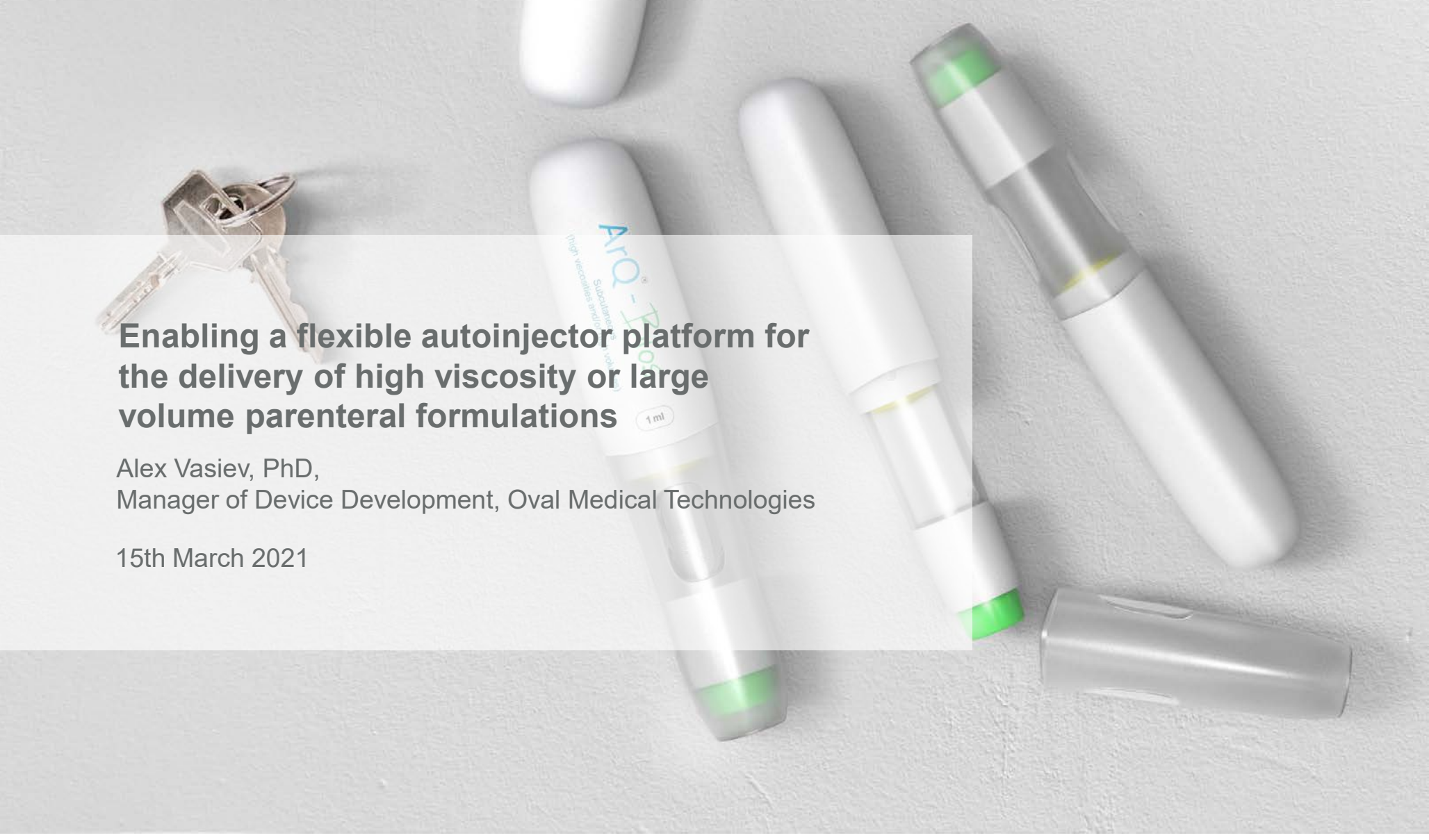


Enabling a flexible autoinjector platform for the delivery of high viscosity or large volume parenteral formulations

Alex Vasiev, PhD,
Manager of Device Development, Oval Medical Technologies

15th March 2021

Introduction

Small molecule drugs (SMDs) have been the focus of the pharmaceutical industry for decades

- Synthetic, defined by chemical reactions
- Supported by established technology
- Small and easy to characterise

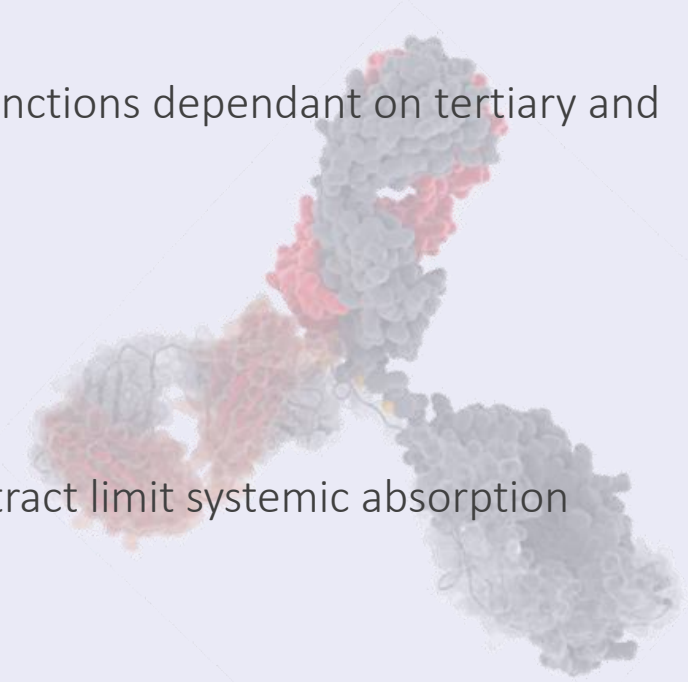
Advances in molecular biology brought a new class of therapeutics

- Biologics offered more targeted therapies, and potentially less side effects
- The market for biologics and biosimilars continues to grow rapidly
  - Driven partially by the increasing application of antibodies

Although their requirements were potentially different, they often inherited technologies and primary packaging developed and proven for small molecules

Otto R., Santagostino A., Schrader U. (2014), "Rapid growth in biopharma: challenges and opportunities". McKinsey & Company Insights.

