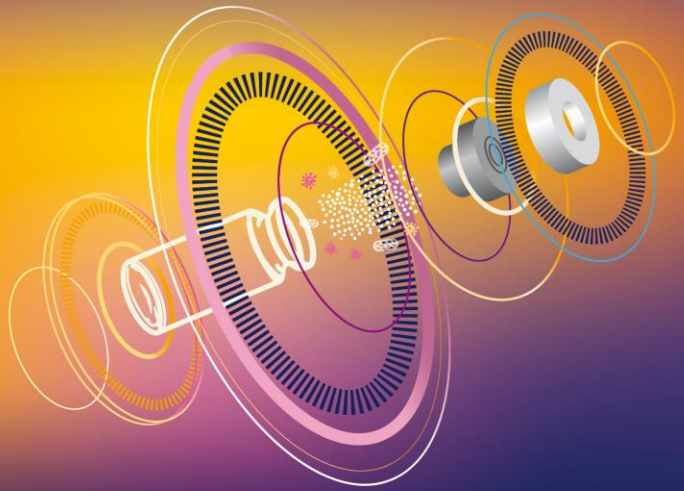
Glass Type Selection's Influence on Vial Interactions



NIPRO PHARMAPACKAGING

Dave Lisman, Technical Director

PDA Parenteral Drug Association

2020 PDA EUROPE
Parenteral Packaging

25-26 FEBRUARY 2020
BASEL | SWITZERLAND

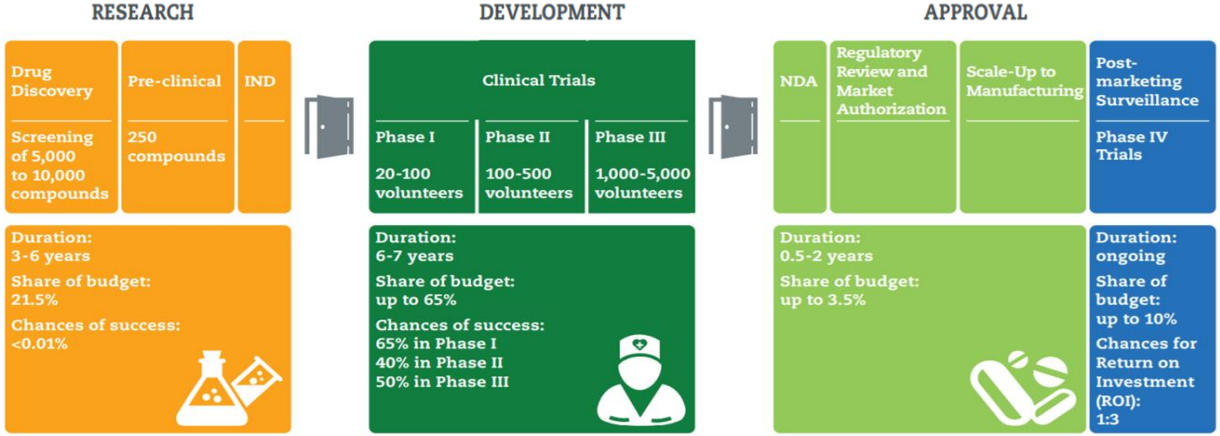
CONNECTING PEOPLE SCIENCE AND REGULATION®

Agenda

- Drug Development & Parenteral Packaging Configurations
- Factors affecting container selection
- In-depth examination of influence of certain buffers on Type 1 glass types

Drug Development

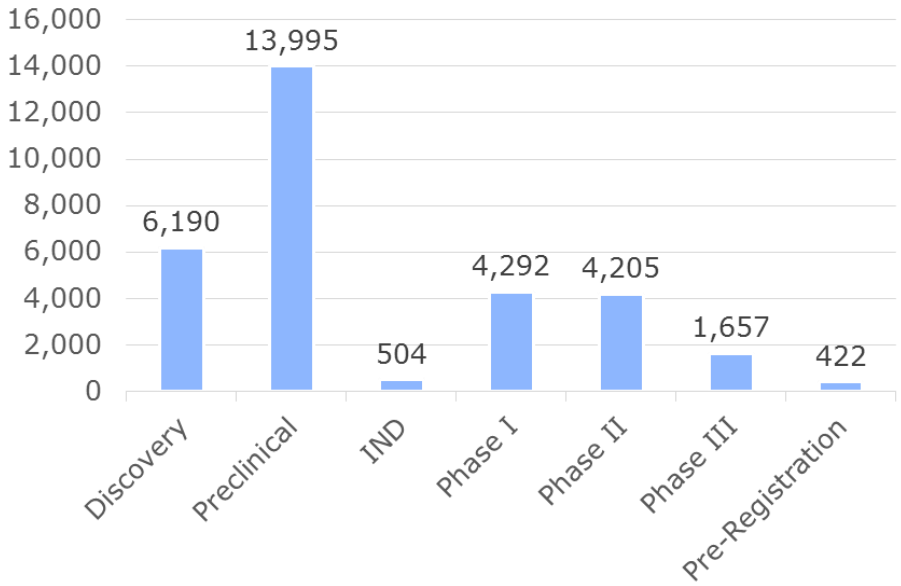
- Drug development is always initiated by a patient need, following a well prescribed R&D pathway to regulatory review and market authorization



- Does investigating the current pipeline and recent drug approvals tell us something about the direction and need for primary parenteral packaging?

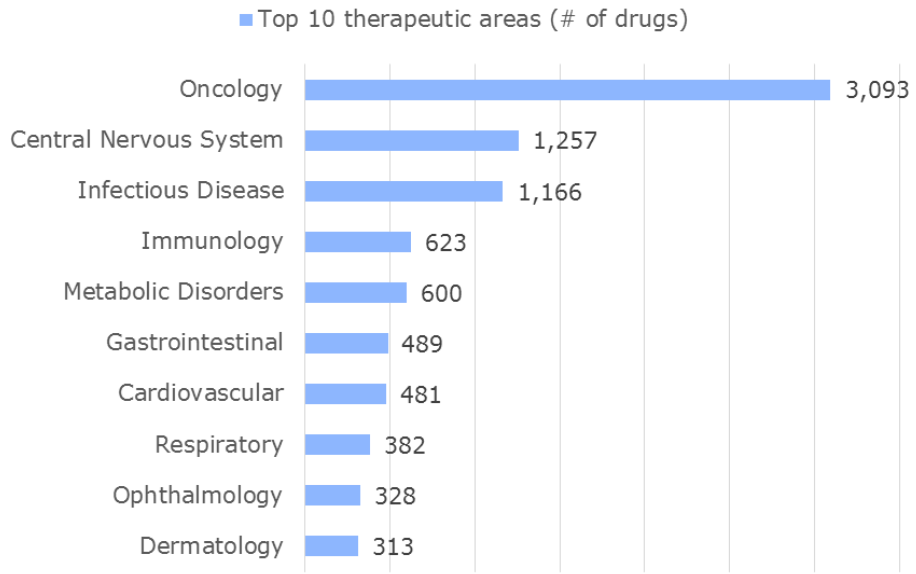
Drugs per Phase (R&D)

- Approximately 6-7 years are required to advance a drug from Phase I to an NDA



Drugs Under Development – Therapeutic Area

- > 10,000 drugs in development

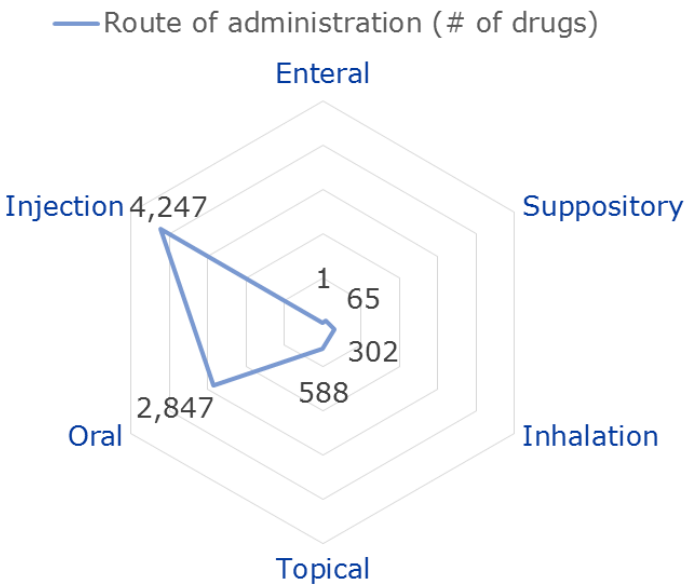


* Phase I, II, III, Pre-registration

www.globaldata.com – Multiple databases

Drugs under Development by Route of Administration

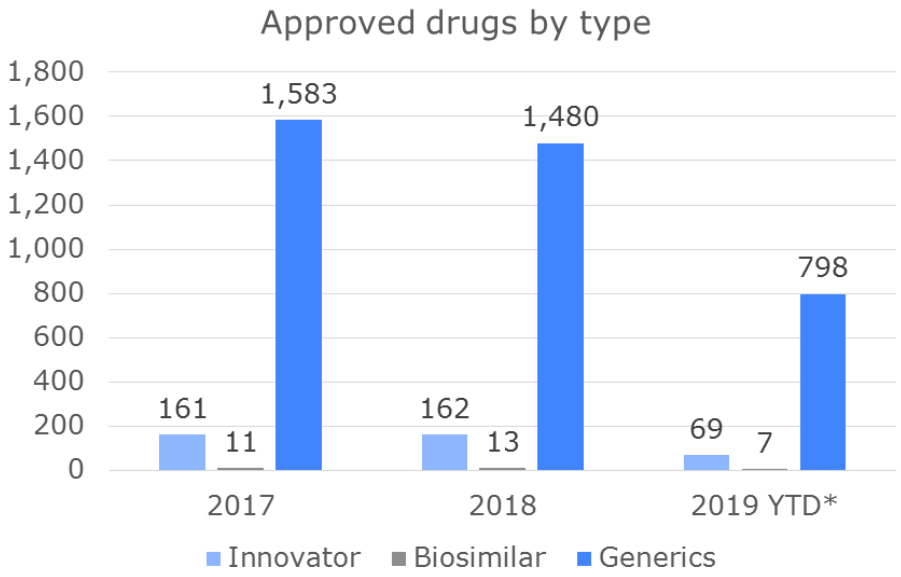
- Within the next 6-7 years injection and oral will stay the most dominant routes of administration



