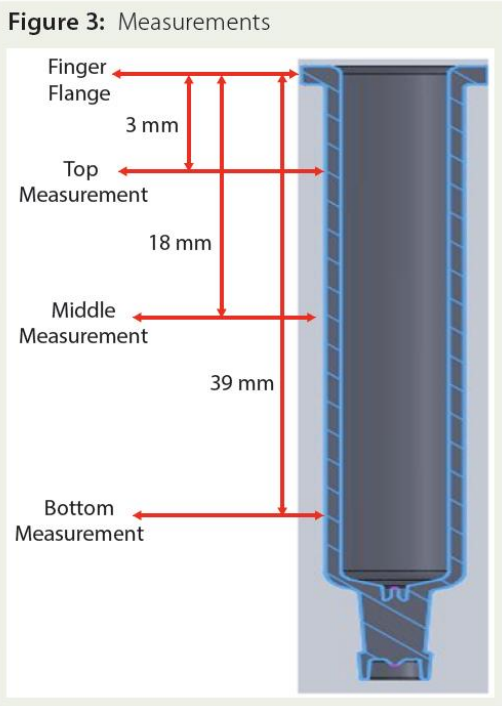


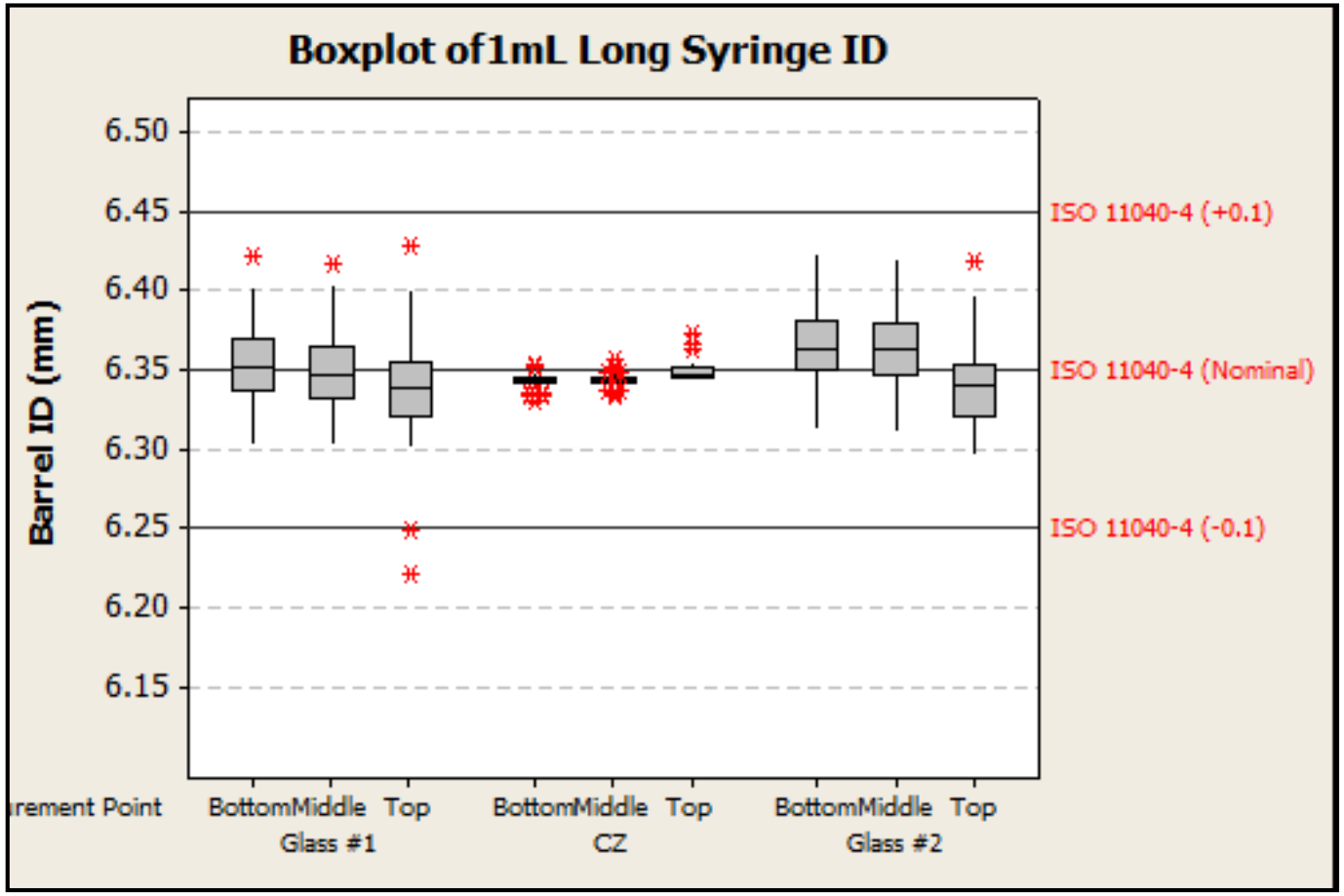


Harold Murray & Robert Froio West study

Engineered Polymers: Tighter Tolerances, Zero Draft

Low dimensional variability of CZ syringes supports functional performance within auto-injector devices





Zero Draft and the Fill Volume Advantage