Parenteral delivery of biologics



Biologics such as antibodies are large molecules with functions dependant on tertiary and quaternary structure (folding)

Their **large size** results in high dosage mass:

- Sumatriptan (0.3 kDa)
- Insulin (5.8 kDa)
- IgG (150 kDa)

They **favour injection** as barriers in the gastrointestinal tract limit systemic absorption

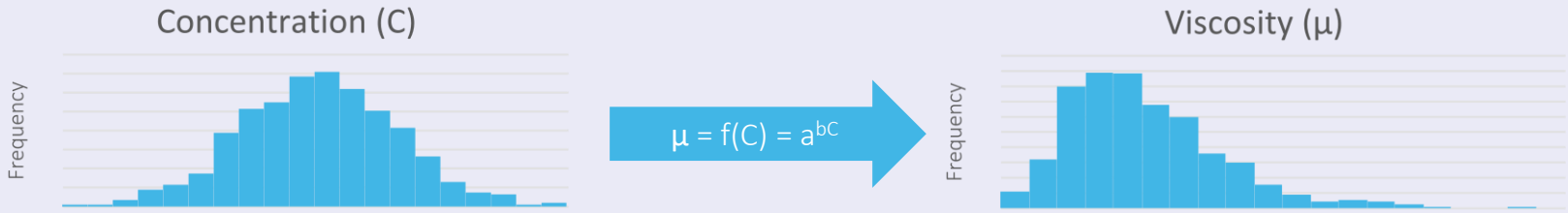
This presents **two routes** for parenteral delivery:

1. High concentrations at high viscosity
   - To fit the volume of a typical autoinjector (1, 2.25 ml), some antibody solutions are concentrated to and above 200 mg/ml
   - Not readily amenable to filtration, so lyophilisation and reconstitution often preferred
2. Large volumes of lower viscosity formulation
   - IV, or on-body wearable device

Delivery of biologics – high concentration

High concentrations of biologics tends to be viscous and require high delivery forces, long times or large needle bores to inject

Their viscosity also changes exponentially with concentration which can be an issue for automated injection where delivery force is tightly defined



Interplay between short-range attractive forces and long range repulsive forces governs the formation of networks at high concentrations

- Fluid shear causes alignment and rearrangement of these networks
- Leads to non-Newtonian behaviour (shear-thinning)
- Makes device performance more difficult to predict

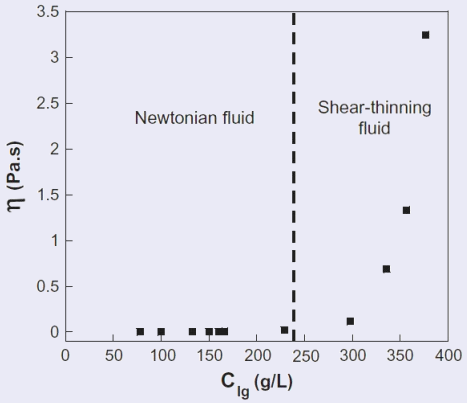


Fig. 3. IgG viscosity variations as a function of IgG concentration.

1. Pathak, J. A., Sologuren, R. R., & Narwal, R. (2013). Biophysical journal, 104(4), 913-23.
2. Dharmaraj, V. L., et al. (2016). Biomicrofluidics, 10(4), 043509.
3. Burckbuchler V, et al. (2010). Eur J Pharm Biopharm. 76(3):351-6.

Delivery of biologics – Large volume

Large volumes of more dilute formulations are the alternative approach

- Amenable to cheaper filtration concentration and sterilisation techniques
- Less associated risk of loss of efficacy caused by freezing (or time to develop protocols), opening the door to a greater variety of biologic molecules

Injecting a large volume requires either a **high flow rate**, which can cause pain for the patient, or longer injection duration

- This has traditionally limited the options for autoinjectors in this space
  - High energy requirement (high force)
  - Perceived useability and pain issues for the patient
- Given rise to a variety of wearable/bolus injectors
  - Gradually inject large volumes of subcutaneous formulations
  - Less pain, less force required, hands-free

Oakley. T (2020),"WEARABLE INJECTORS: LATEST DEVICES & RECENT TRENDS" – On Drug Delivery

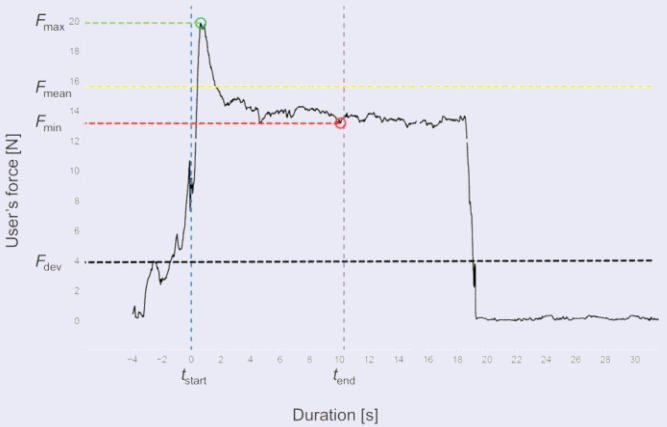
Wearable injectors for large volume biologics

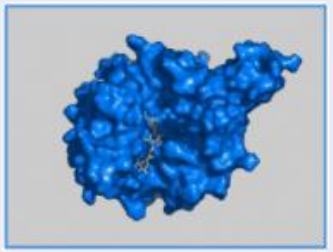
- **Wearable injector** use was predicted to be widespread in many indications, but that has not yet happened (although many exist and others are being developed)
- Reasons presented for this in recent industry assessments are that:
  - Pharmaceutical companies tend to look at packaging in vials and prefilled syringes, and then continue to autoinjectors or pen injectors for increased usability
  - Wearable injectors are more complicated to use and come at a higher cost
  - There needs to be a clear case to use them (such as a use case or opportunity that other devices cannot support)

Oakley. T (2020),"Wearable Injectors: Latest Devices & Recent Trends" – On Drug Delivery.

Autoinjectors for large volume biologics?

- Recent studies suggest users can hold an autoinjector in place for up to a minute (~50 s)
  - Potentially increasing the number of applications for autoinjectors
- The advent of recombinant hyaluronidase adjuvants such as Halozyme's Enhanze technology can increase the dispersion and absorption of subcutaneously injected drugs
  - Catalyses the degradation of hyaluronic acid and increase the permeability of subcutaneous tissue
  - Potential to reduce tissue resistance and pain associated with high flowrates and injected volumes
- Licensing of the technology by companies such as Roche, Baxalta, Pfizer, Janssen, AbbVie, Lilly, BMS, Alexion and Argenx indicates broad industry acceptance





3-D model of rHuPH20 hyaluronidase

Schneider A, Mueller P, Jordi C, Richard P, Sneeringer P, Nayyar R, Yovanoff M, Lange J. Hold the device against the skin: the impact of injection duration on user's force for handheld autoinjectors. Expert Opin Drug Deliv. 2020 Feb;17(2):225-236.
Locke KW, Maneval DC, LaBarre MJ. ENHANZE® drug delivery technology: a novel approach to subcutaneous administration using recombinant human hyaluronidase PH20. Drug Deliv. 2019 Dec;26(1):98-106.

