Glass Delamination: choosing the right glass container for your drug product

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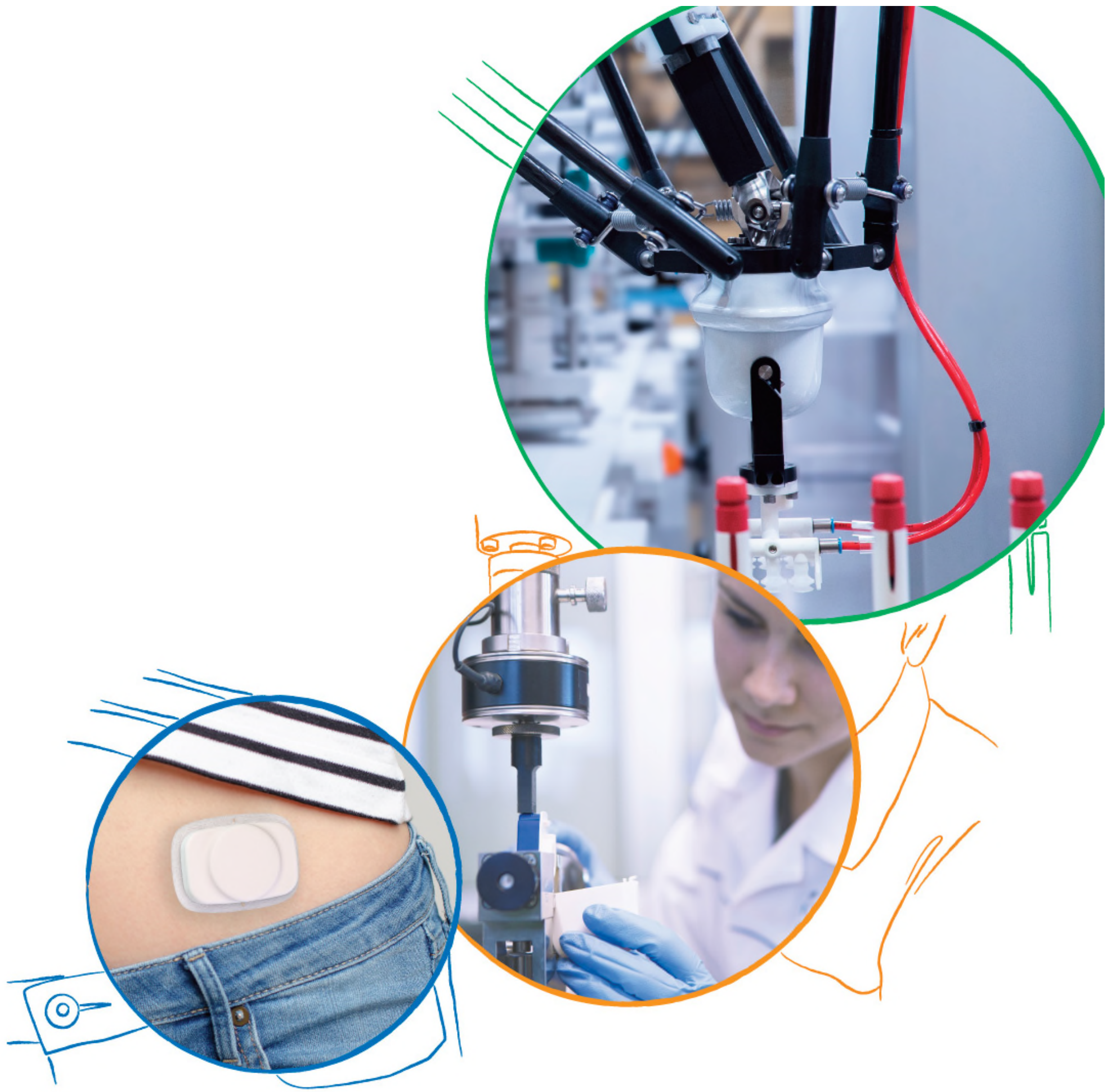

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Agenda

- Introduction
- Underlying Glass Science
- Case Study 1: Choosing the “right glass”
- Case Study 2: Impact of processes and treatments

Chapter

1

Introduction

Introduction

*"The finished drug product must be **safe** and **effective**, and **ALL PARTIES** that have a hand in the generation of the final drug product (including its manufacturing, packaging, and/or delivery systems) have a vested interest in accomplishing this objective"

Chemical Analysis

To detect the risk of chemical interaction with drugs

- Delamination Propensity Studies
- Extractables & Leachables Testing
- Contamination Identification
- Material Characterization

Surface Characterization

To enable deeper investigation

- Surface Morphology Investigation
- Silicone Layer Distribution
- Surface Defects Evaluation

Container Interaction

To preserve and protect drug integrity

- Glass Tubing Suitability
- Glass Container Definition
- Closures System Selection

Container Performance

To ensure compatibility with customer needs

- Gliding-Injection Force Testing
- Sub Visible Particles Release
- Mechanical Properties
- Failure Analysis
- CCI / Leakage testing
- Customized Functional testing

Main obligation given to the CCS manufacturers is that they must ensure "***the container-closure system to maintain the integrity of its microbial barrier, and hence the sterility of a drug product throughout its shelf life***" (US FDA)

*"An Extractables/Leachables Strategy Facilitated by Collaboration Between Drug Product Vendors and Plastic Material/System Suppliers" **DENNIS JENKE** ***PDA*** *J Pharm Sci and Tech* 2007

Introduction

When and How to approach analytical investigations to enhance Customer Confidence?