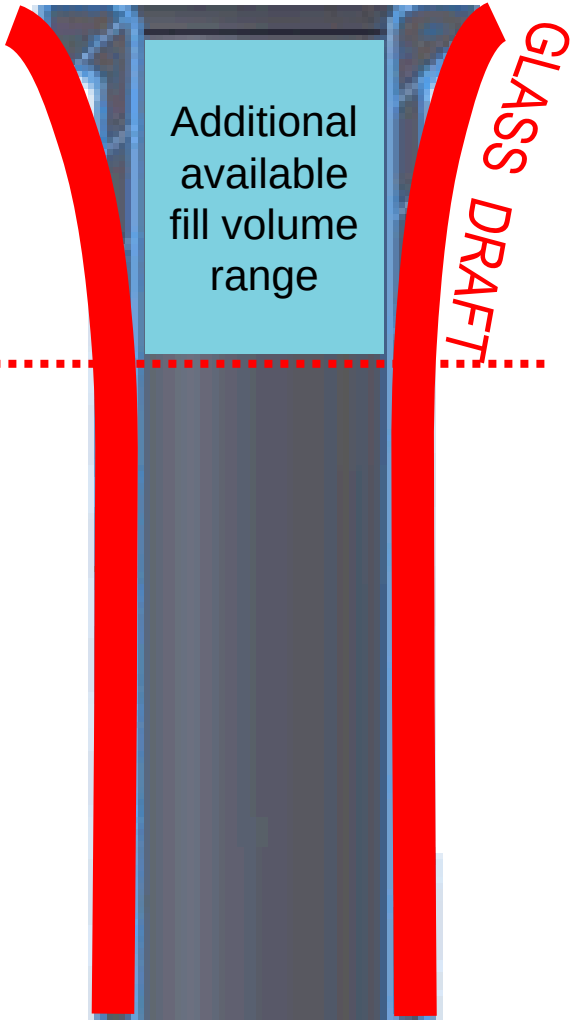
Glass syringes have a draft near the flange while **Engineered Polymer syringes do not**. Plungers can be placed higher (towards flange) in these syringes thus **accommodating greater fill volumes**.

Additional fill volume can potentially take a 3 syringe dosing schedule down to 2 syringe dosing