Understanding formulation delivery

Formulation Characterisation

Unforeseen difficulties such as settling, aggregation or shear thinning may only become apparent when injecting through a needle

To aid optimisation of containers for new applications, Oval has developed the Injection Characterisation System (ICS)

Purpose of characterisation

1. Understanding the physical characteristics of the formulation
2. Conducting testing in a way representative of the device
3. Establishing delivery consistency

    - Understanding the extent of batch to batch variation
    - Exploring the impact of environmental conditions and ageing
    - Clogging or settling of suspensions

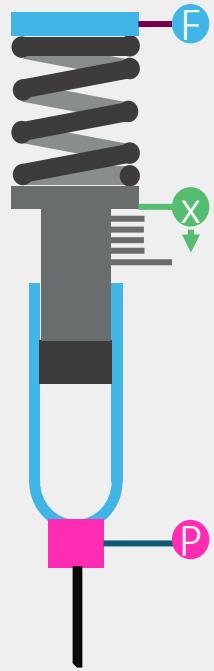
This allows performance criteria to be rapidly translated into tangible design options

Injection Characterisation System

The ICS monitors the delivery of a formulation through a system representative of an autoinjector

A combination of sensors allow the delivery force, pressure and delivery rate to be decoupled to better understand the flow and friction are affected by container pressure and delivery rate

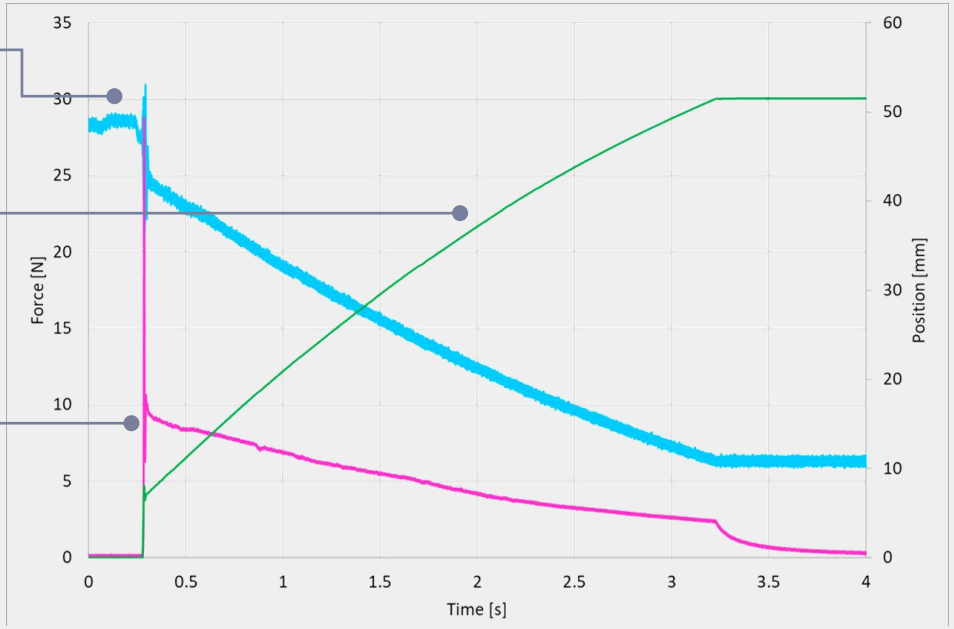
Sensitive enough to detect unforeseen fluid properties and flow effects



Load cell: Monitors the spring force in the rig during injection (total force)

Linear encoder: Monitors the progress of the injection (used to determine flow rate Q)

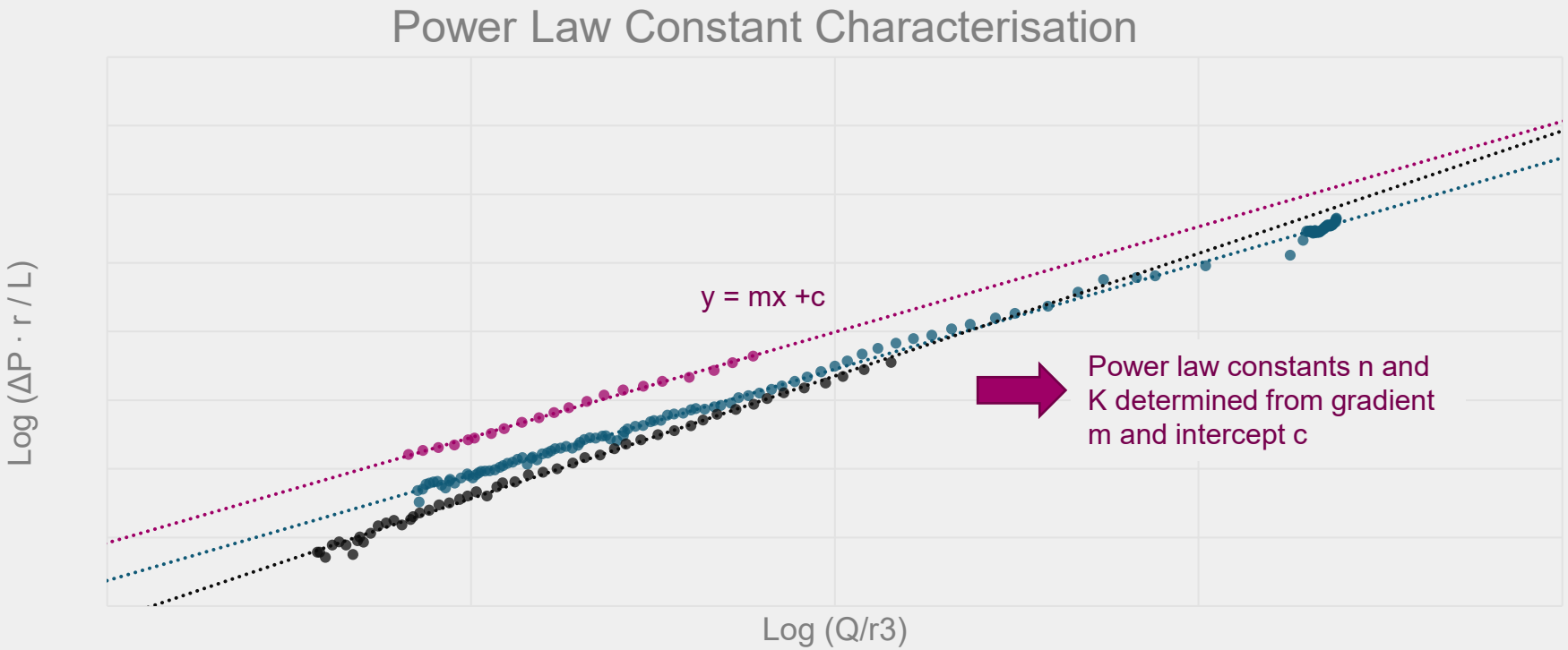
Pressure sensors: Monitor the pressure generated inside the syringe immediately ahead of the needle (available force and total force used to calculate friction)



Modelling fluid behaviour

The Injection Characterisation System (ICS) data can be used to fit a mathematical model to the flow

- An example is shown below for a formulation which exhibits the behaviour of a Power Law fluid
- Non-linear relationship between pressure applied and flowrate