- **NEW DRUG PRODUCT**: selection of the proper packaging system:
  - Materials evaluation
  - Pre-formulation screening studies
  - Stability studies and stress tests

- **ALREADY MARKETED PRODUCT**
  - As per **Authority** request
  - Evaluation of the state/condition of the inners glass surface:
    - **Shelf-life** (stability studies)
    - Impact of **processes and treatments** (i.e. washing, depyrogenation, sterilization etc.) and risk assessment related activities

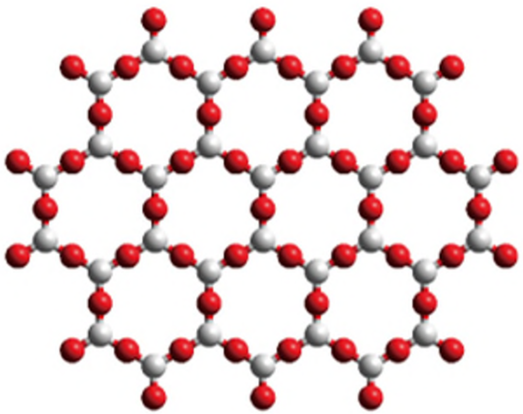
Chapter 2

Underlying Glass Science

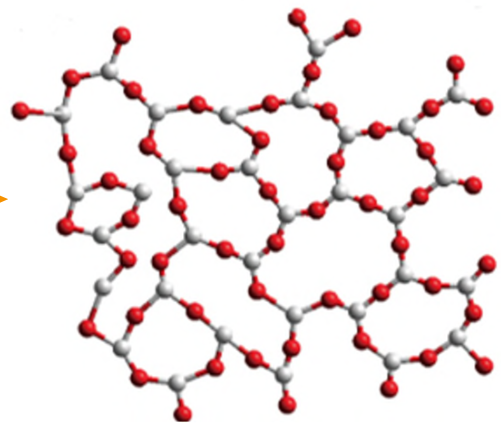
Underlying Glass Science

GLASS is a non-crystalline amorphous solid,
the most common and known based on
silica and silicates

Crystalline silica (SiO_2) turns into the glassy amorphous material after melting at high temperature (> 1500 °C) and cooling down



Crystalline pure silica (quartz)
short-range and long-range order



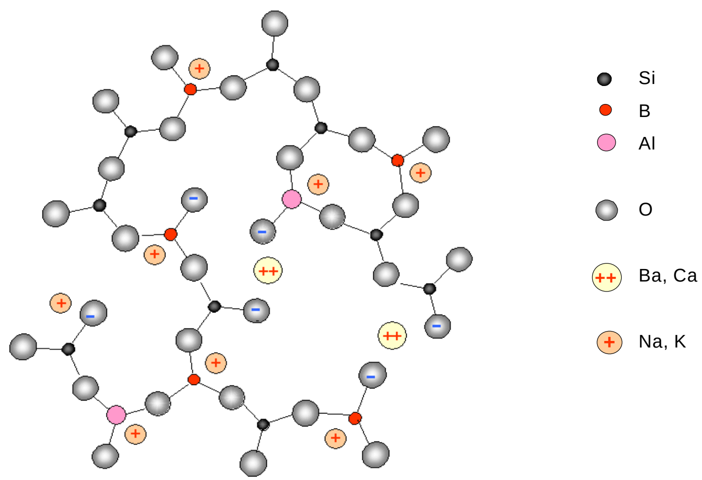
Amorphous glass
short-range but no long-range order

Main composition of Pharmaceutical Glass (Type I - Borosilicate)

CONSTITUENT	AMOUNT (%)	FUNCTION
Al_2O_3	6 – 7	Stabilizer
B_2O_3	10	Network forming and stabilizer
SiO_2	70 – 73	Network forming
Na_2O	2 – 9	Network modifying
K_2O	1 – 2	Network modifying
CaO	0.7 – 1.0	Stabilizer
BaO	0.1 – 2.0	Stabilizer
MgO	0 – 0.5	Stabilizer
ZnO	0 – 0.5	Stabilizer

Glass Pharmaceutical packaging

Main composition of Pharmaceutical Glass (Type I - Borosilicate)



State of art about the understanding of glass degradation process

1- An hydrated (de-alkalinised) silica layer is formed:

$$-Si-O^{-}M^{+}_{(glass)} + H_3O^{+}_{(aq)} \longrightarrow -Si-OH_{(glass)} + H_2O + M^{+}_{(aq)}$$

Acid

$$-Si-O-Na_{(glass)} + H_2O_{(aq)} \longrightarrow -Si-OH_{(glass)} + Na^{+} + OH^{-}_{(aq)}$$