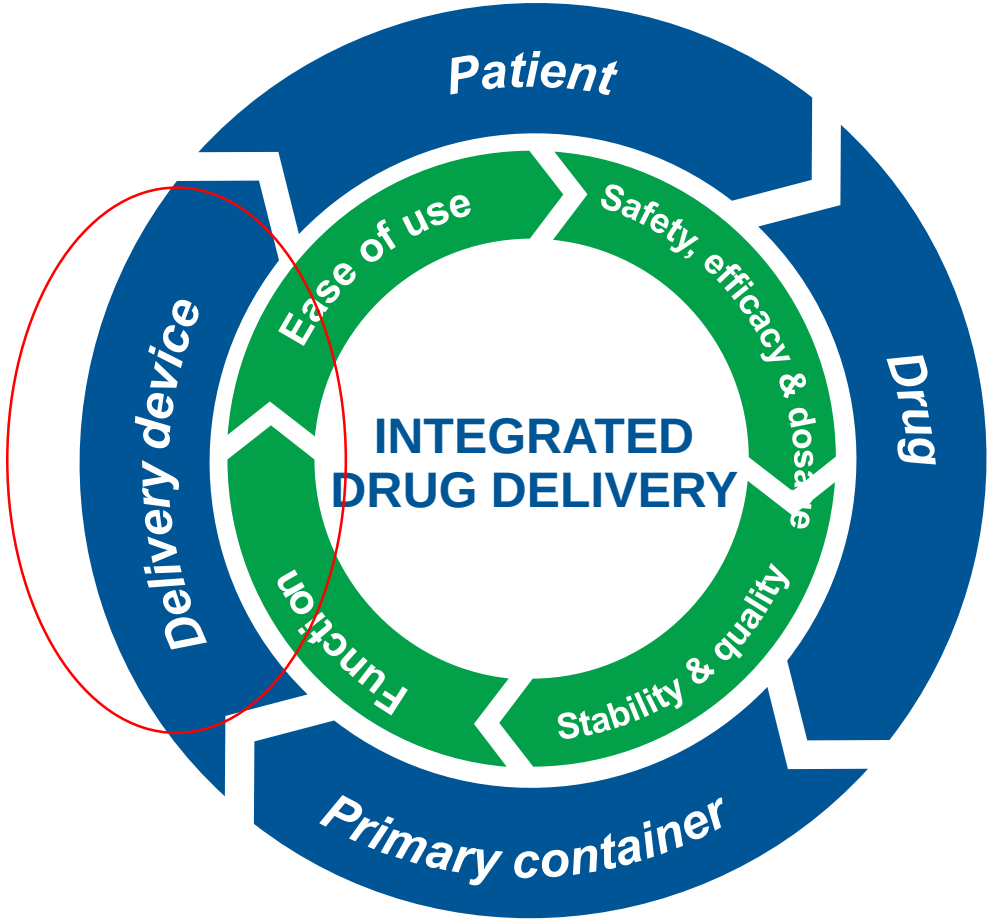
*Max. plunger height for CCI in **Crystal Zenith®** syringes*