* Phase I, II, III, Pre-registration

Approved Drugs

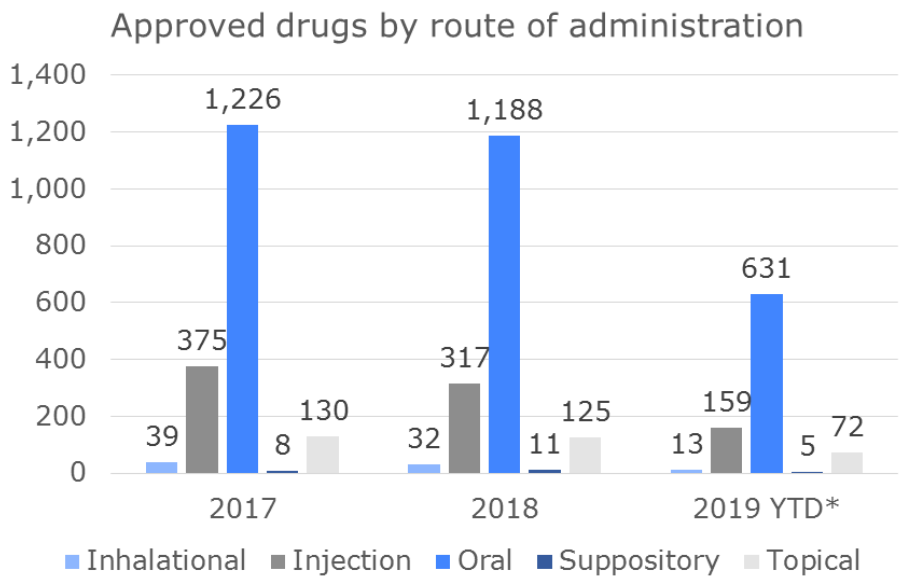
- Innovators = Patented drug
- Generics lead the way over the last 3 years
  - Speed to market is a critical component



*Jan 2019 – Aug 2019

Approved Drugs – Route of Administration

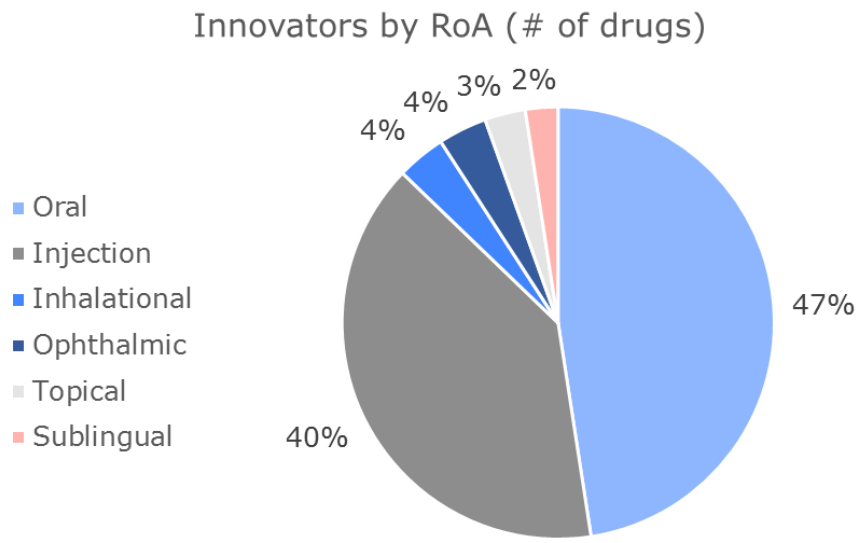
- Oral appears as the dominating route of administration
- Earlier, we saw injection as the strongest route of administration in drug development
- Multiple routes of administration are possible for one drug



*Jan 2019 – Aug 2019

Approved New Drugs – Route of Administration - Innovators 2018

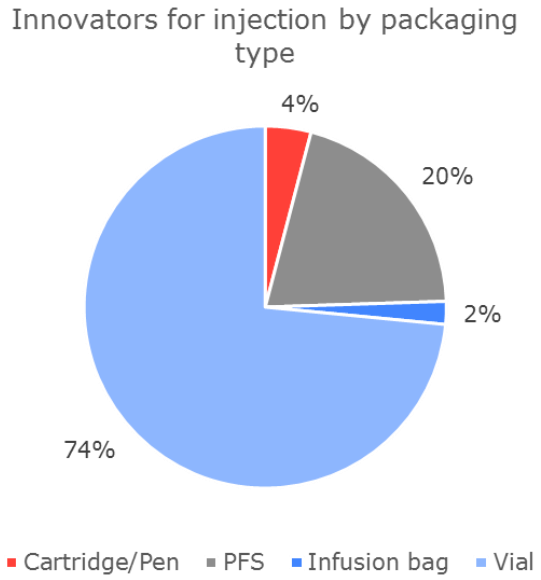
- To ensure no trends are overlooked, we look at the pool of innovators only
- Injection and oral administration remains the largest share



www.globaldata.com – Multiple databases

Approved New Drugs – Innovators for Injection 2018

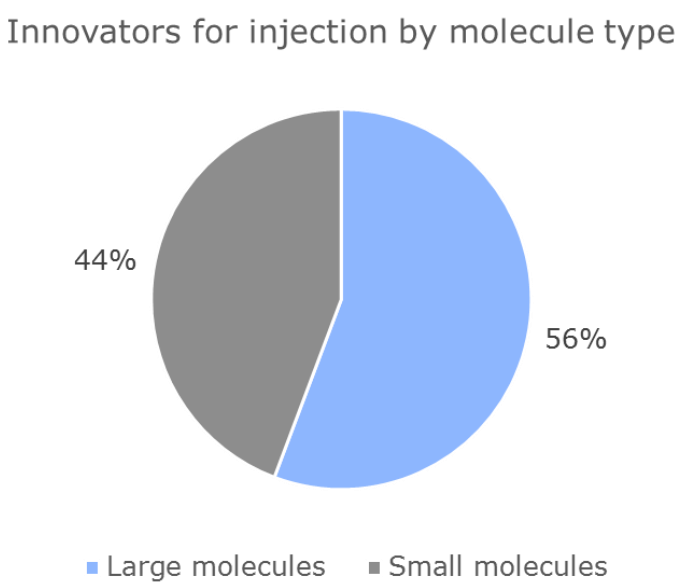
- Looking even closer, we see vials remain as the largest share



www.globaldata.com – Multiple databases

Approved New Drugs – Innovators for Injection 2018

- Types of Molecules
  - Large molecule drugs are highly sophisticated and require the best protection in glass packaging



www.globaldata.com – Multiple databases

Container Selection – Injectable Example

Patient Need

Drug Research & Development

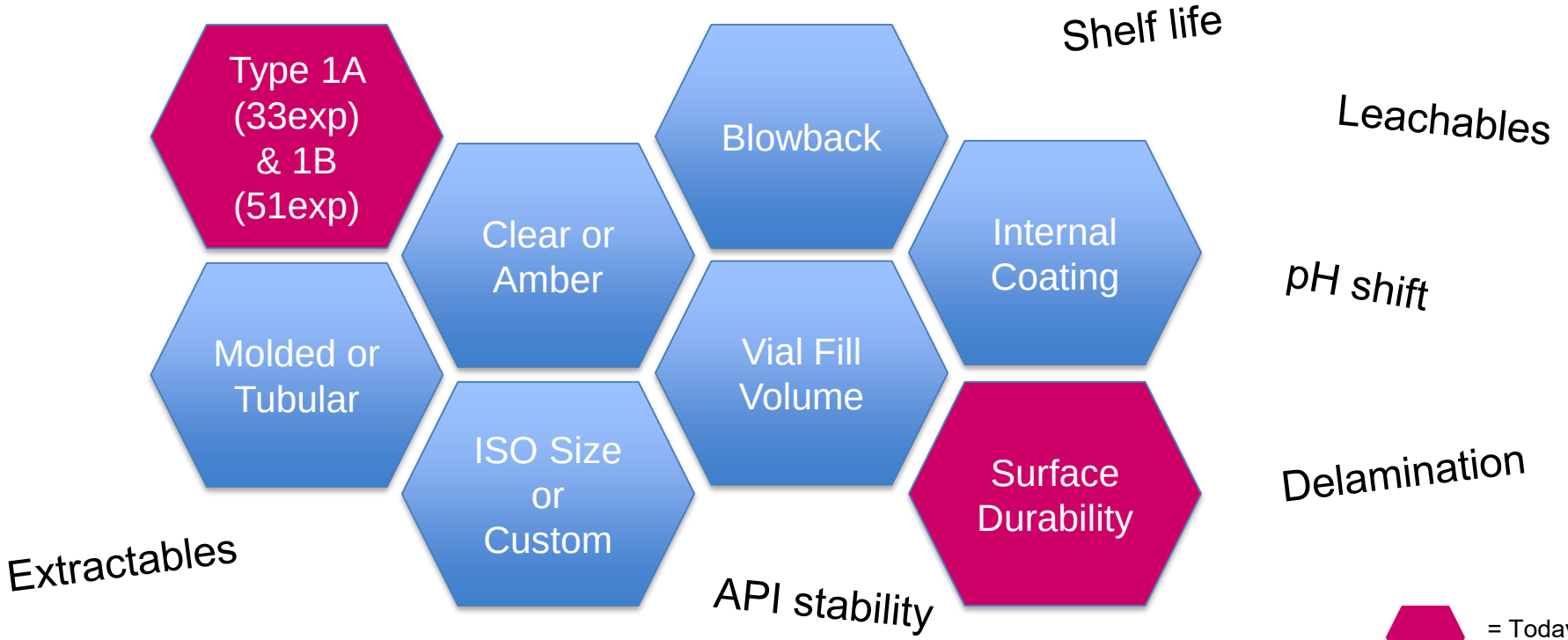
Injectable Packaging Selection

(vial, syringe, cartridge, ampoule, etc.)

Vial Selection and Requirements

Safety and Efficacy

Vial Selection



Stability Test Outline

- Long term stability test conducted examining impact of surface durability and glass type on overall interaction with defined buffers
- Conditions:
  - Inline with ICH Q1A(R2)
  - 40°C for minimum of 6 months
- Metrics included:
  - Hydrolytic Resistance per EP 3.2.1 and USP <660>
  - Extractables
  - Surface interaction

Type 1A (33exp), 1B (51exp) Comparison ASTM E438

Approximate Constituents from ASTM

Element Weight %	1A (33exp)	1B (51exp)
SiO_2	81	73
B_2O_3	13	10
Al_2O_3	2	7
BaO	-	0-2
CaO	-	1
Na_2O	4	6
K_2O	-	1

Drives Physical & Chemical Properties

Property*	1A (33exp)	1B (51exp)
Expansion 10^{-7} K^{-1}	32-33	48-56
Annealing Pt (°C)	560	574
Softening Pt (°C)	815-820	783-799
Density (g/cm^{-3})	2.23-2.23	2.33-2.36
Chemical Durability (titration with 0.02N H2SO4 / 10g)	1.0ml Max	1.0ml Max

**Nominal Values Shown from ASTM*

Material List

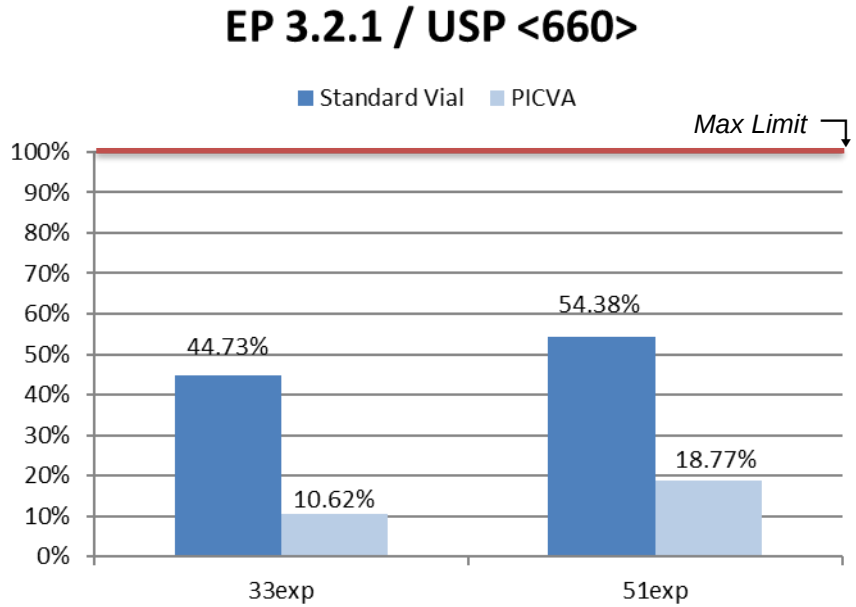
Surface Durability

Type 1A (33exp) & 1B (51exp)