Modelling fluid behaviour

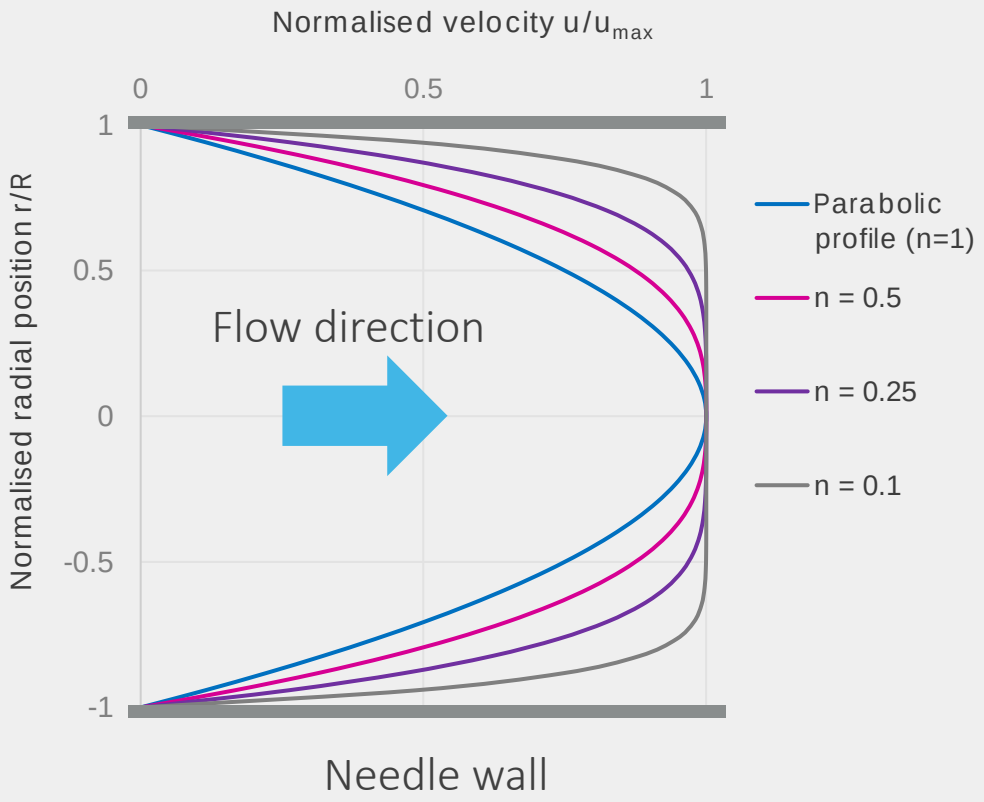
non-Newtonian fluids shear to a greater extent at the wall of the needle than the core

Unlike Newtonian fluids they do not form a parabolic flow profile

Flow profile is defined by the following expression for flow velocity u at a given radial location r:

$$u(r) = \frac{n}{n+1}\left(\frac{dp}{dl}\frac{1}{2\mu_0}\right)^{1/n}\left(R^{\frac{n+1}{n}} - r^{\frac{n+1}{n}}\right)$$

Where n is the flow behaviour index, R is the maximum internal radius and dp/dl is the pressure gradient along the length of the needle.



Reference:
Vilaplana M, Vasiev A, White S, "Function-Based Primary Packaging Design for Injecting Viscous Non-Newtonian Formulations". ONdrugDelivery Magazine, Issue 101 (Oct 2019), pp 20-25.

Modelling fluid behaviour

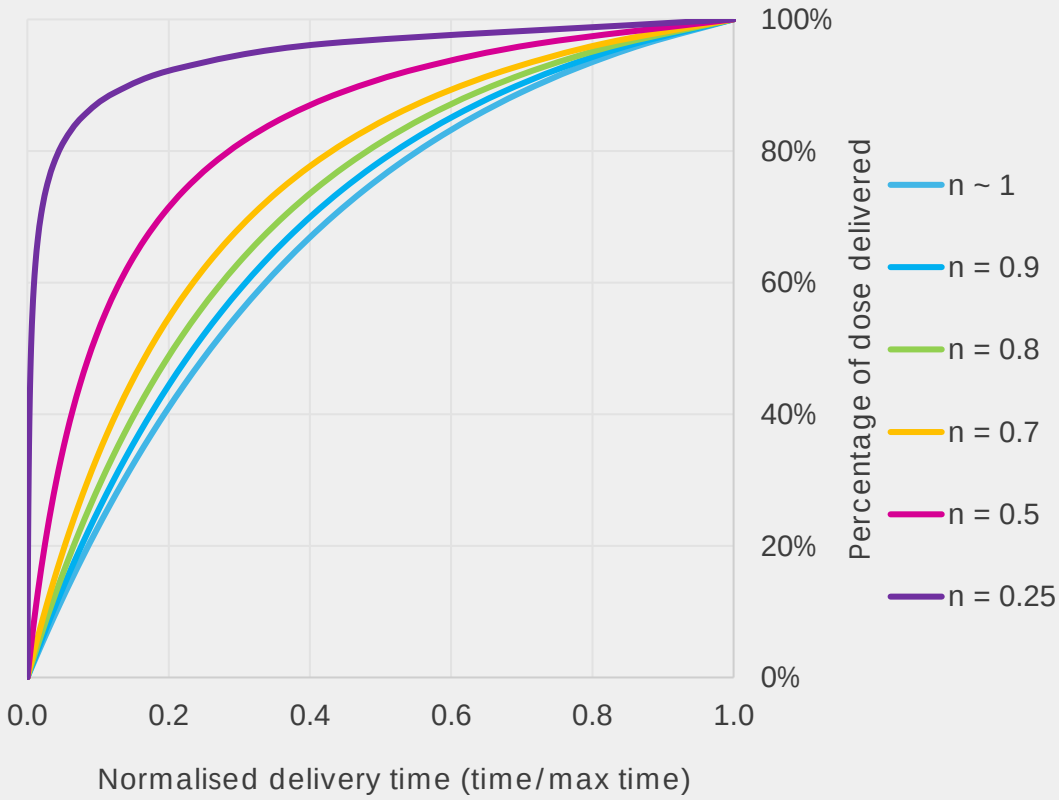
Power law fluids can have a highly variable delivery rate, defined by:

$$Q = \frac{\pi d^3}{8\left(\frac{1}{n}+3\right)}\left(\frac{Fd}{\pi D^2 l \mu_0}\right)^{\frac{1}{n}}$$

Where d is needle internal diameter, F is the applied force and l is the needle length

The impact of increasing n is a less uniform injection profile as the delivery spring force decays

- The end of injection can have a very long and pronounced tail



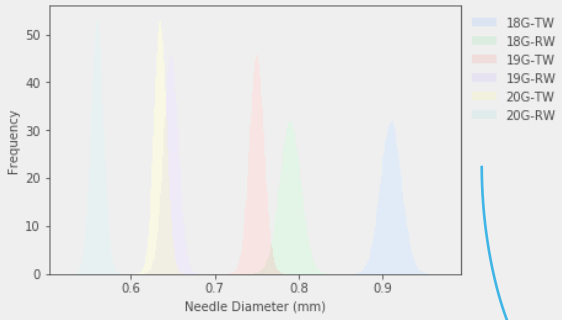
Reference:
Vilaplana M, Vasiev A, White S, "Function-Based Primary Packaging Design for Injecting Viscous Non-Newtonian Formulations". ONdrugDelivery Magazine, Issue 101 (Oct 2019), pp 20-25.