>10% increase

*Max. plunger height for CCI in **glass** syringes*



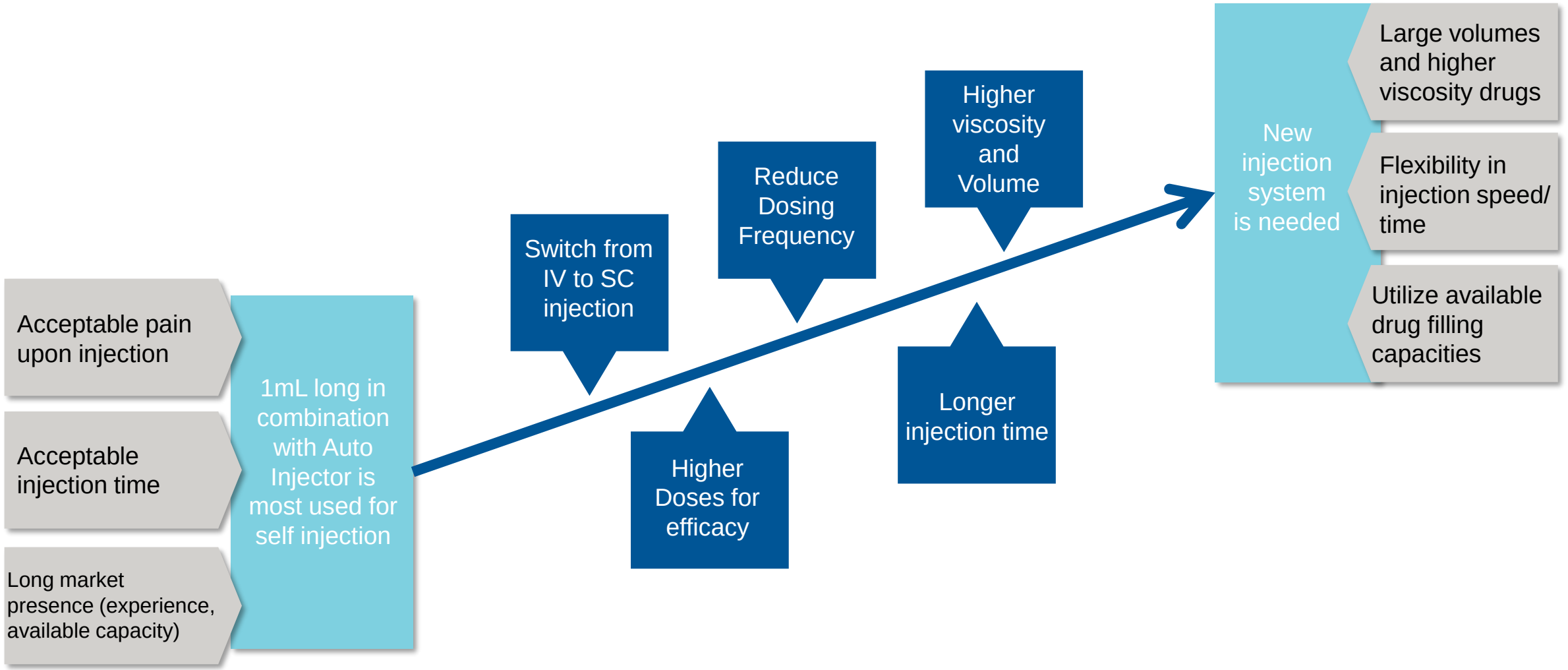
Why Delivery Matters



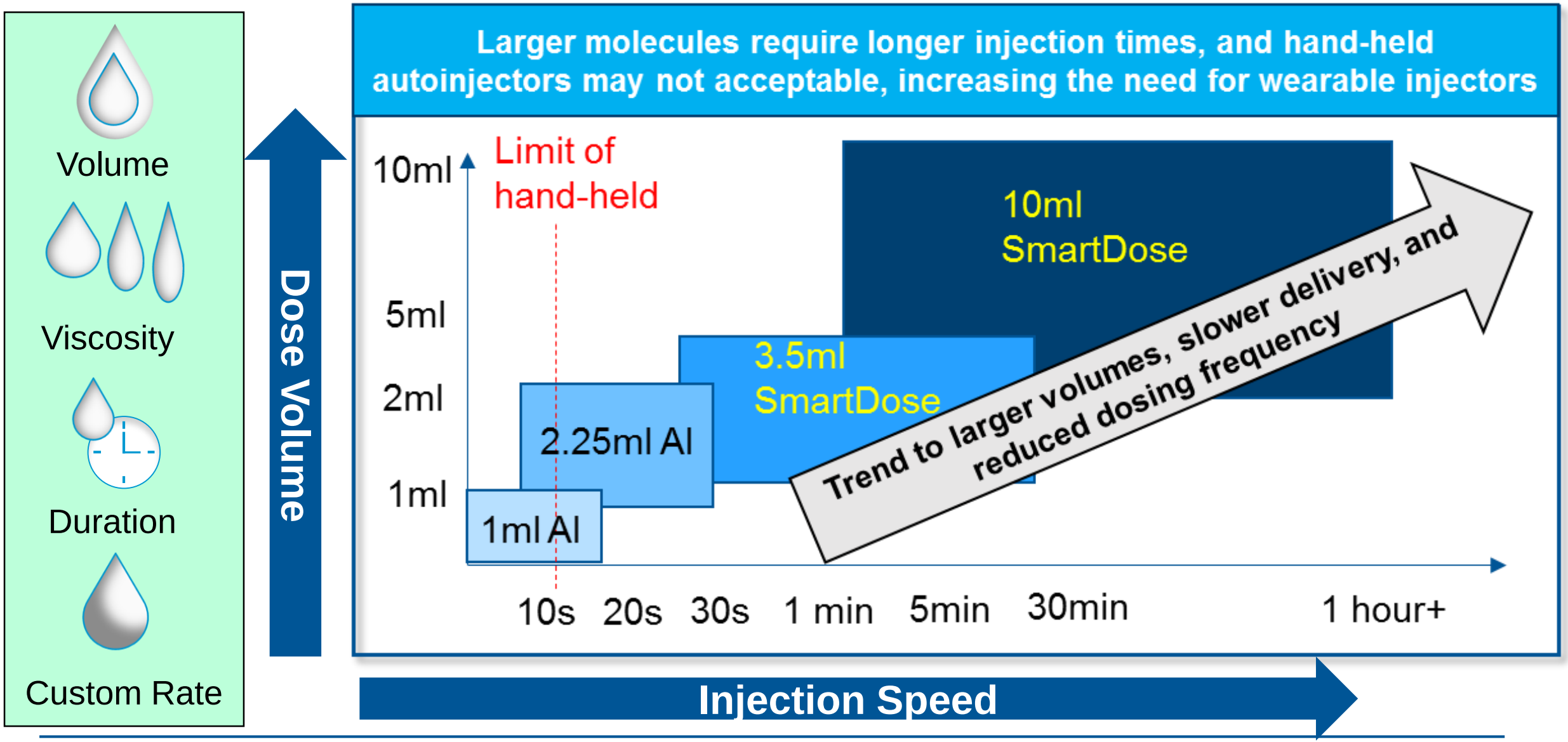
Large Volume Drug Delivery Trends

- Use of biological drugs with complex and large molecules produce formulations that are very viscous.
- To make these viscous formulations injectable, they need to be diluted, resulting dose volume up to 5, 10, 20 even 30mL.
- Single injected dose of up to 2.5mL are now being actively explored by the pharma industry and device companies using syringes and auto-injectors.