Neutral

Leaching

2- Dissolution of the silica network (hydrolysis):

$$-Si-O-Si- + OH^{-} \longrightarrow -Si-OH + -SiO^{-}$$

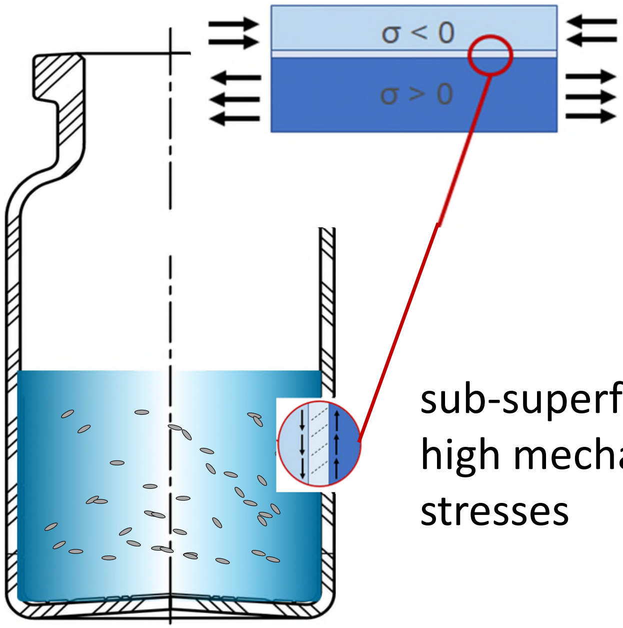
$$-Si-O^{-} + H_2O \longrightarrow -Si-OH + OH^{-}$$

Basic

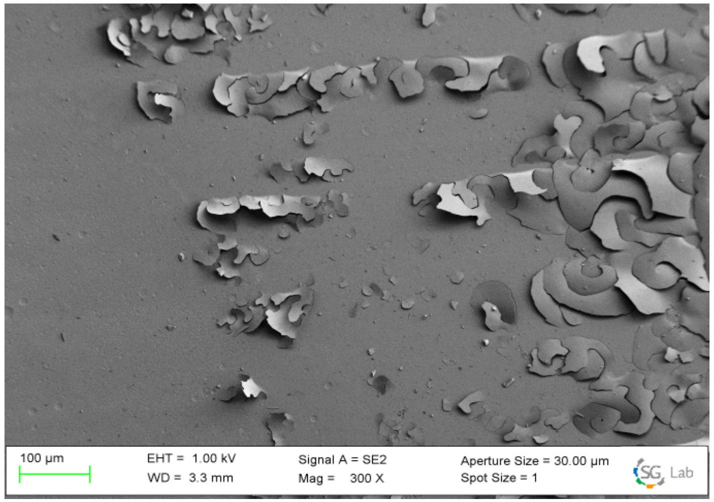
Corrosion

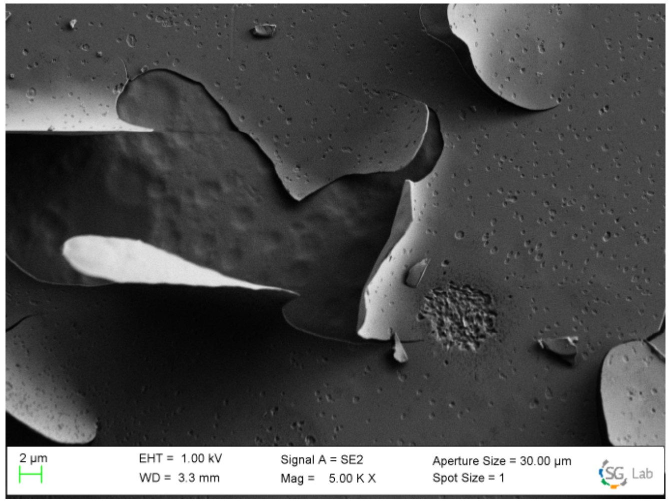
Glass Delamination

Delamination is a form of glass corrosion results in the appearance of visible glass particles, generally known as flakes (lamellae).