Modelling delivery performance

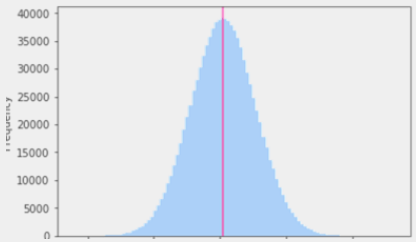
Using these models a Monte Carlo simulation can be created to predict likely autoinjector performance

- This simulation looks at the likely variation in injection time across millions of simulated devices, constructed by random selection of different input variables

Design parameters



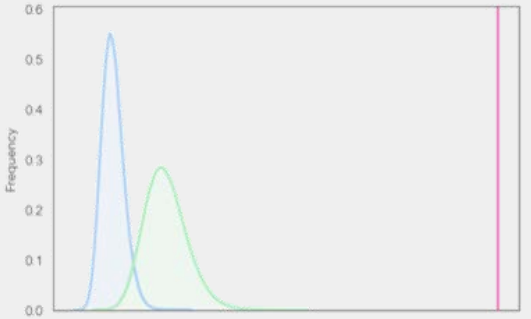
Fluid Constants



Mathematically integrated relation for injection time for Power Law fluids:

$$T = \frac{1}{Ck\left(1 - \frac{1}{n}\right)}\left[{F_0}^{1-\frac{1}{n}} - (F_0 - L\kappa)^{1-\frac{1}{n}}\right]$$

Device performance

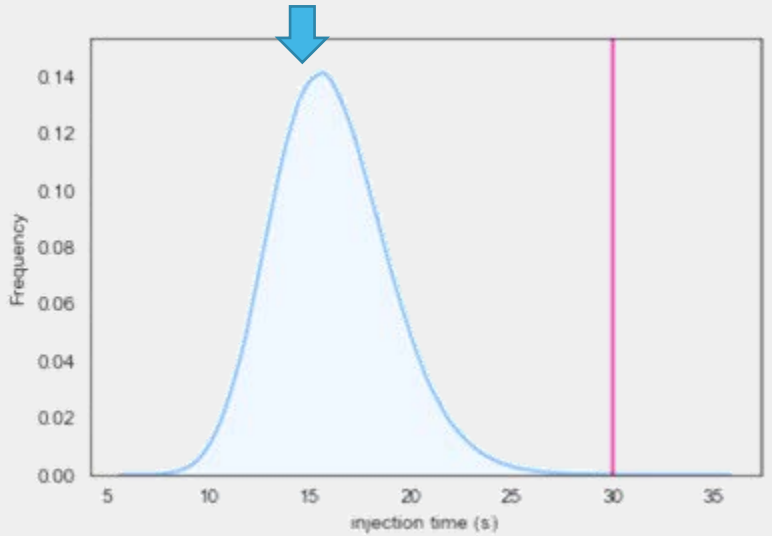


Reference:
Vilaplana M, Vasiev A, White S, "Function-Based Primary Packaging Design for Injecting Viscous Non-Newtonian Formulations". ONdrugDelivery Magazine, Issue 101 (Oct 2019), pp 20-25.

Technical Demonstration

- Spring powered ArQ Bios proof of principle devices demonstrated delivery of a +100000 cP LAI
- Power-law fluid initially analysed using the ICS
- Delivery of 0.5 mL confirmed to be just under 15 seconds

Simulation:

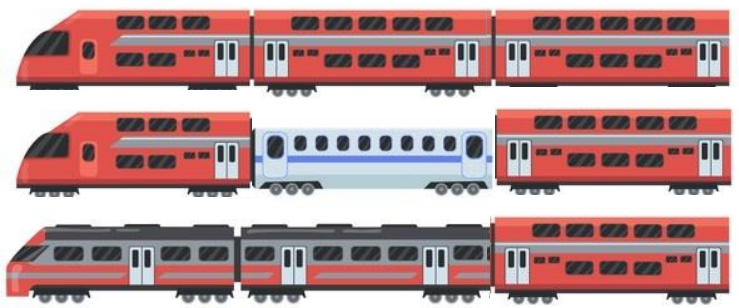


POP : 14 seconds

Defining a flexible platform

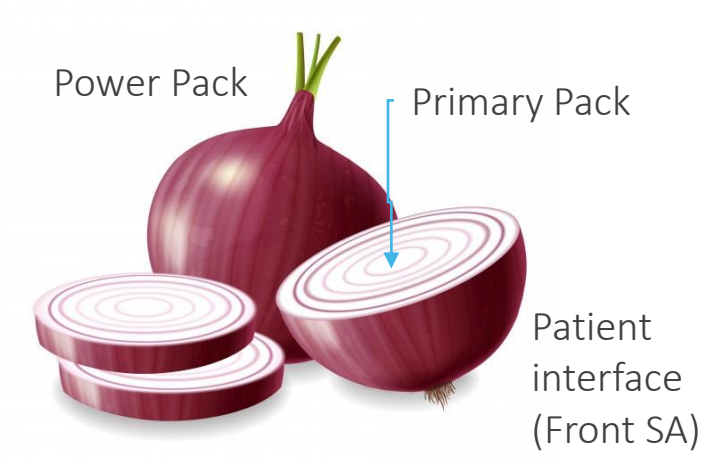
Device architecture: Train Vs. Onion

Modular: Cars can be substituted with minimal impact on the overall structure



Power Pack Primary Pack Patient interface (front SA)

Layered: Changes in one layer impact the structure of all subsequent layers



Overview and Benefits of ArQ Bios

Decoupling the patient triggering injection from the Power Pack:

Actuator (Pressurises the drug on cap removal)

- Drug pressurised during cap removal
  - Patient does not feel spring release with device on skin

Container (tolerates extremely high pressures)

- Oval's cyclic olefin Primary Drug Container (PDC)
- Lubricant and adhesive free
- Robust and Safe – can tolerate up to 300 bar of pressure