- Pre-programmable, easy to use wearable injectors that can hold larger volumes of drugs, and infuse them SC at a long period of time becomes a viable way to achieve self-administration while patient can continue an active life style.

Improving Therapy Management for Large Vol Injection



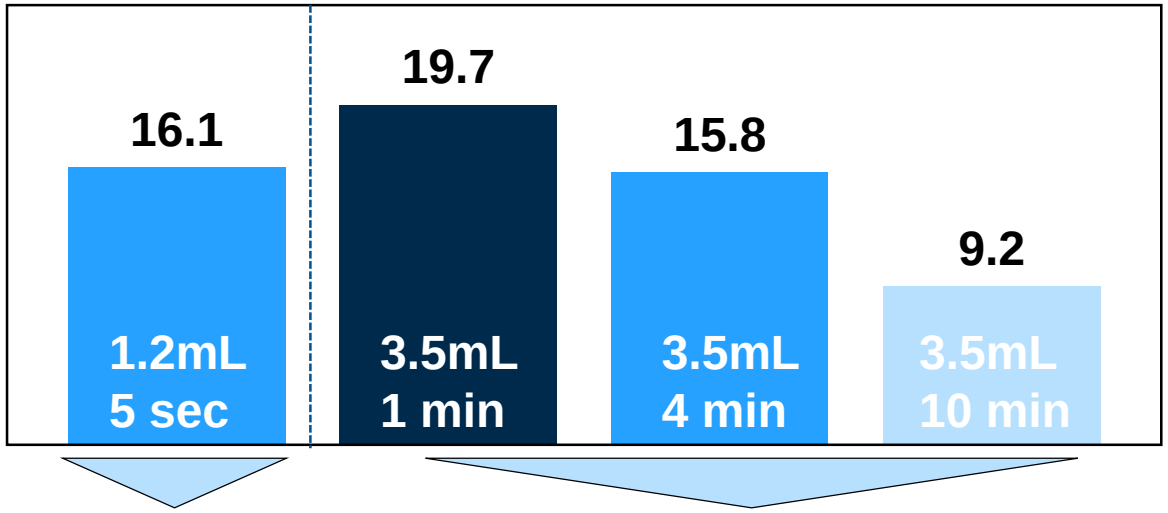
Tends are driving towards wearable injection systems



Pain perception is reduced with lower flow rate

Measure Tolerability of subcutaneous injection of 1.2 mL and 3.5 mL with viscosity of 5cP

- Mean VAS scores: Immediately after administration before removal of needle
- VAS: Visual Analog Scale = measure of perceived pain