sub-superficial high mechanical stresses

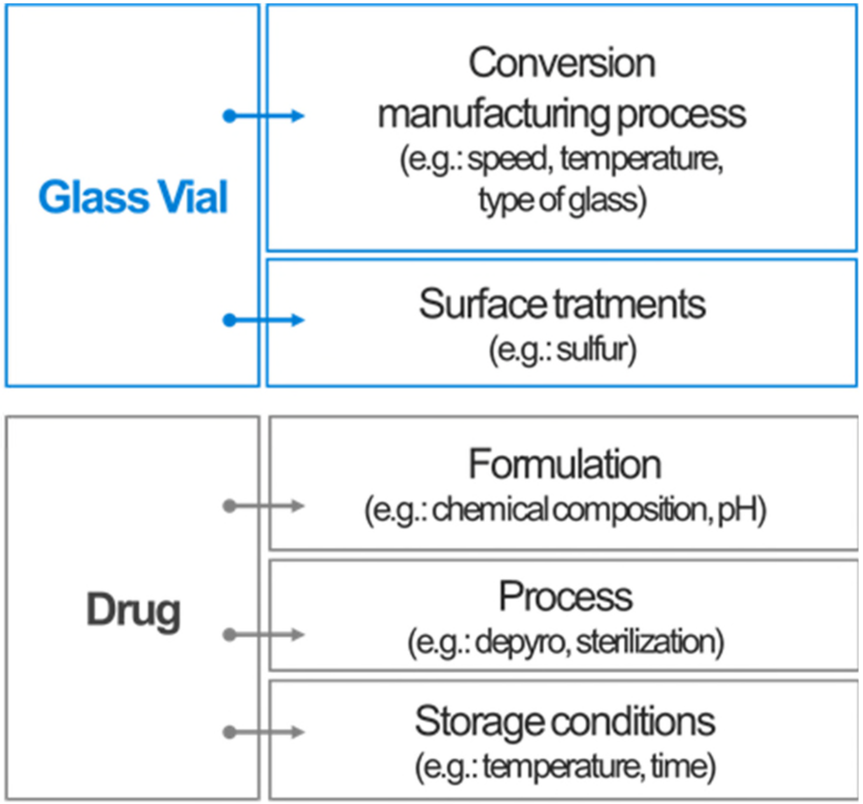




Several Factors Affect Corrosion Propensity of Pharmaceutical Glass

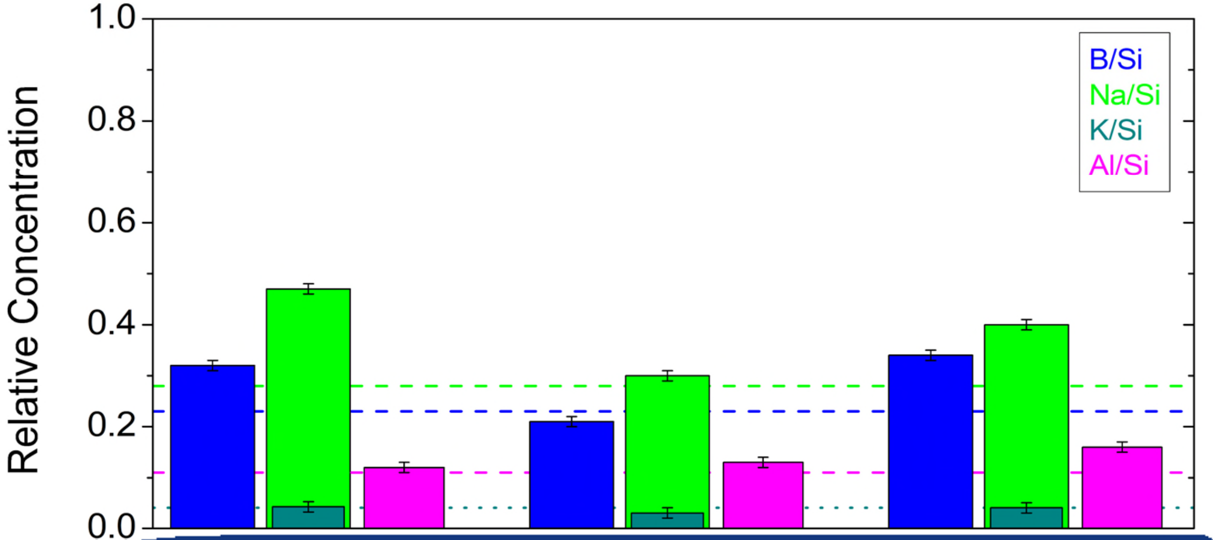
Container manufacturer direct influence

Pharma company direct influence

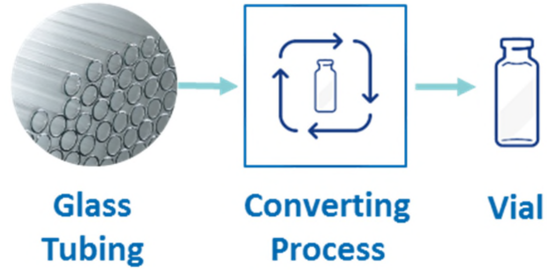


Several Factors Affect Corrosion Propensity of Pharmaceutical Glass

Converting Process



- XPS (X-ray Photoelectron Spectroscopy) analysis
- Sampling depth: 10 nm
- Dashed lines indicate values measured on glass tubes



Chapter 3

Case Study 1: Choosing the “right glass”

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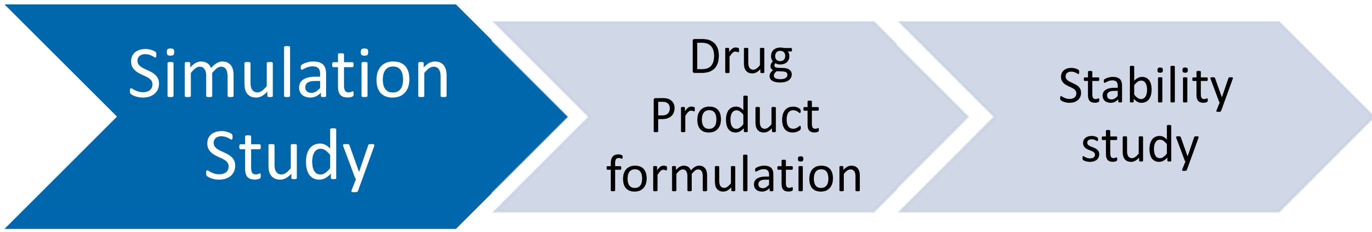
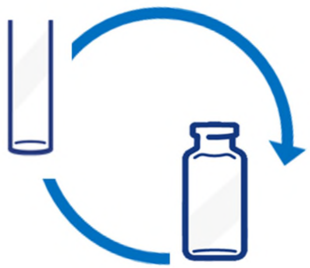
Purpose: Investigation over the glass tubes for new Drug Product application