- Vial Selection
  - 2R (defined by ISO 8362-1)

Glass Type	Category
Class A (33exp)	Standard
Class A (33exp)	VIALEX™ (PICVA)
Class B (51exp)	Standard
Class B (51exp)	VIALEX™ (PICVA)

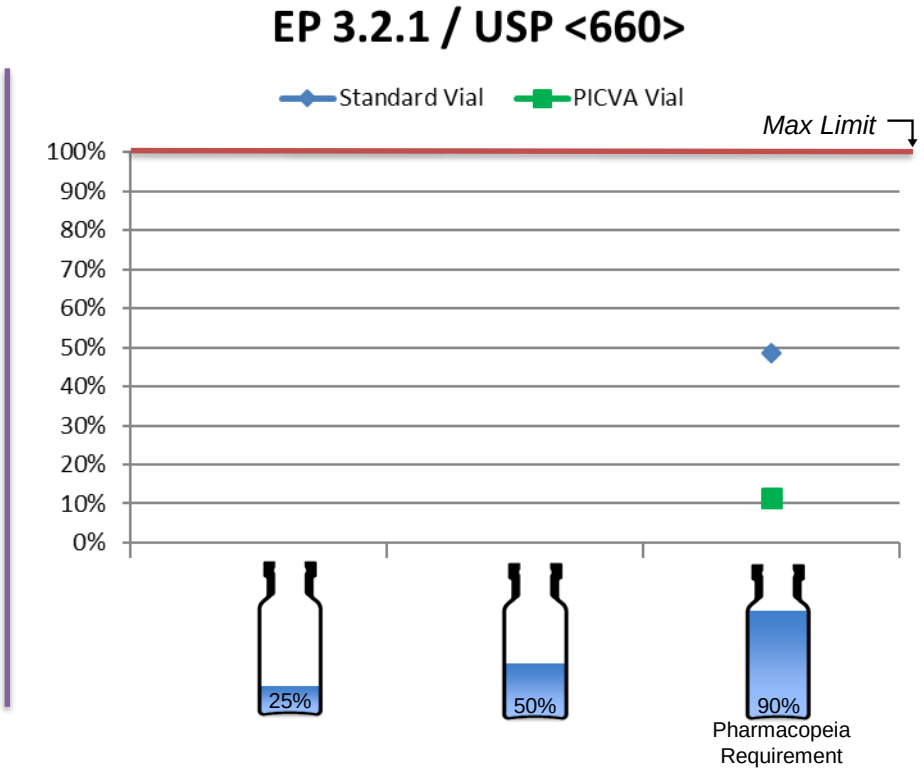
- Stopper Selection
  - Westar RS B2-40 Fluro-Tec stoppers



VIALEX™ achieved through Plasma Impulse Chemical Vapor Ablation (PICVA) process, delivering a step change improvement in surface durability.

Fill Level Impact

- Chosen at 90% of overflow in line with pharmacopeias
- Varying fill levels can effect results
- Low concentration of mobile alkali and consistency of inner surface can decrease impact especially in small fills



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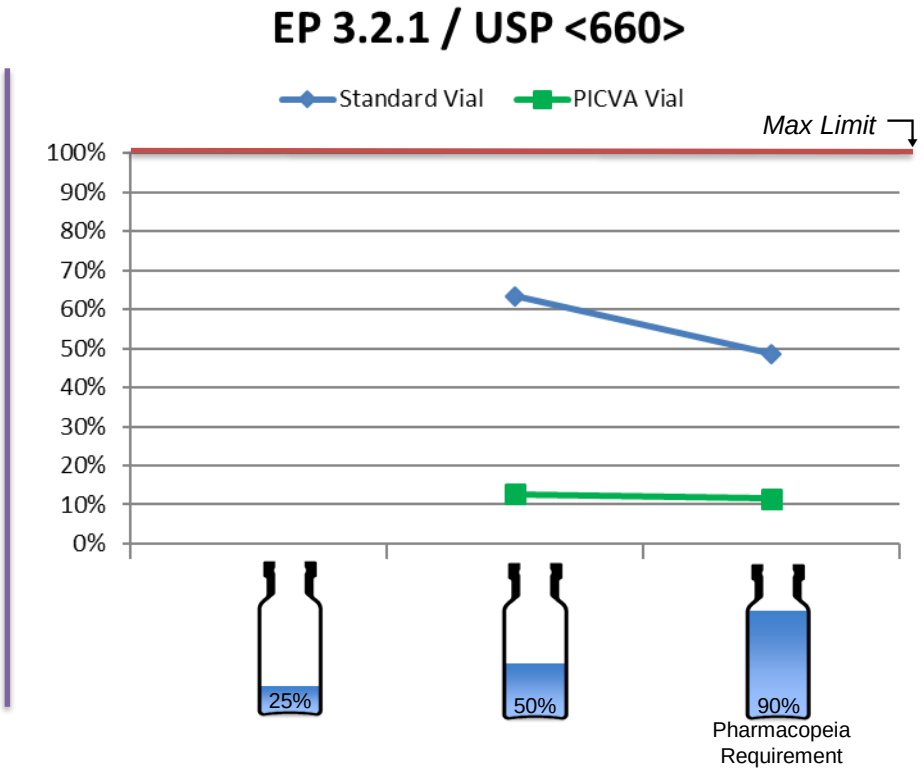
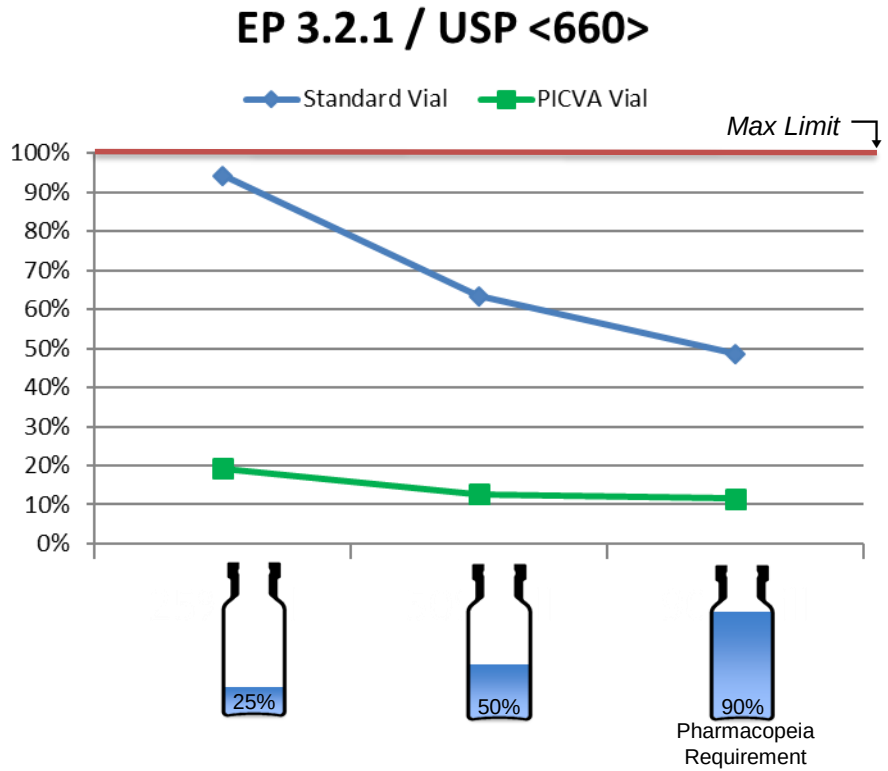


Fill Level Impact

- Chosen at 90% of overflow in line with pharmacopeias
- Varying fill levels can effect results
- Low concentration of mobile alkali and consistency of inner surface can decrease impact especially in small fills
  - Notice consistency of alkali concentration in PICVA vial regardless of fill volume



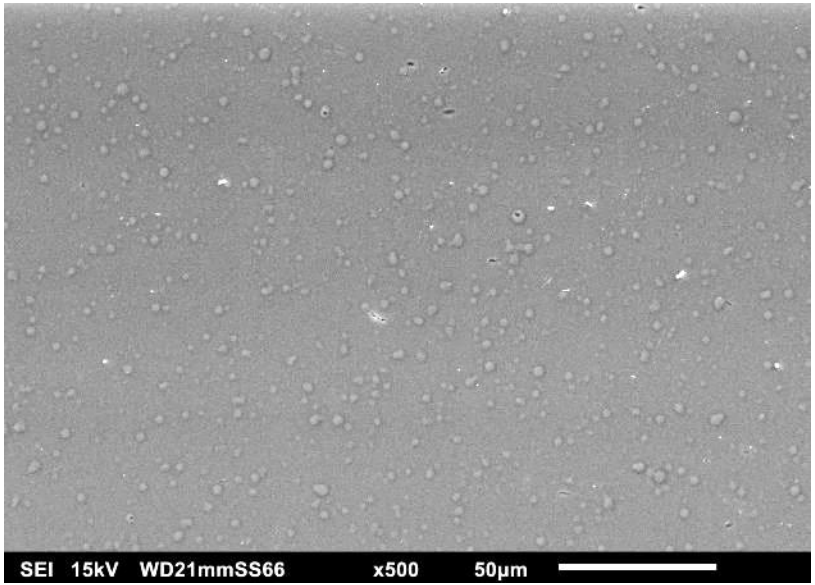
Buffers

- Phosphate
  - 10 mMol: pH 7.0 with 150 mMol NaCl and 0.005% Tween 20
- High Purity Water
  - 5.5pH
- Citrate
  - 10 mMol: pH 6.0 with 150 mMol NaCl and 0.005% Tween 20
- NaCl with Terminal Sterilization
  - 0.9%, 5.2pH