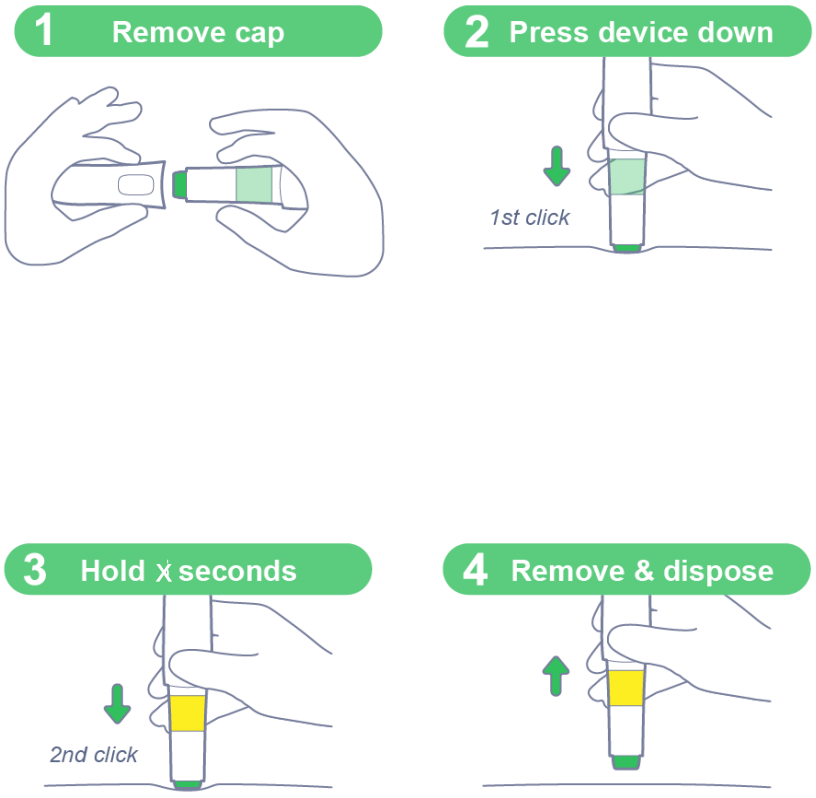
Patient interface (Triggers injection)

- Injection gently triggered using a proprietary valve incorporated into the PDC
- Valve and Front SA are common across device variants allowing container to be changed easily with minimum impact on the device

ArQ Bios User Steps

Sequence during use:

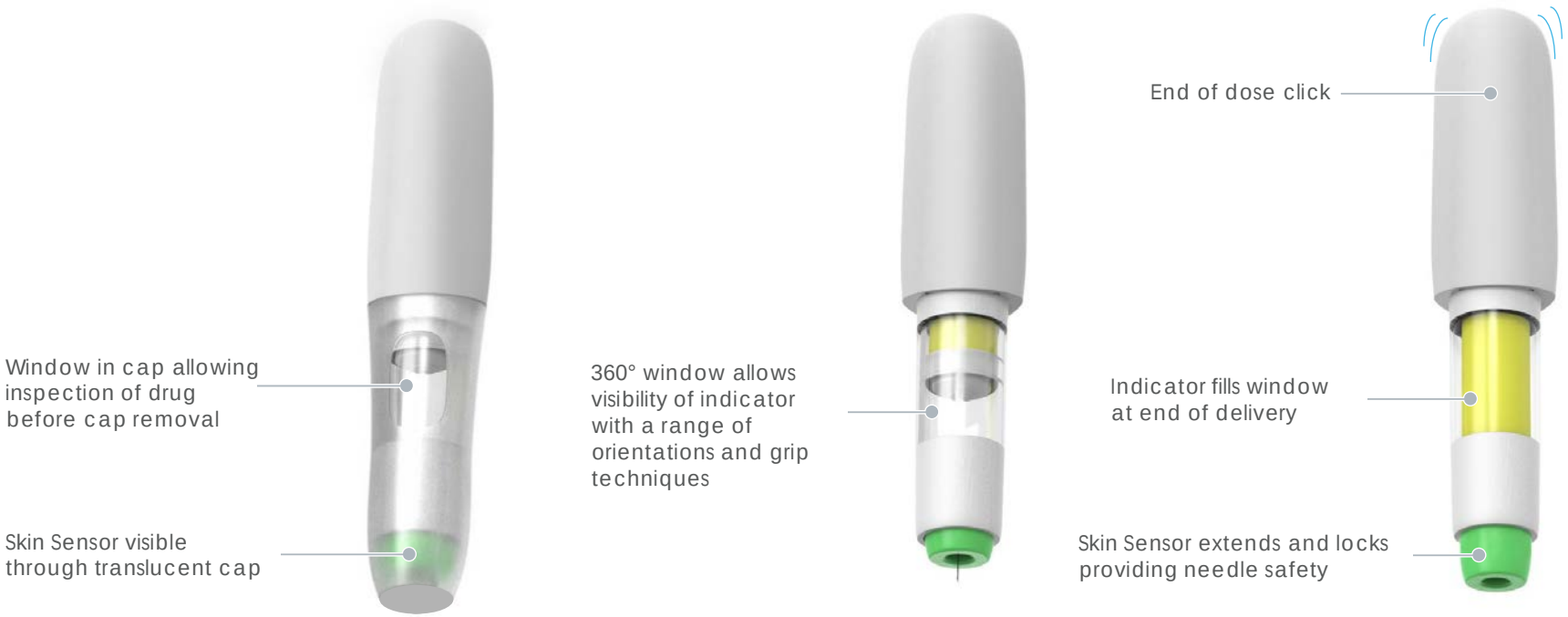
1. Cap removal
   - CCI interfaces open
     - Cap cannot be replaced
   - Power Pack released
     - Drug Pressurised
2. Activation against the skin
   - Needle insertion
   - Audible start of dose click
   - Activation of Hydraulic Valve
   - Start of drug delivery
3. Drug delivery
   - Visual progress indication (indicator moves in window)
     - Window is visible from every direction
   - Audible end of dose click
4. Removal and disposal
   - Passive needle safety mechanism



Indication during longer injection times

Convenient indication during longer deliveries:

- 360 degree window to show delivery progress from any angle
- Audible start and end of dose clicks



Overview of Bios Primary Drug Containers (PDCs)

SQ 10 ml

HV SQ 1 ml

Foil
Sterile barrier in storage

Container
COC, size based on size of standard glass cartridges

Cap
Retains the Valve components & Needle

Needle
Variety of needle gauges available (currently 27GTW and 25GTW)