GOAL

Identify the glass tube that fits the Drug Product needs to support the selection rationale of the glass container system

Case Study 1: Choosing the “right glass”

Samples

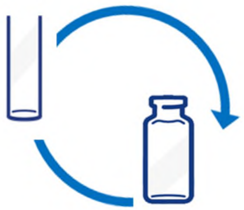
PDA Journal
of Pharmaceutical Science and Technology

Investigating the effects of the chemical composition on glass corrosion. A case study for Type I vials

Serena Panighello and Odra Pinato

PDA Journal of Pharmaceutical Science and Technology **2019**,
Access the most recent version at doi:10.5731/pdajpst.2019.010066

2 TYPES OF GLASS TUBE



2R VIALS

	SiO_2	B_2O_3	Al_2O_3	Na_2O	K_2O	CaO+ BaO	Other	HR
GLASS A	>70	8-10	6-8	7.8	<0.1	1-2	0.7	0.79
GLASS B	>70	8-10	6-8	6.0	1.9	1-2	0.6	0.56

Glass chemical composition and vial hydrolytic resistance (HR)

Case Study 1: Choosing the "right glass"

Simulation conditions

- Depyrogenation
- Filling with a high ionic strength solution
- Low filling volume (high SA/V)
- Terminal sterilization
- Accelerated and real time stability

Surface evaluation and morphological analysis

- Light Microscopy DIC (Differential Interference Contrast)
- High resolution inspection of inner surface morphology by SEM (Scanning Electron Microscopy)

Chemical Analysis

- ICP-OES (Al, B, Si, Ca quantitative analysis)

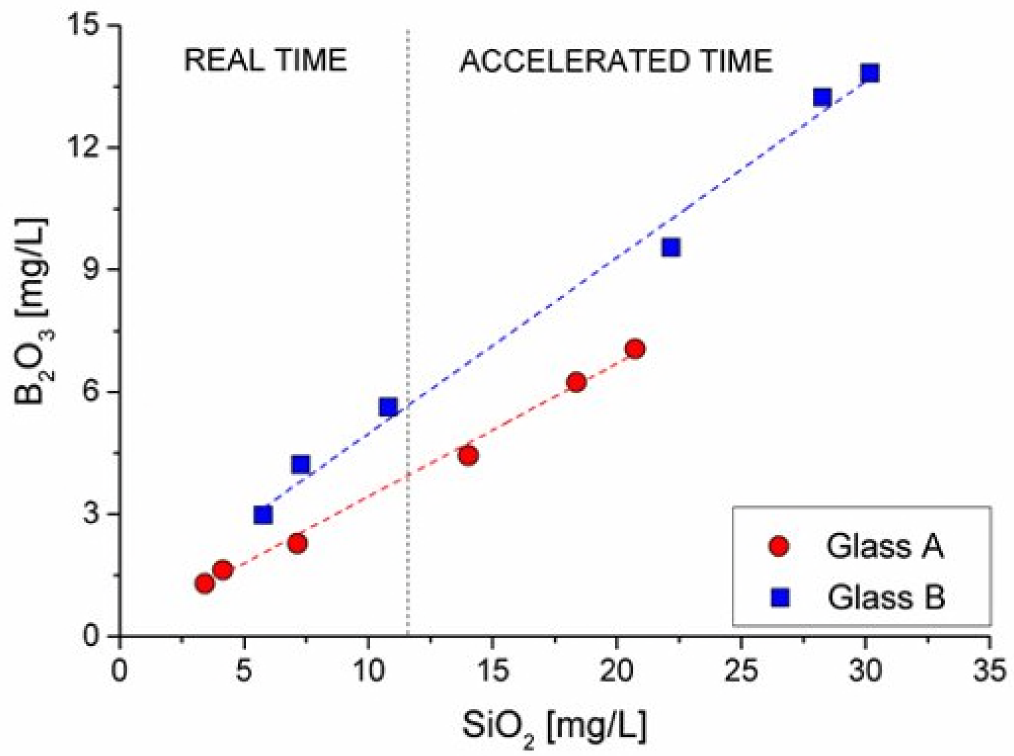
Visual Inspection

- Visual Inspection (EP 2.9.20 Particulate contamination: Visible Particles)

Case Study 1: Choosing the "right glass"

Aging and Chemical Analysis

ID	Actual Duration	Conditions	Simulated or Equivalent Time(months)
T0	Freshly filled	-	0
RT5	5 months	25 °C± 2°C; 40%HR	5
RT12	12 months		12
RT24	24 months		24
AT12	5 weeks	60 °C ± 2°C; 40%HR	12
AT24	10 weeks		24
AT36	15 weeks		36
AC	60 minutes	121 °C	24