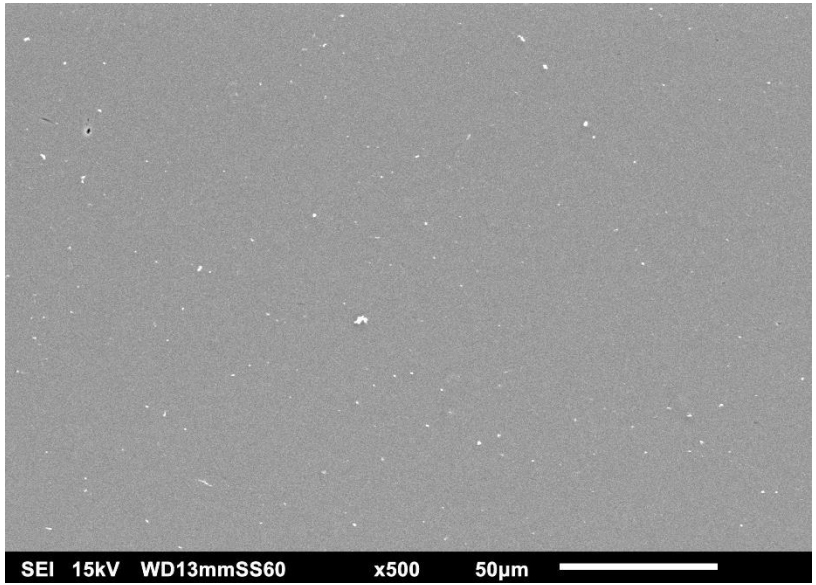
Initial State

SEM Inner Surface Condition

Initial State – SEM – 51exp



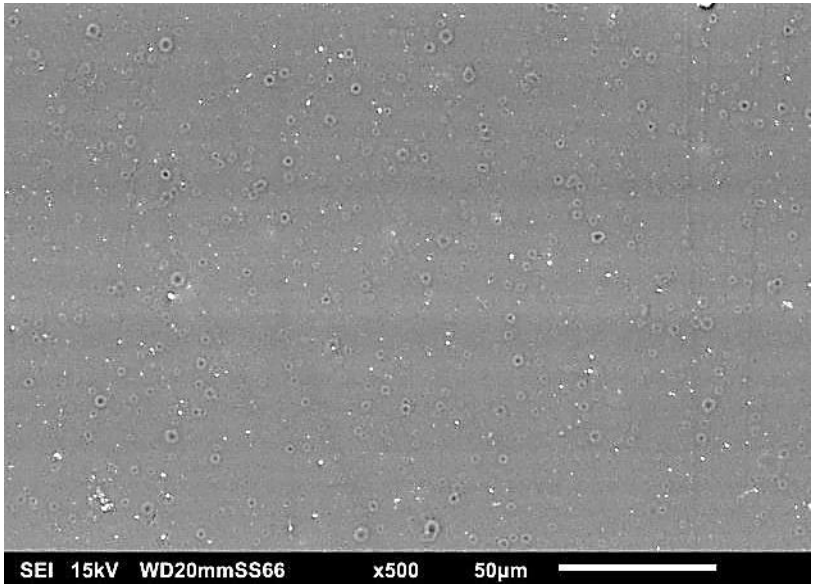
Standard Vial



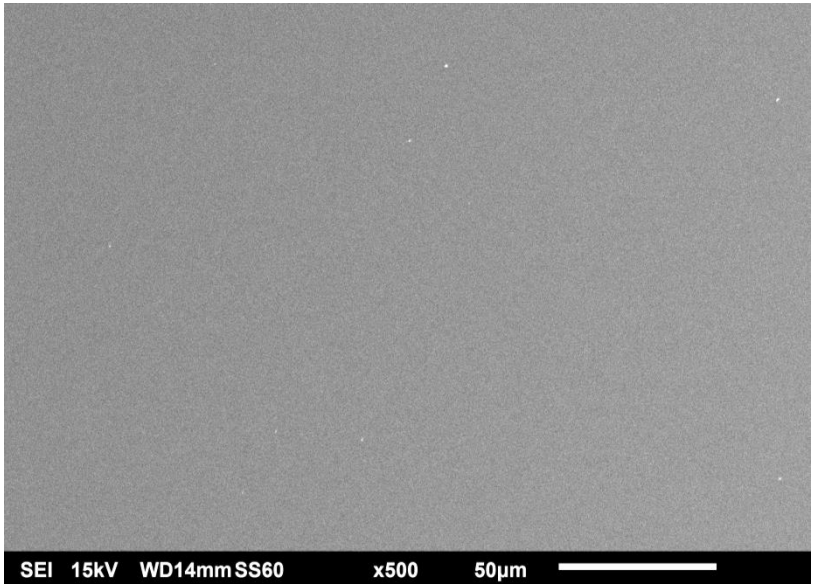
PICVA Vial

- Noticeable reduction in surface alkalinity

Initial State – SEM – 33exp



Standard Vial



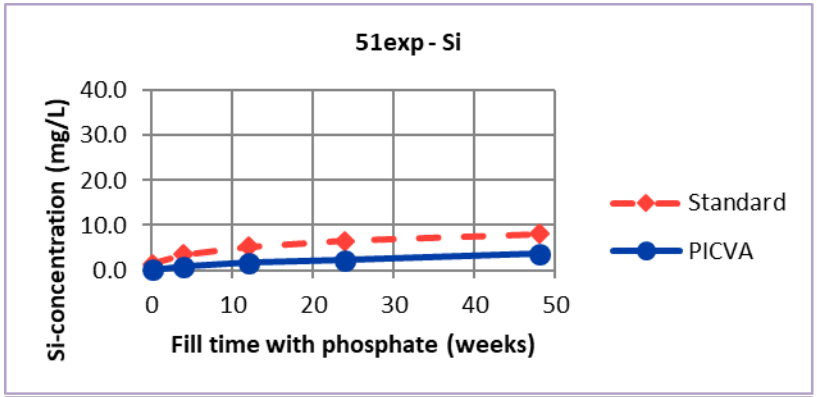
PICVA Vial

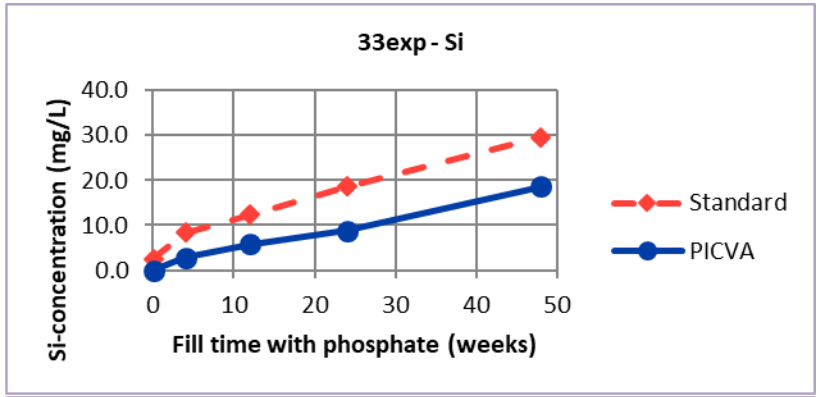
- Noticeable reduction in surface alkalinity

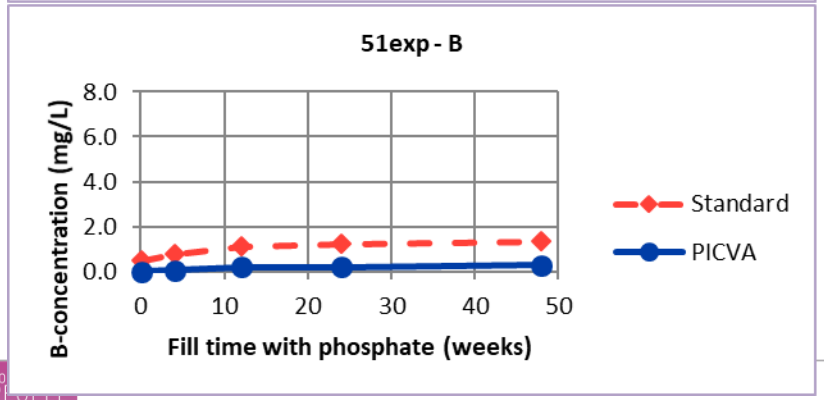
Phosphate

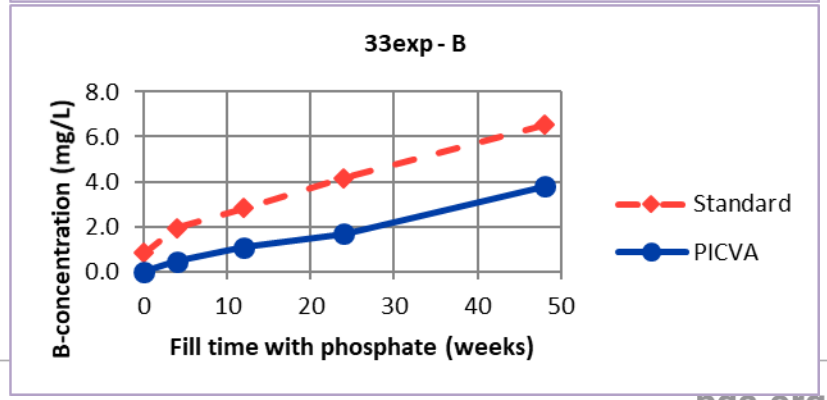
10 mMol: pH 7.0 with 150 mMol NaCl and 0.005% Tween 20