Piston
Liquid barrier

Drug Volume

Needle Shield
Sterile barrier in storage

Glide force at high pressure

It is imperative that the plunger/piston operates effectively at high pressures

- low glide force
- preventing leakage past the seal

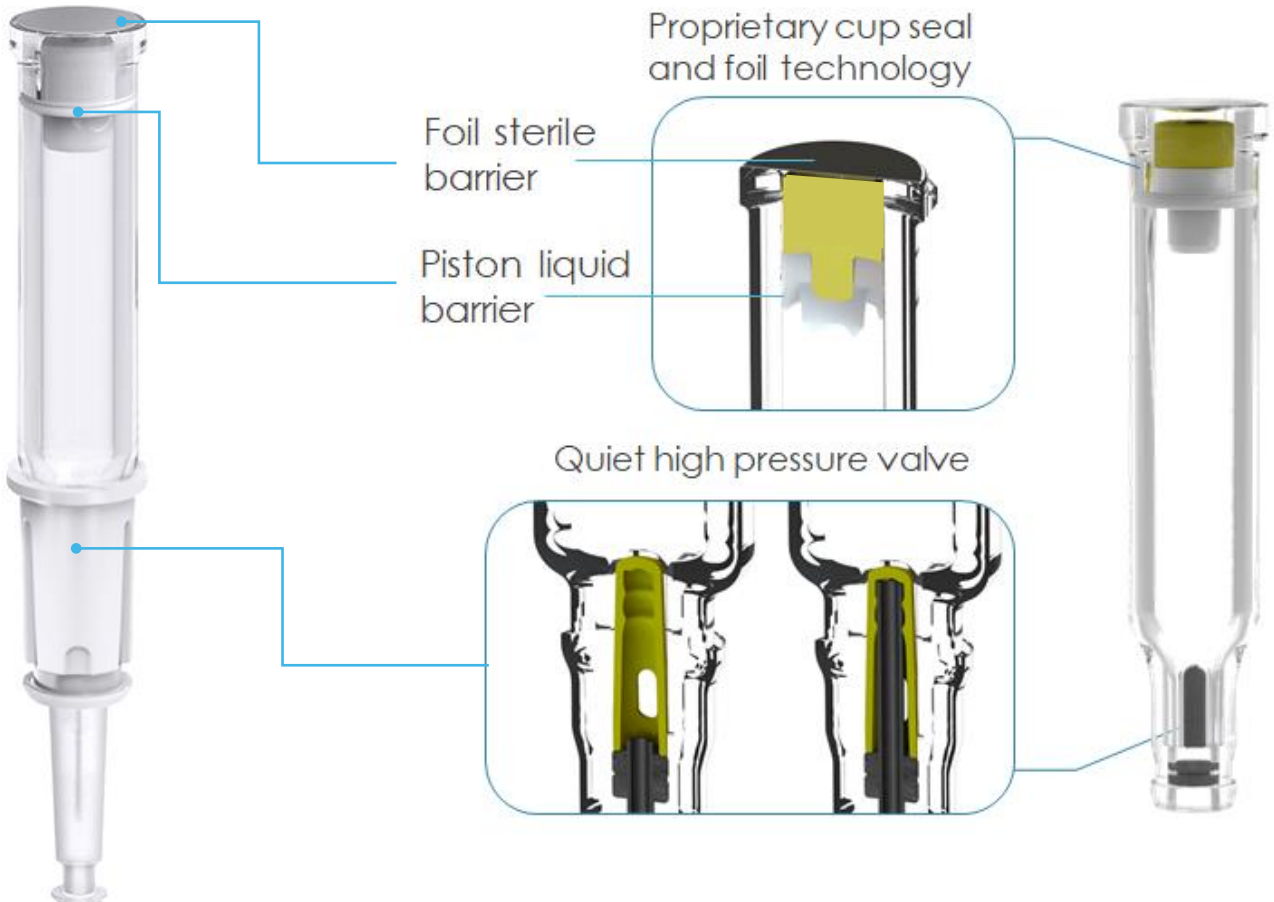
Rubber stoppers also act as sterile barriers, a challenge which can present conflicting requirements:

- Rubber stoppers have a large contact area (to seal effectively)
- Rubber is incompressible so much of the applied delivery force is translated into friction with the container wall over its entire contact area

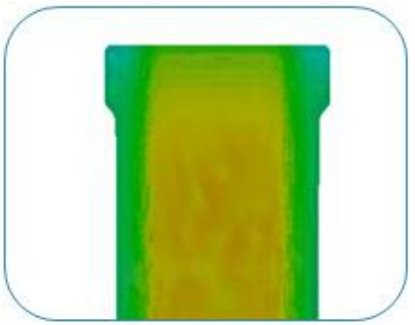
The high-pressure **cup seal and foil** technology employed by Oval decouples the sterile and liquid barrier functions from one another

- HDPE cup seal (lubricant free fluid seal)
  - Lubricious,
  - Self energising
- Foil (Sterile barrier) pierced during pressurisation

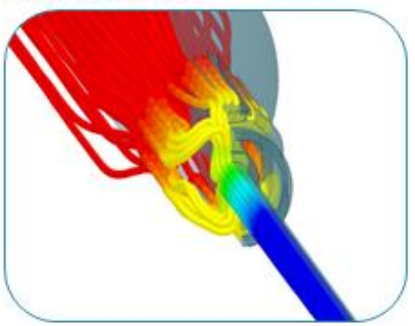
Overview of Bios Primary Drug Container (PDC)



FEA optimisation of Container wall



Optimised flow path for viscous fluids

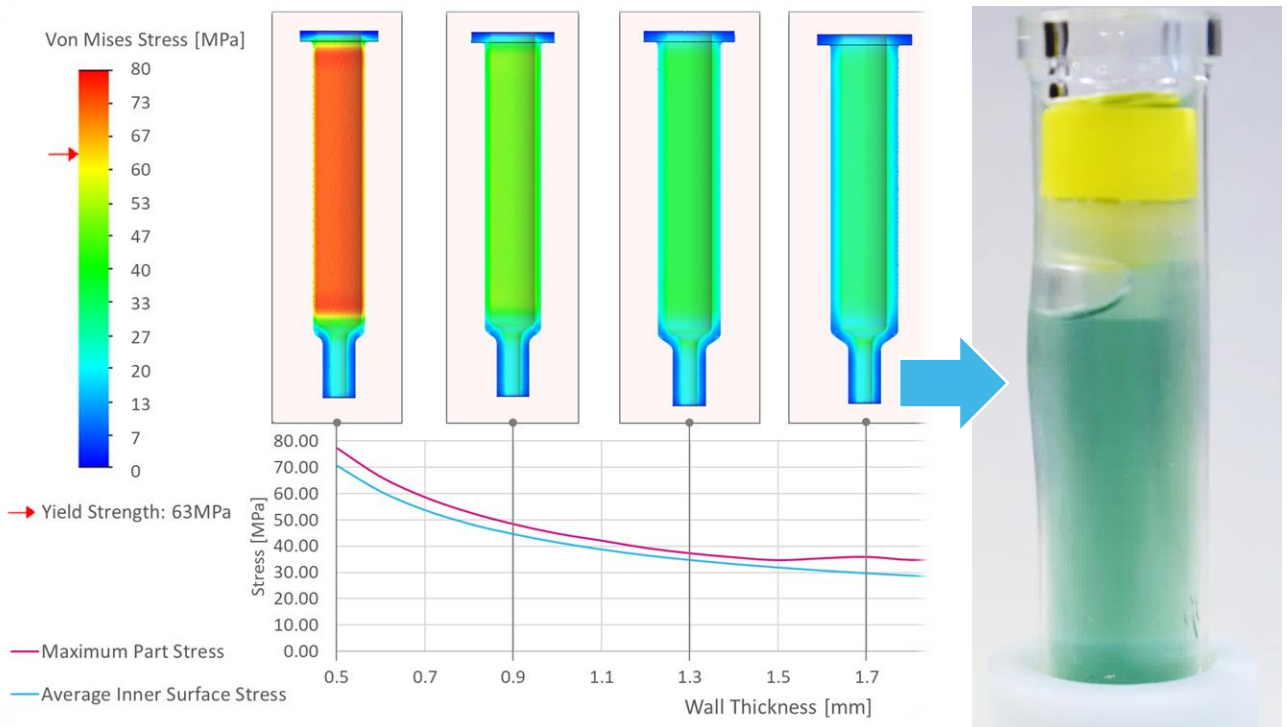


Container robustness

- FEA optimisation of Container & Piston for maximum burst pressure

- COC container optimized using FEA to tolerate maximum pressure of 300 bar (100 bar operating pressure)