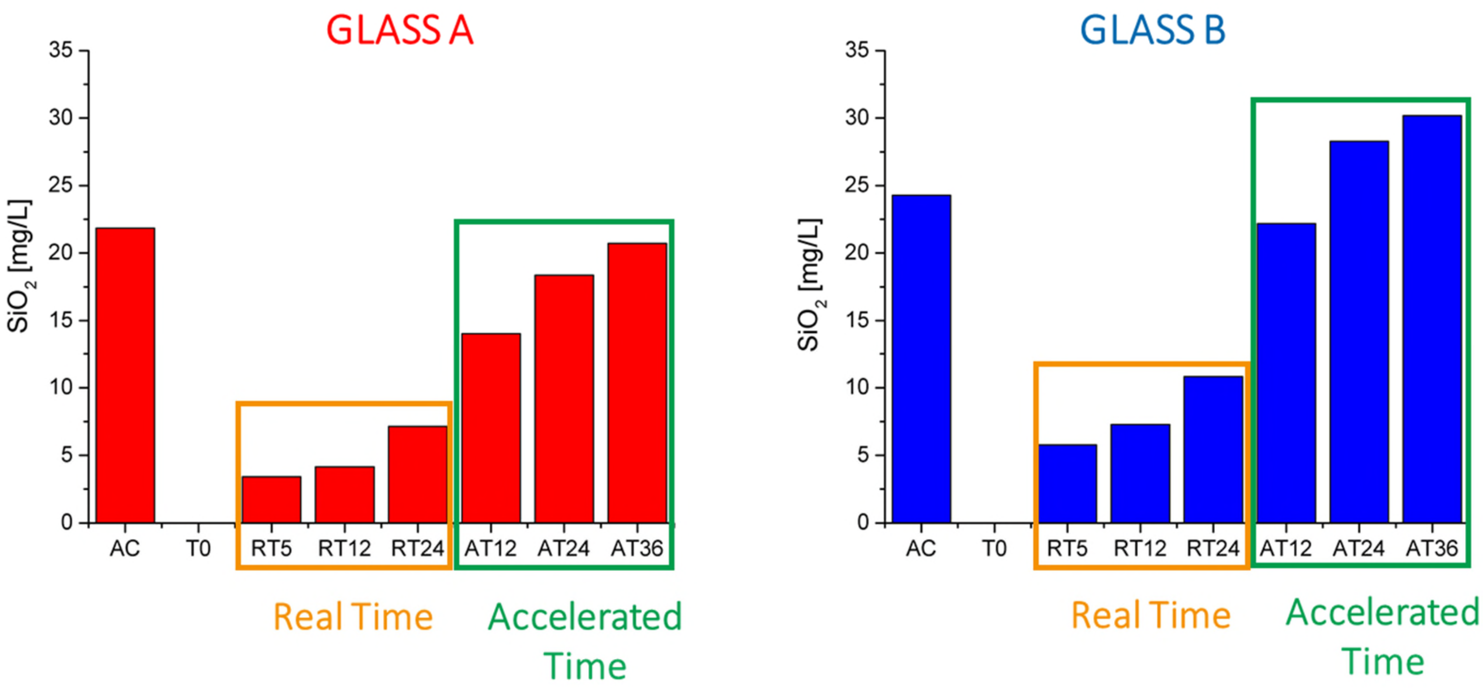


Storage conditions description: RT=Real-time; AT=Accelerated Time; AC=Autoclave Cycle

Case Study 1: Choosing the "right glass"

Aging and Chemical Analysis

Autoclave Ageing **VS** Stability Testing



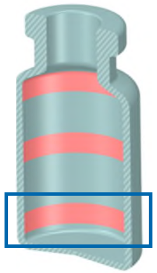
RT=Real-time; AT=Accelerated Time; AC=Autoclave Cycle

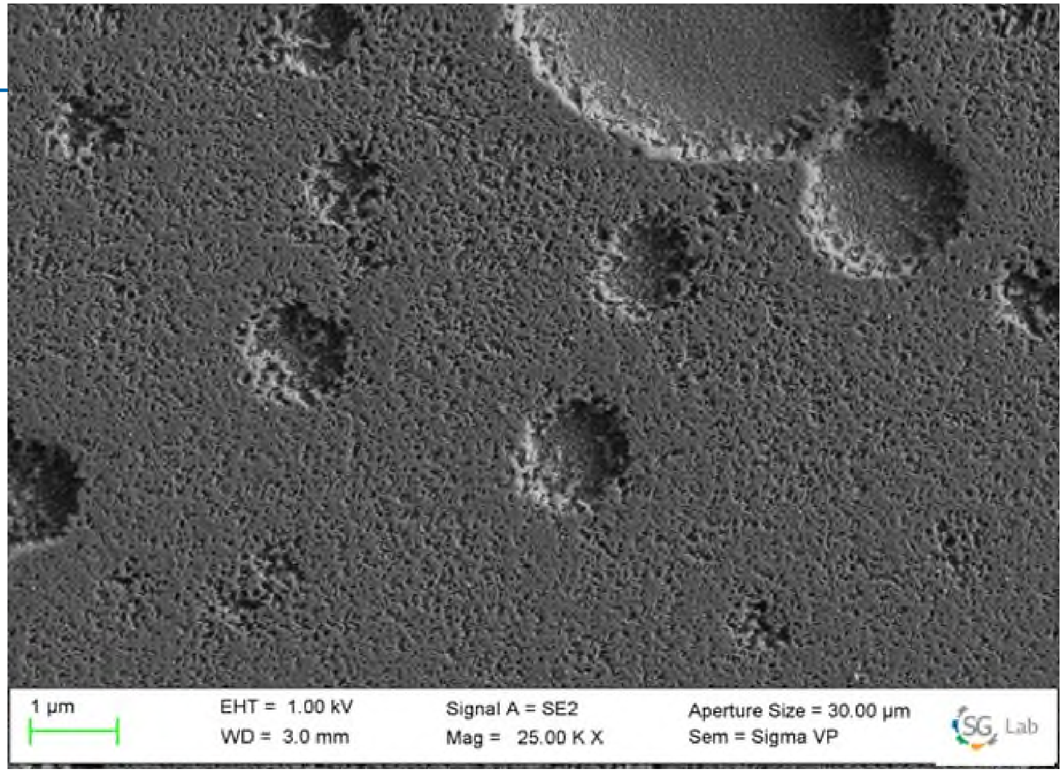
Case Study 1: Choosing the “right glass”