Extractables - Phosphate



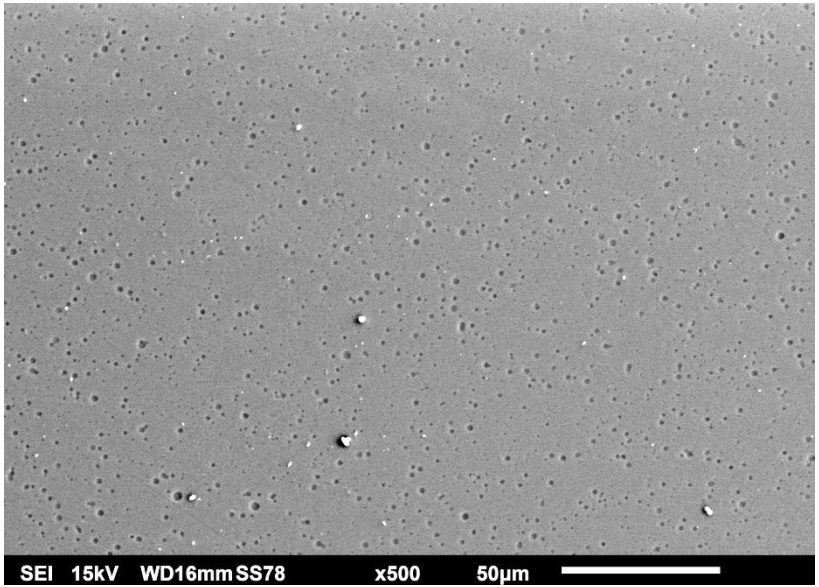




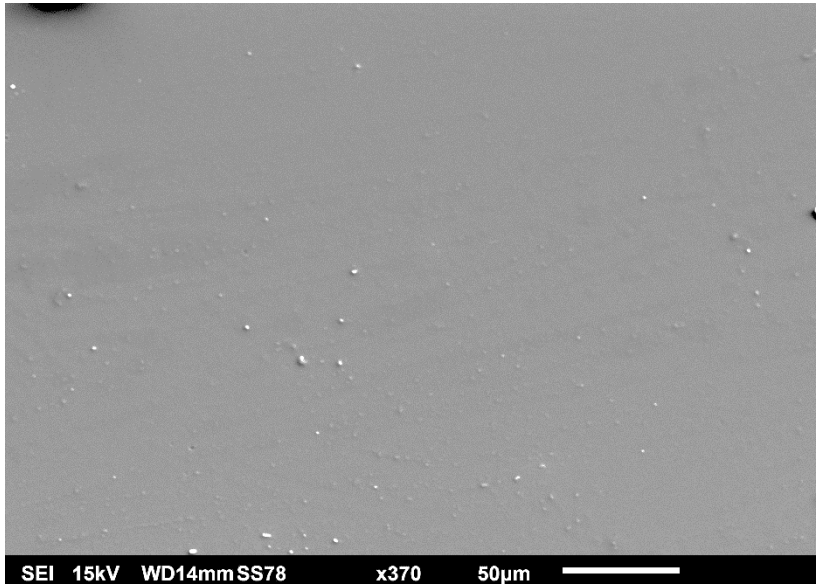


SEM – 24 weeks @ 40ºC – 51exp

Phosphate



Standard Vial

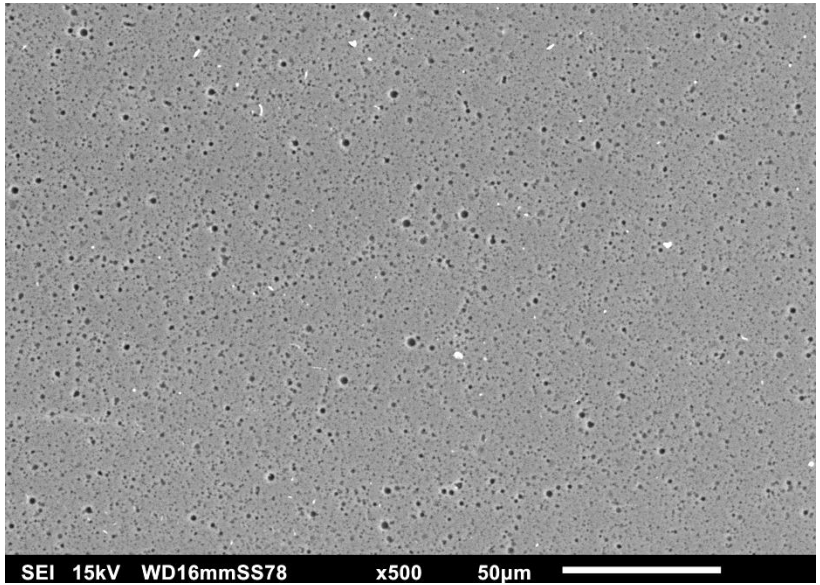


PICVA Vial

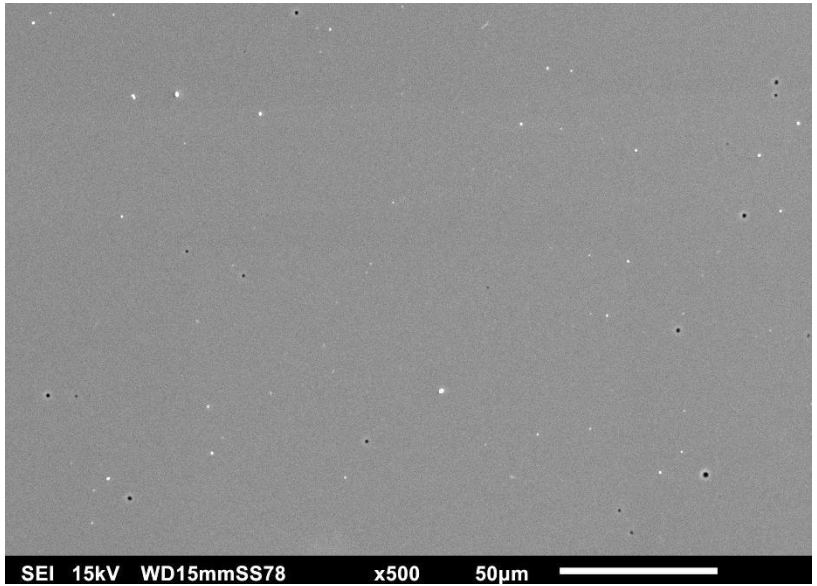
- Noticeable improvement in surface durability (less interaction)

SEM – 24 weeks @ 40ºC – 33exp

Phosphate



Standard Vial



PICVA Vial

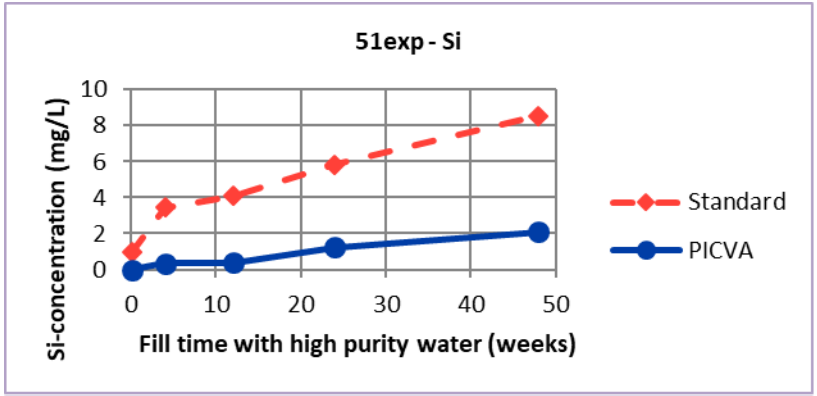
- Noticeable improvement in surface durability (less interaction)

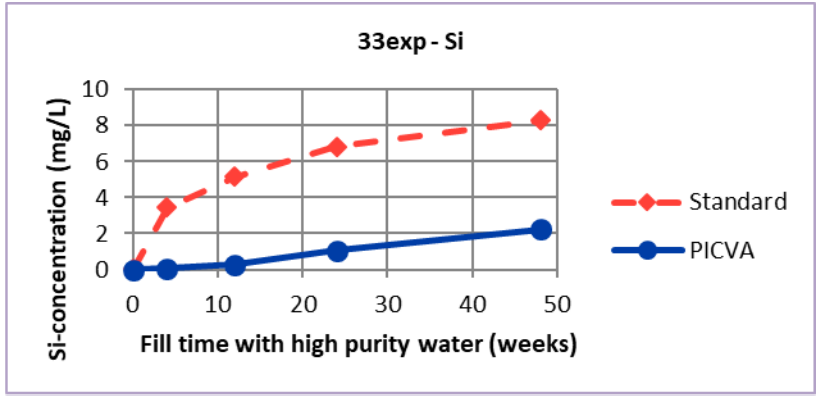
High Purity Water

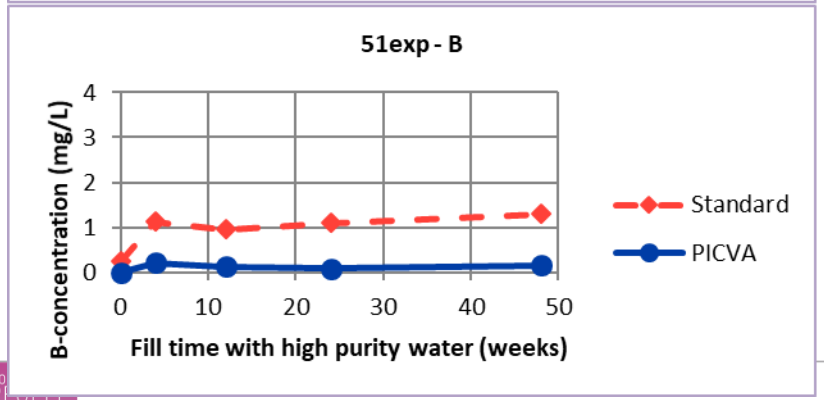
Compliant with USP/EP (>18megaohm·cm)