- In testing failure occurs in a plastic and gradual manner, without the brittle and sometimes explosive behavior seen with glass

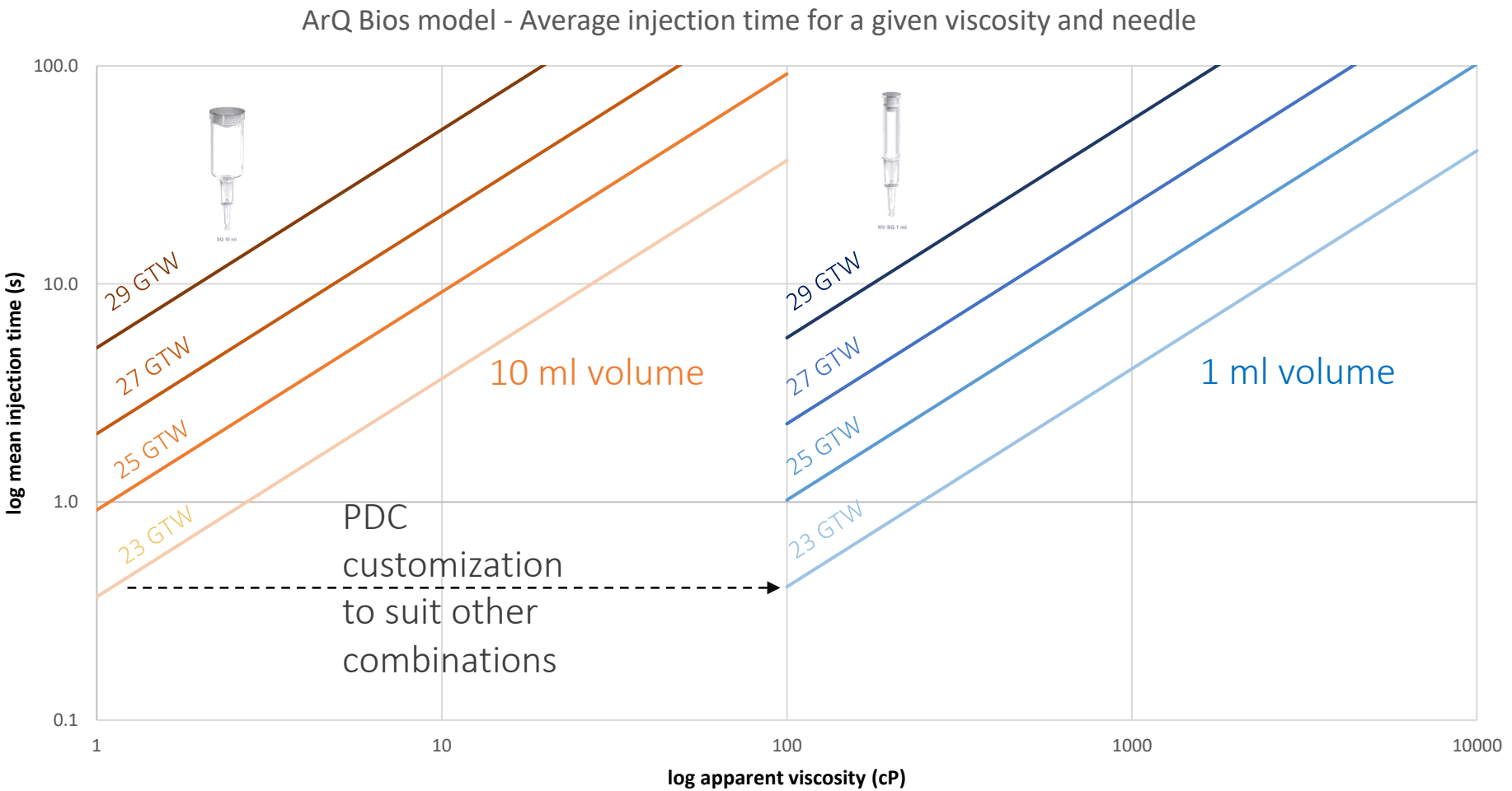


Container robustness

Specimen ID	Maximum Force (N)	Top of container		Bottom of container	
		Diameter (mm)	Pressure (bar)	Diameter (mm)	Pressure (bar)
01	937.010	6.42	289.600	6.28	302.660
02	980.450	6.42	303.030	6.28	316.690
03	865.950	6.42	267.640	6.28	279.710
04	934.050	6.42	288.690	6.28	301.710
05	947.090	6.42	292.720	6.28	305.920
σ	41.722		12.896		13.475
μ	932.910		288.336		301.338
μ+3σ	1058.076		327.023		341.764
μ-3σ	807.744		249.649		260.912

- The ArQ Bios High Pressure COC containers testing illustrates the strength of the COC containers as well as the gradual and plastic failure as over-pressure is reached

Possible range of times and viscosities



Representative assumptions made about glide force (formulation dependant)

Manufacture

Manufacturing, Filling and Sterilisation

Standard Fill in aseptic environment (Nest and Tub format)

1: Sterilised SA (Nest and Tub)

2: Bottom-up filling (peristaltic or piston pump)

3: Piston Insertion (Vacuum)

4: Foiling

Manufacturing, Filling and Sterilisation

Variant 2: Tip fill with high viscosity
(virtually bubble free fill,
requires custom filling line)

1. Sterilised Sub Assembly (SA)

2. Tip Fill

3. Valve attachment

4. Foiling

Manufacturing, Filling and Sterilisation

Variant 3: Tip fill with low viscosity
(virtually bubble free fill,
requires custom filling line)

1. Sterilised and Foiled Sub Assembly (SA)

2. Bottom-up filling through front

3. Valve attachment

4. Placed in Nest

Summary

- Most combination-product experts consider the best time to incorporate a device is in early stages of drug development
- Introducing a device platform in early clinical stages leaves time to discuss the proposal with regulatory agencies and respond to contextual questions (decreasing cycle time for new product development)
- Committing to a device early poses a risks if it cannot achieve the required performance

Advantages of ArQ Bios:

- Easy to use in a home environment (less restricting technology than wearables)
- Capable of sustaining higher pressures than possible with glass primary packaging
- Lubricant and adhesive-free
- Can change container size without significantly affecting design architecture
    - As much flexibility as possible during drug/formulation development

Thank you

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