Morphological analysis

SEM

GLASS B





Case Study 1: Choosing the "right glass"

Goal achieved

Identify the glass tube that fits the Drug Product needs to support the selection rationale of the glass container system

Take home messages

- **Hydrolytic Resistance** value is not a reliable indicator of corrosion/delamination propensity
- **Real time stability** testing provides the most reliable data related to glass corrosion
- Acceleration of glass durability test by autoclave does not accurately predict and simulate the surface changes for low temperature glass storage (e.g. 25°C)

Chapter 4

Case Study 2: Impact of processes and treatments

Case Study 2: Impact of processes and treatments

PURPOSE

Investigate the impact of processes and treatments on glass container durability

USP <1660> provides advice on the *evaluation of the inner surface durability* for glass containers in direct contact with different pharmaceutical products

GOAL

Changes in process parameters do not affect glass durability → improvement of the risk assessment rationale

Case Study 2: Impact of processes and treatments

Screening Conditions

- Different Depyrogenation parameters
- Filling with 0.9% KCl pH 8.0 at 90% of brimful capacity
- Autoclave cycle (1h, 121 °C)
- Accelerated stability (40 °C ± 2 °C / 75% RH ± 5% RH)

Surface evaluation and morphological analysis

- Light Microscopy DIC (Differential Interference Contrast)
- High resolution inspection of inner surface morphology by SEM (Scanning Electron Microscopy)

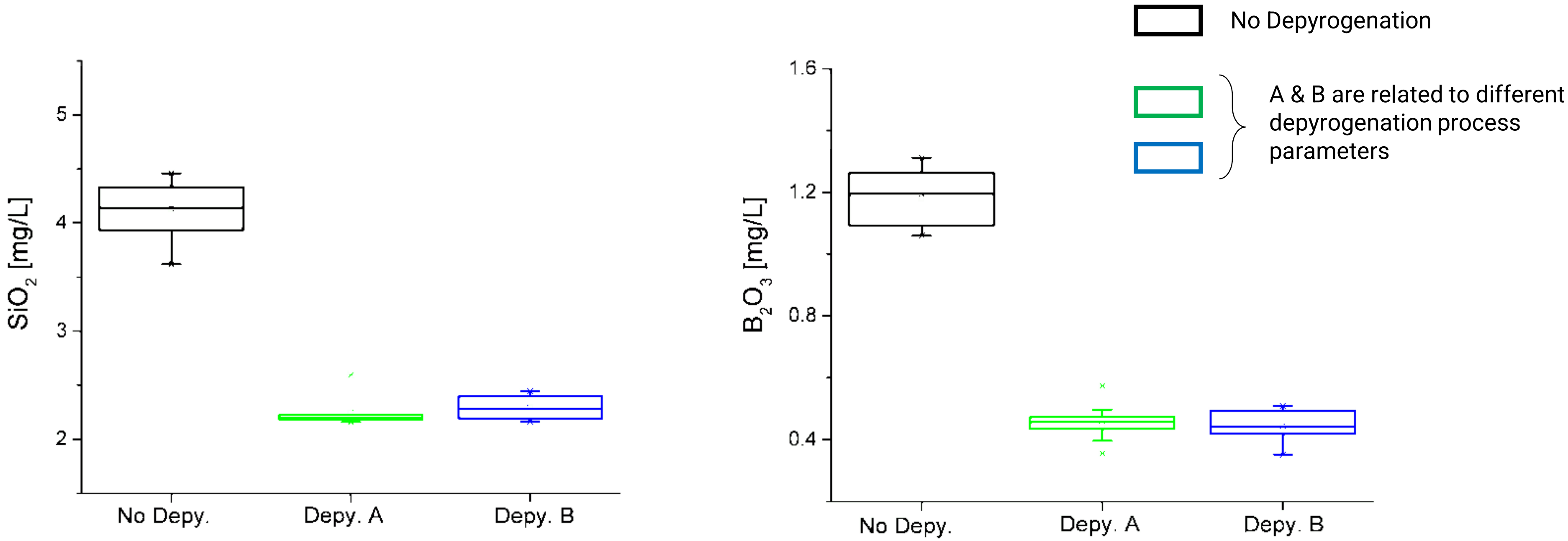
Chemical Analysis

- ICP-OES (Al, B, Si, Ca quantitative analysis)
- pH measurements

Visual Inspection

- Visual Inspection (EP 2.9.20 Particulate contamination: Visible Particles)