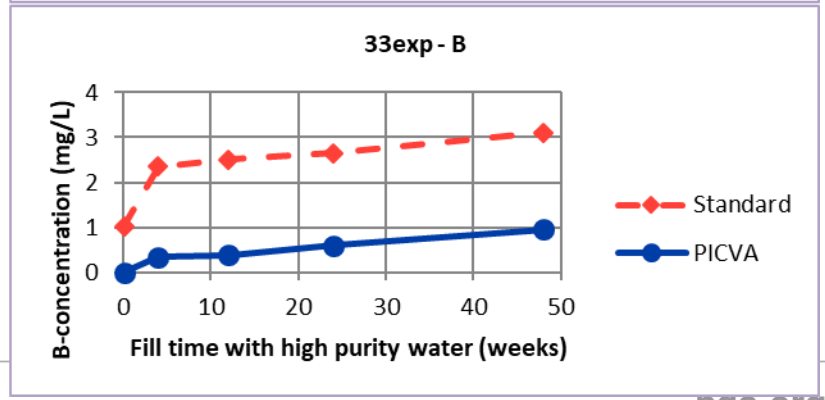
5.5pH

Extractables – High Purity Water

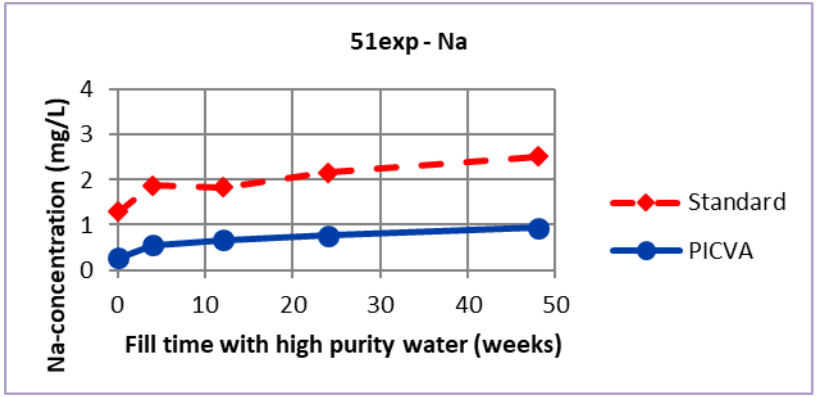


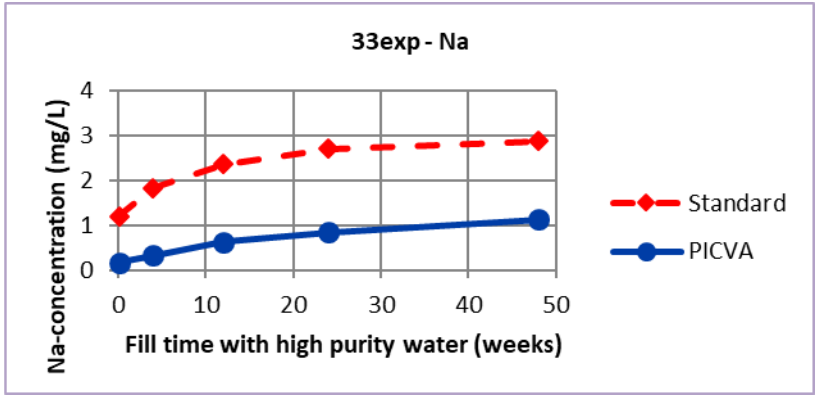






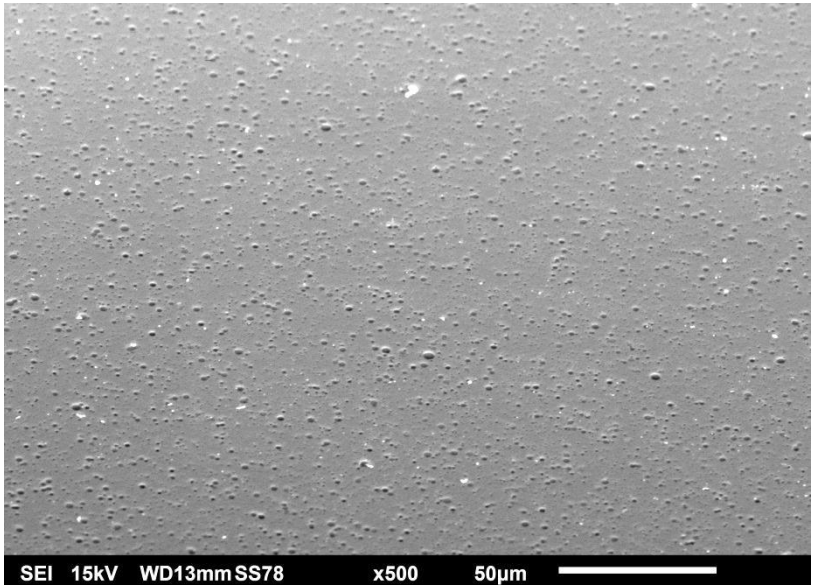
Extractables – High Purity Water



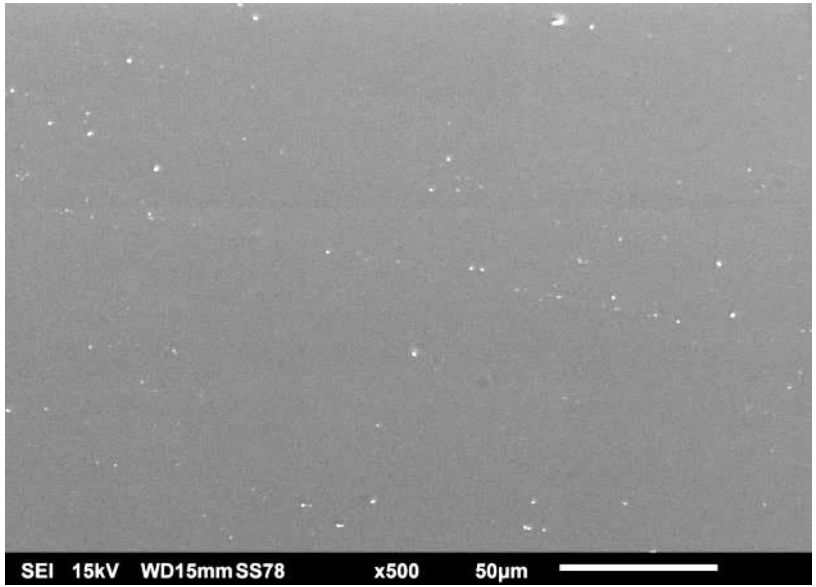


SEM – 24 weeks @ 40ºC – 51exp

High Purity Water



Standard Vial

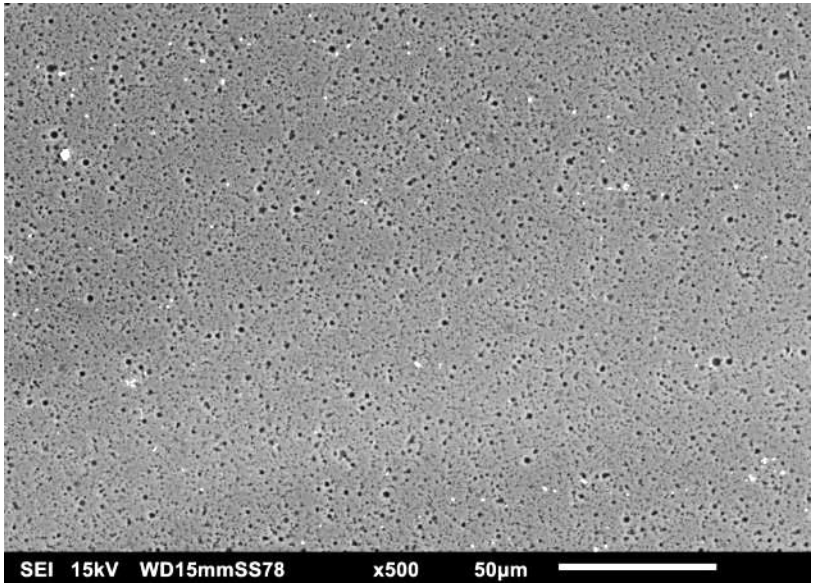


PICVA Vial

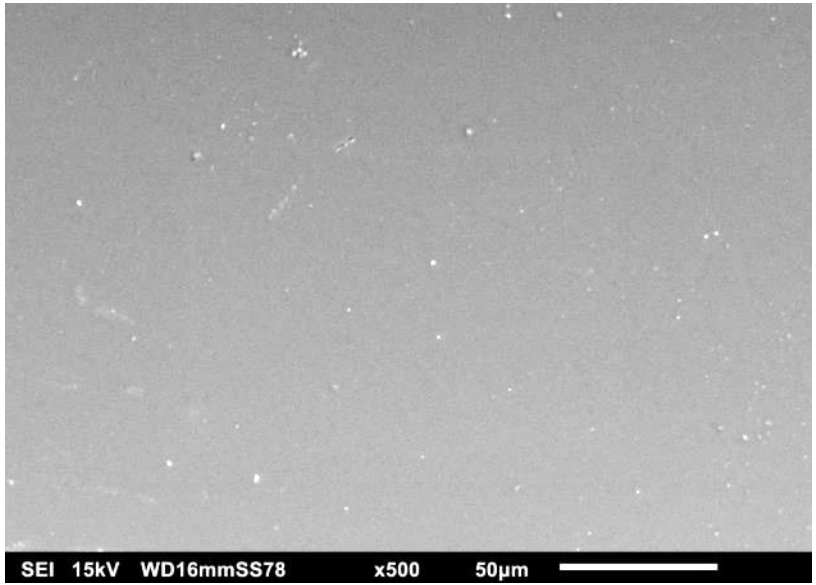
- Noticeable improvement in surface durability (less interaction)

SEM – 24 weeks @ 40°C – 33exp

High Purity Water



Standard Vial



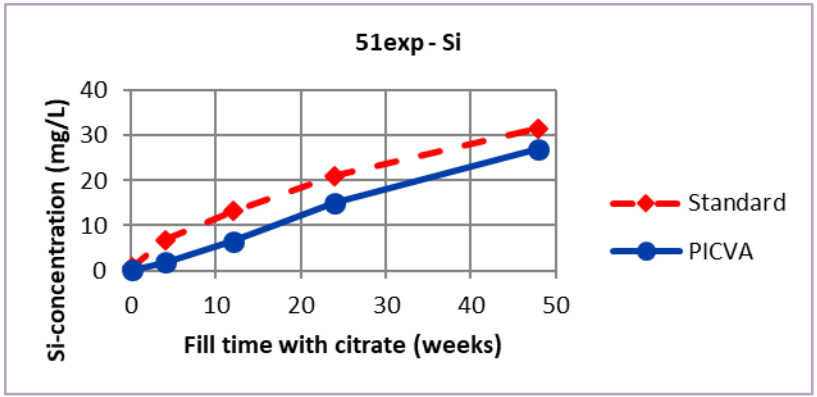
PICVA Vial

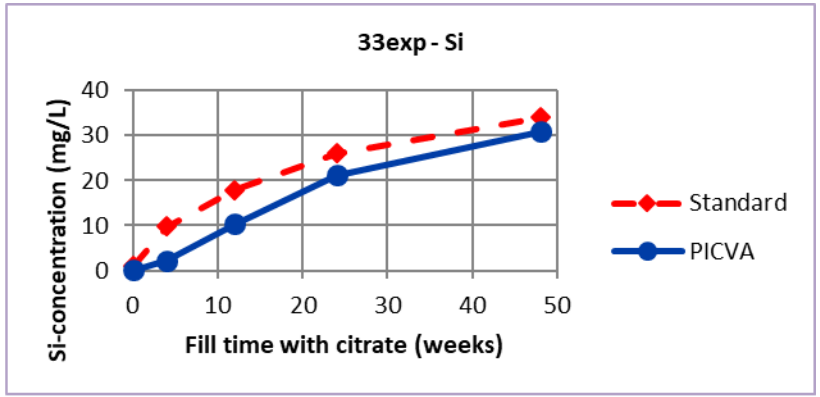
- Noticeable improvement in surface durability (less interaction)

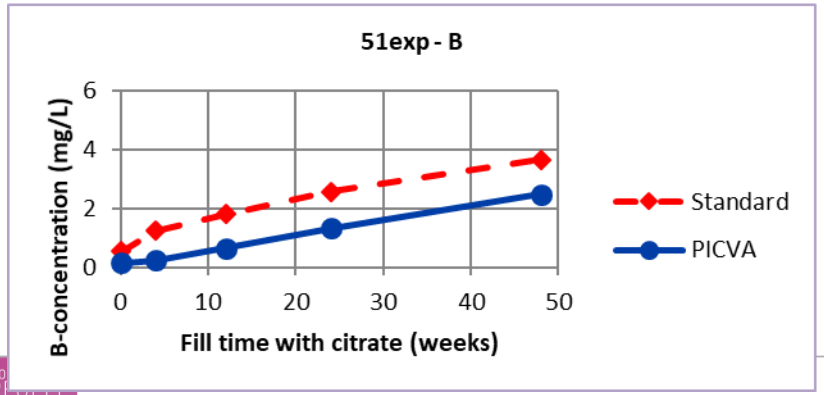
Citrate

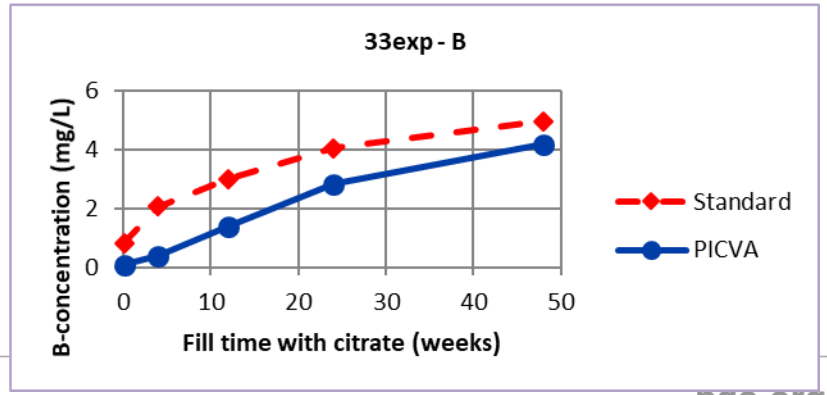
10 mMol: pH 6.0 with 150 mMol NaCl and 0.005% Tween 20