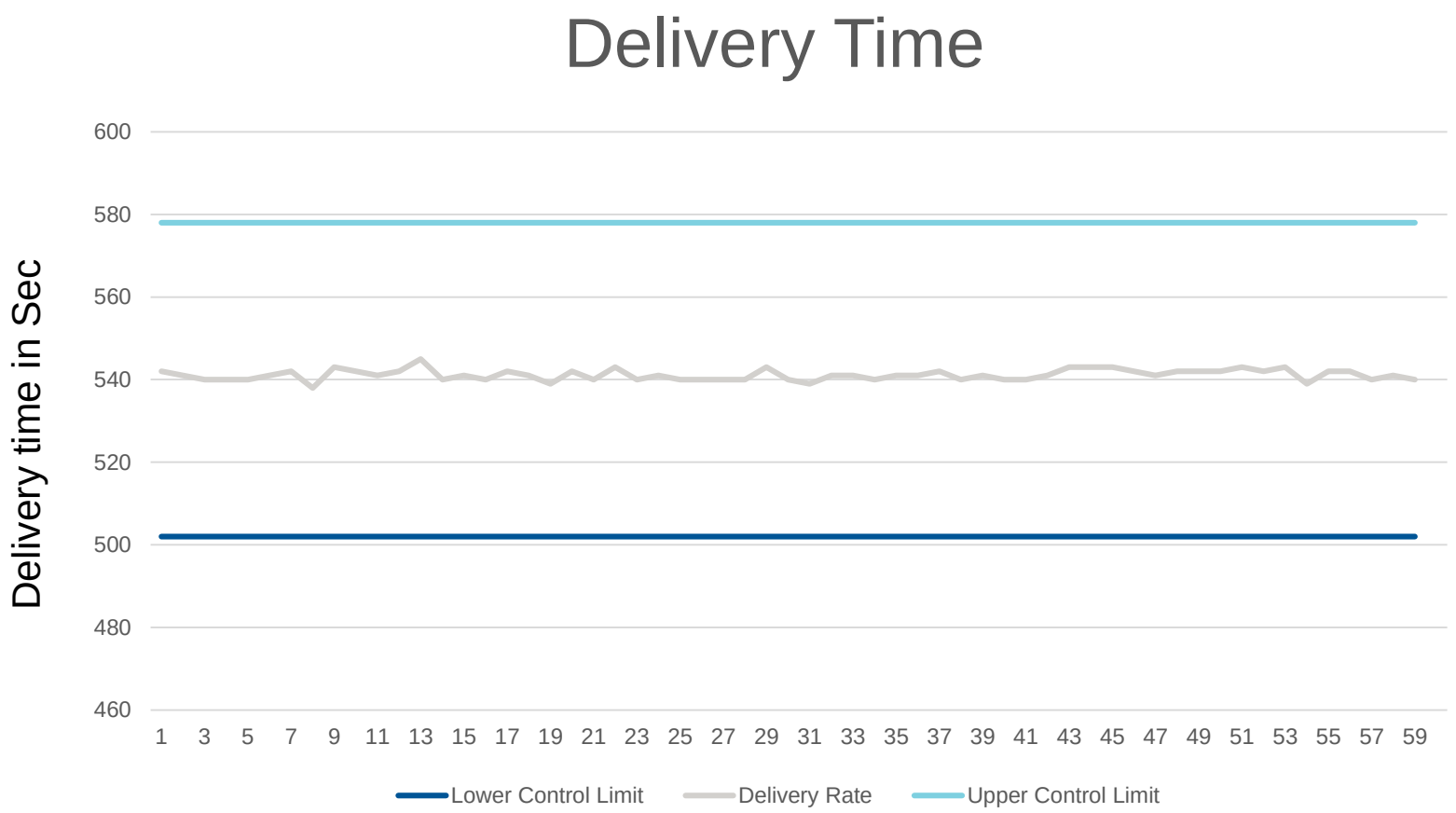
Source:
Dias C et al, Amgen, Tolerability of High-Volume Subcutaneous Injections of a Viscous Placebo Buffer, *AAPS*, 2015

Injection pain from larger injections can be minimized with a lower flow rate

Wearable On-Body Injectors: Key Considerations

	Electromechanical (wearable on-body injector)	Mechanical (auto-injector)
Reliability	Senses end of delivery Injection monitored – can indicate occlusion in the system Alarm indication of malfunction	Audible indication only No monitoring No indication of error
Consistency	Delivery time is constant Motor drive system delivers high viscosity drugs Delivery time variability < 1%	High viscosity = longer delivery time Low viscosity = faster delivery times Delivery time variability = Unknown