Extractables – Citrate



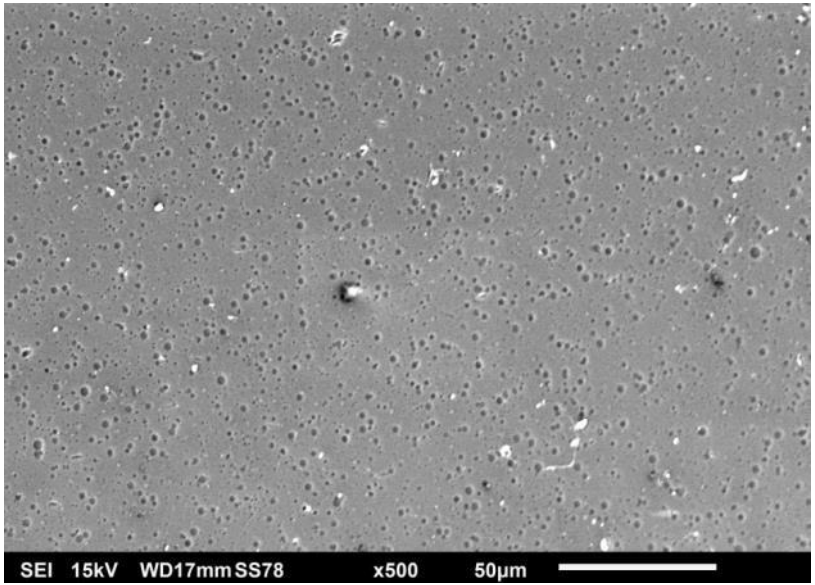




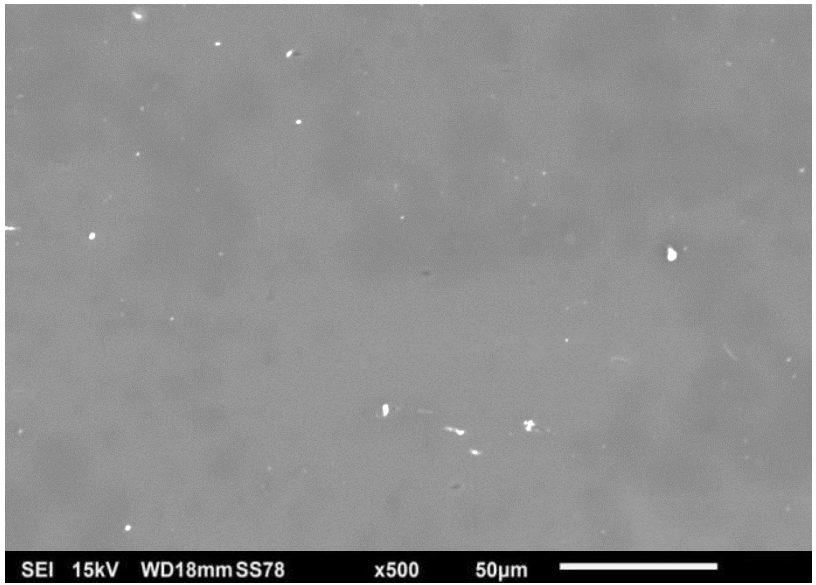


SEM – 24 weeks @ 40ºC – 51exp

Citrate



Standard Vial

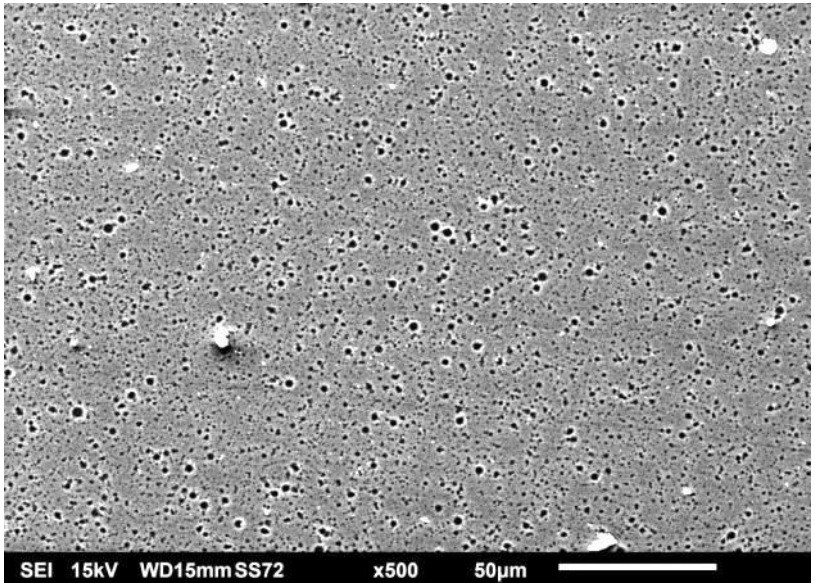


PICVA Vial

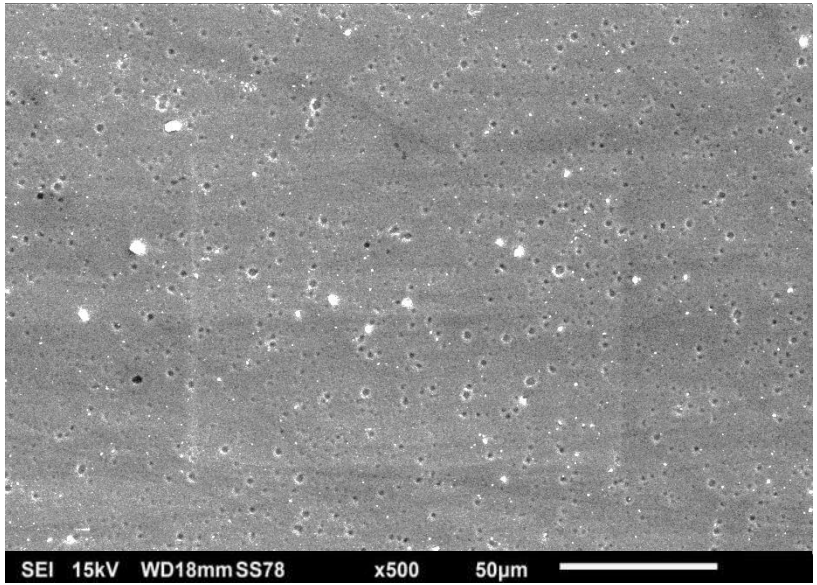
- Noticeable improvement in surface durability (less interaction)

SEM – 24 weeks @ 40ºC – 33exp

Citrate



Standard Vial



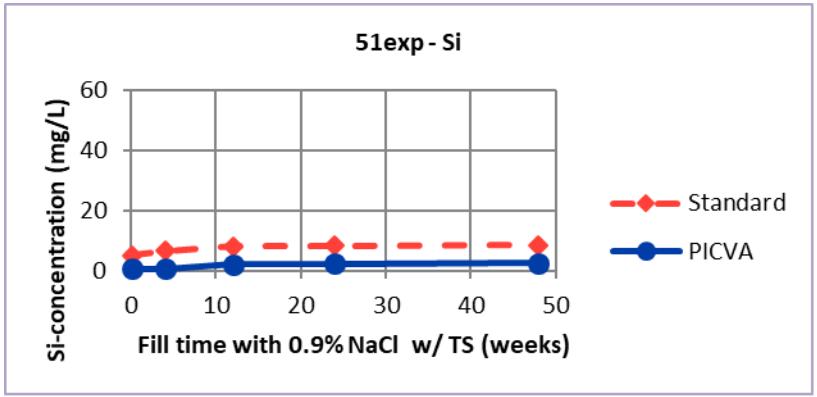
PICVA Vial

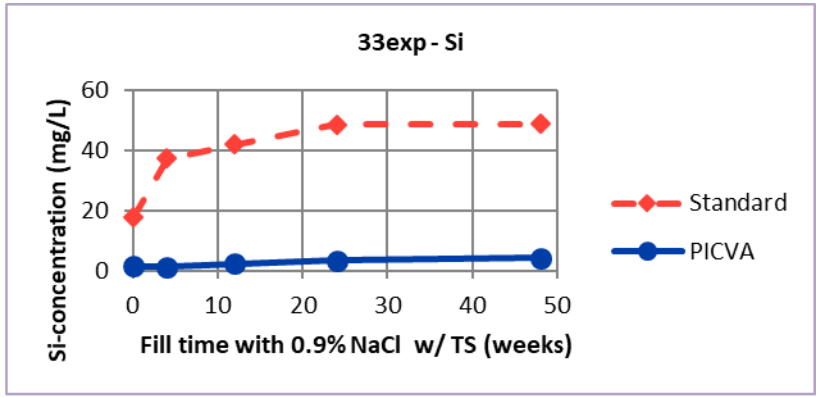
- Observable interaction in both cases suggests non-ideal arrangement of buffer and glass type

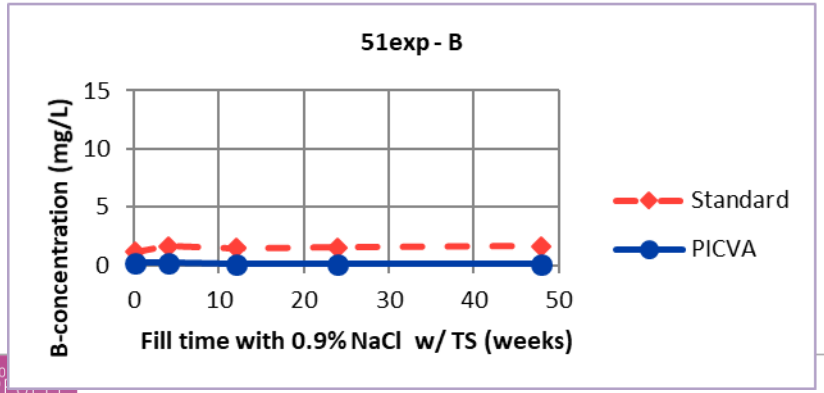
Isotonic NaCl

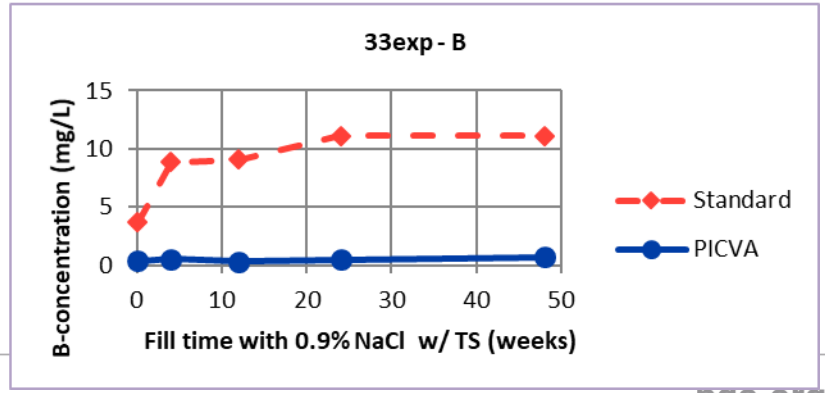
0.9%, 5.2pH, with Terminal Sterilization

Extractables – NaCl with Terminal Sterilization



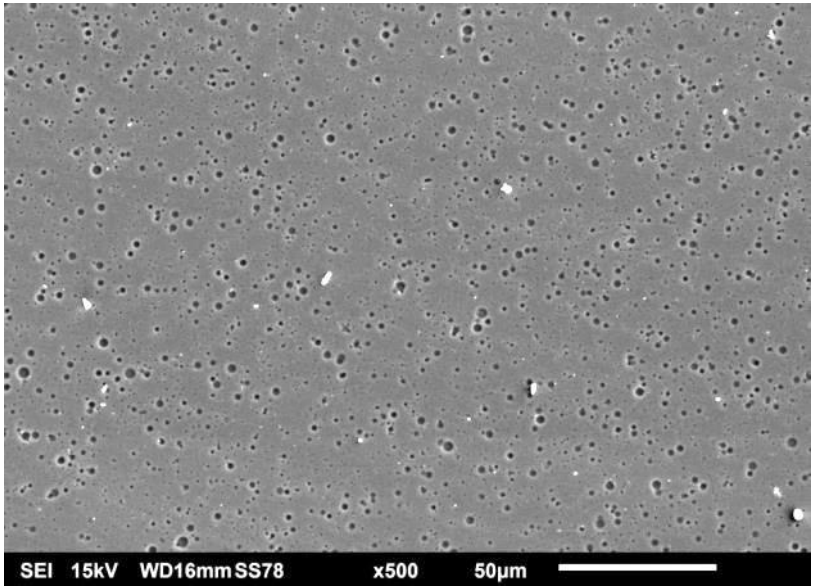




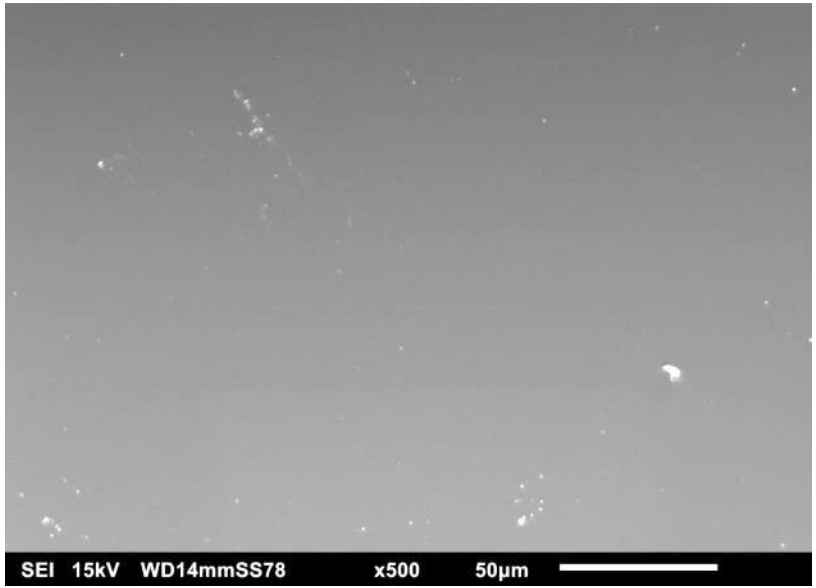


SEM – 24 weeks @ 40°C – 51exp

NaCl w/ Terminal Sterilization



Standard Vial

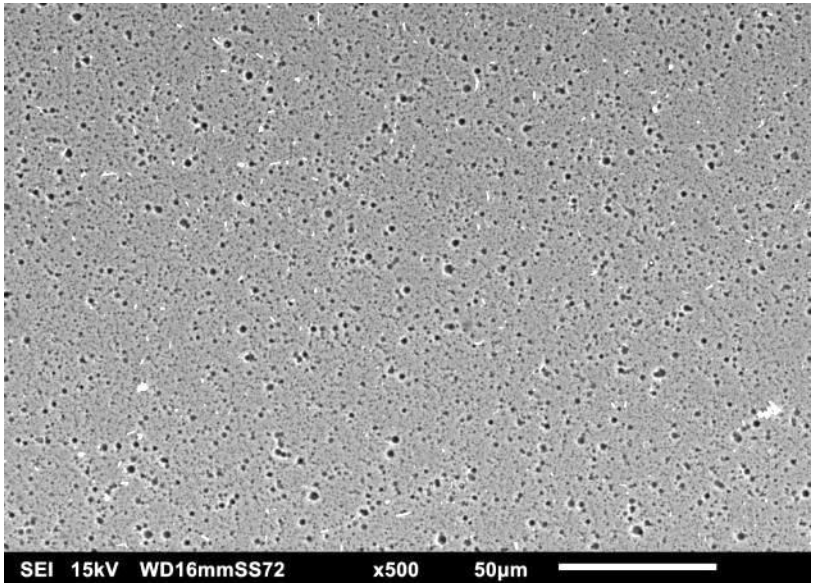


PICVA Vial

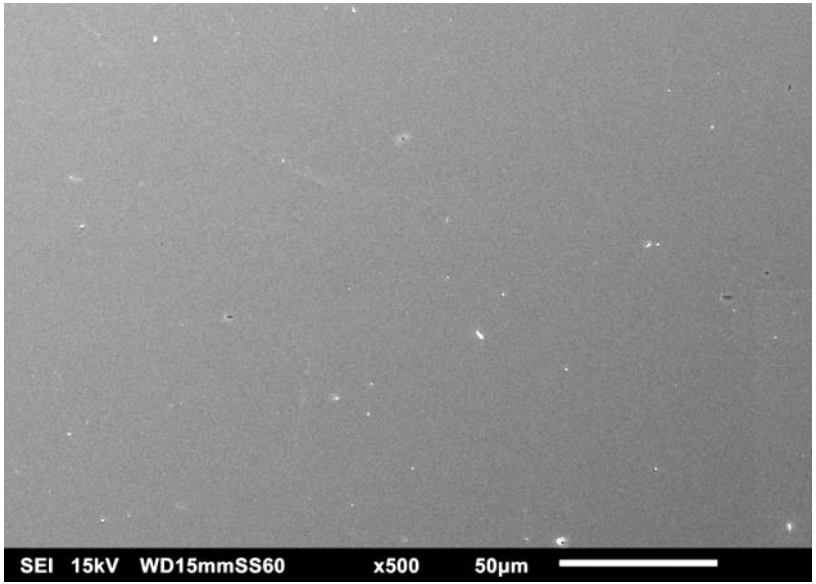
- Noticeable improvement in surface durability (less interaction)

SEM – 24 weeks @ 40°C – 33exp

NaCl w/ Terminal Sterilization



Standard Vial



PICVA Vial

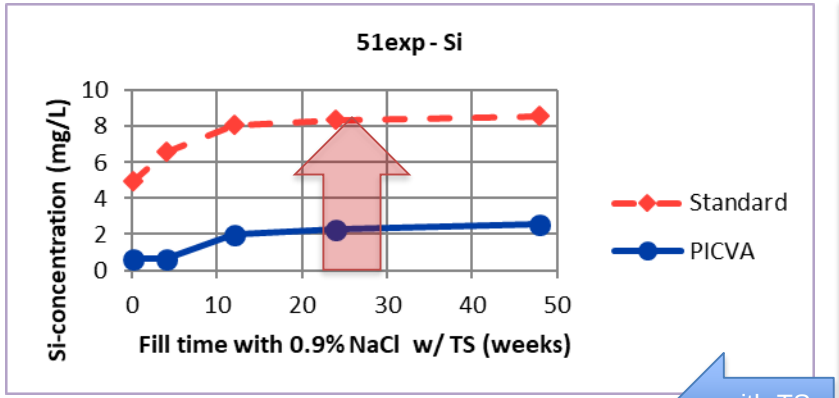
- Noticeable improvement in surface durability (less interaction)

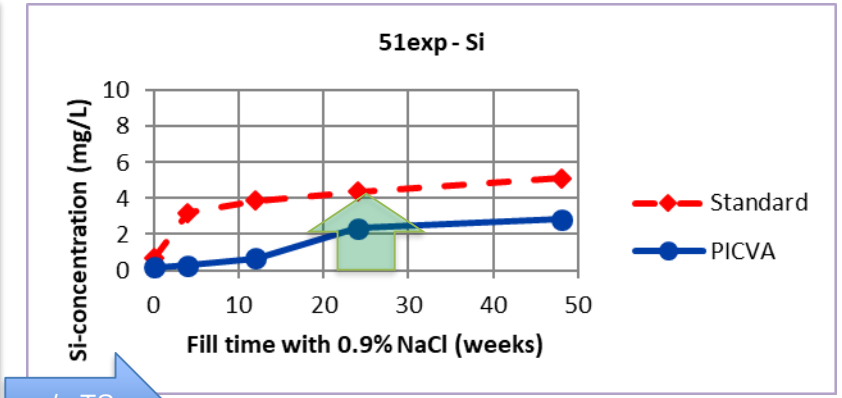
Isotonic NaCl

0.9%, 5.2pH

Effects of Terminal Sterilization (known risk factor as stated in USP <1660>)

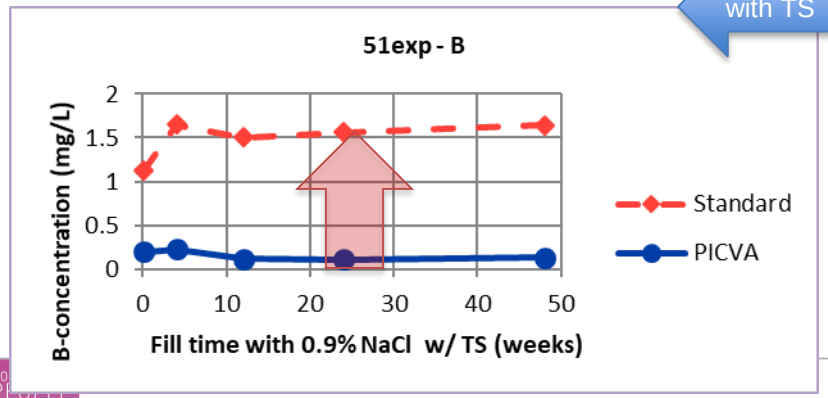
Extractables – NaCl – Impact of Terminal Sterilization (TS)

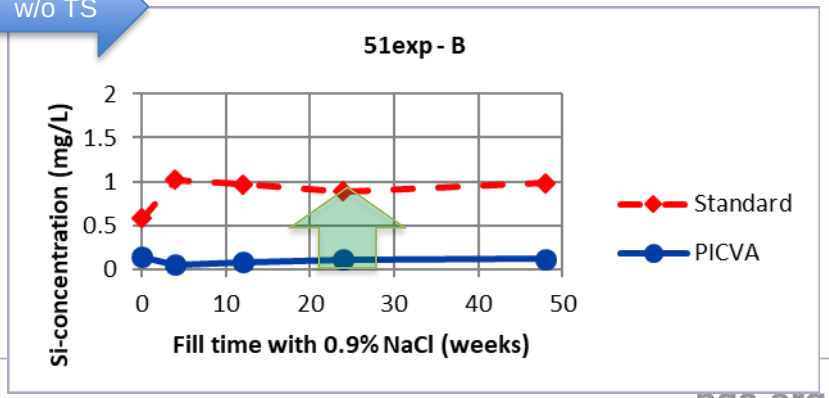




with TS

w/o TS





Takeaways

- Type 1 glass types (1A, 1B) do matter when combined with certain buffers regarding interactions and drug product control
  - Different glass types will have an effect on extractables and durability over the shelf life of the drug product
- Offerings that improve the surface durability such as VIALEX™ through PICVA greatly reduce buffer interaction effects, and in some cases reduces the effect of the alternate glass types
  - Improvements to the surface alkalinity through processes such as VIALEX™ can also minimize effects of low fill volumes, while maintaining full compliance with Type 1 glass pharmacopeias

Acknowledgments

- Nipro PharmaPackaging Marketing
- Nipro PharmaPackaging Lab Services

Thank you for your attention!