Consistency: Electromechanical System



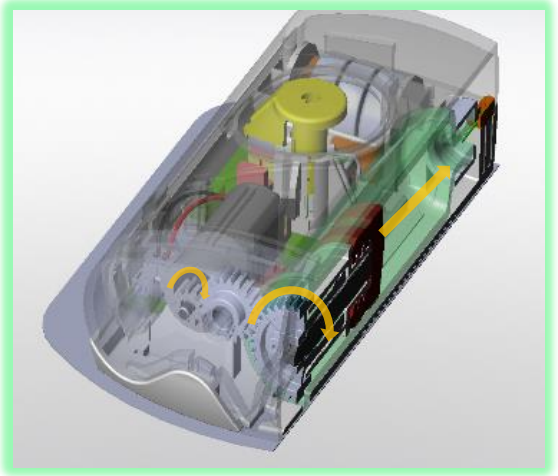
Delivery time is within 1%
No discernable difference to the user

Wearable On-Body Injectors: Key Considerations

	Electromechanical (wearable on-body injector)	Mechanical (auto-injector)
Delivery	Audible/visual indicators Low motor noise	Visual only
Dose Completion	Repeating audible/visual indicators	Single click
Error Handling	Consistent monitoring Visual and audible alarm	Visual monitoring only No indication of error
Flexibility	Variable injection time and volume information can be optimized for drug needs Longer delivery times possible	Limited variable delivery and uncontrolled consistency of delivery

Wearable On-Body Injector Commercialized Example

- Fully integrated delivery system
  - Container – Elastomer – Device
- Electromechanical drive
  - Delivery volume up to 3.7 mL
  - Viscosity tested up to 70cP
- Pre-programmable injection time
- Patient centric design
- Bar code connectivity
- Commercially available for Amgen's single monthly 420 mg dose of Repatha (evolocumab), 3.5mL in 9 Minutes



Engineered Polymer Cartridge

- Highly break-resistant primary container
- Tight Dimensional Control during Molding
- Predictable and Consistent gliding forces
- Superior barrier protection for E&L
- Suitable for high-viscosity drugs

Combination Product Development Workflow between Customer and Partner

Platform Interest

Customer Inputs:
- Drug viscosity
- Delivered volume
- Delivery time
- Device design changes: Color, form Needle gage
- Phase III clinical time frame and anticipated filing dates
- User requirements specifications

Combination Feasibility

Partner will test device with drug/mimic to establish optimal delivery parameters (SW)::
- Delivery time @ drug viscosity(ies) in operation conditions
- Electrical & Mechanical performance
- Reliability

Customer Technical Evaluation

Customer Responsibility
- Preference studies, and/or Human Factor studies
- Internal device testing, if needed
- Animal testing, if needed
- Partner can begin DHF activities in parallel

Design Control Activities

Partner will conduct
- DHF activities: including design input and output documentations, Risk management activities
- Customized device design change development (e.g. color, form)
- Design verification testing

Customer will conduct:
- Design Validation activities: HF summative, PK clinical study, as needed

Customer Clinical Trial And Submission

Primary Container Evaluation

- Manual filling
- Drug stability
- Drug compatibility

CMO Selection & Validation

- Customer for change parts
- Container and packaging purchase
- Component and filling validations

Time: Approximately 9 -12 Months to Human Clinical Trial Readiness

Evolution of Wearable On-Body Injectors

Market Drivers

Higher Volume
Frequency
Electronics
Pre-Programmable
Patient comfort
Precision
Innovation
Differentiation
Breakage

Improvements to reflect user and customer needs

Better usability
Pre-loaded
Connectivity
Faster Injection
Training system
Range of volumes

Summary

- Drug Containment and delivery is becoming more complex especially biologics, due to:
  - More sophisticated and challenging molecules
  - Increasing quality and performance expectations
  - Increased self-injection and transitioning out of a clinical setting
- Effective drug delivery relies on taking an integrated approach
  - Starts with a comprehensive understanding of the patient and their needs
- Collaboration by partners helps optimize success

Thank You

West