Case Study 2: Impact of processes and treatments

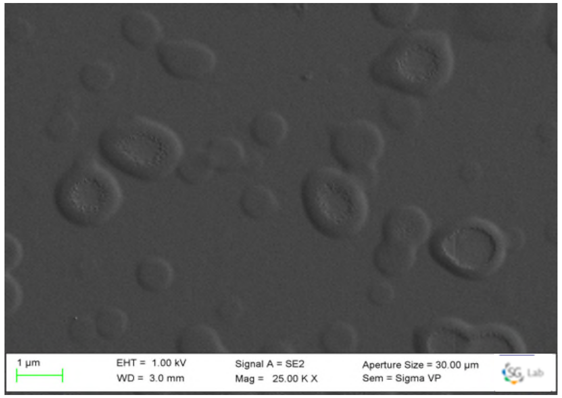


SiO_2 and B_2O_3 extracted after 6 months of accelerated stability [40 ˚C ± 2 ˚C and 75% RH ± 5% RH]

Case Study 2: Impact of processes and treatments

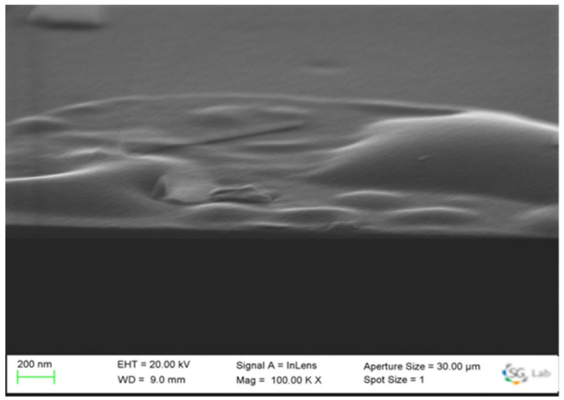
pH measurement

	No Depy.	Depy A	Depy B
Autoclave	8.4	7.8	8.0
T1	8.2	7.8	7.8
T3	8.0	7.7	7.8
T6	8.2	7.9	7.9



Elements present in the extract solution: SiO_2 > Na_2O+K_2O > B_2O_3 > $CaO+BaO$ > Al_2O_3

SEM CROSS-SECTION



Final pH:

Acidic contribution

\+

Basic contribution

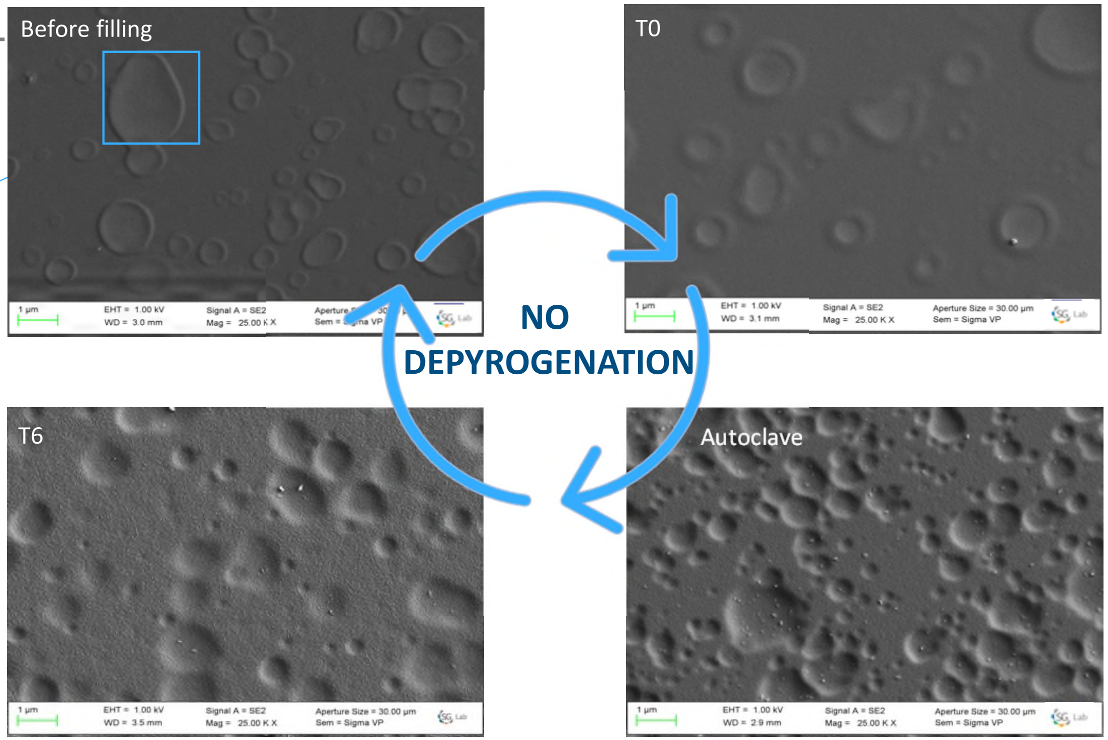
\+

Amphoteric contribution

Case Study 2: Impact of processes and treatments

Morphological analysis

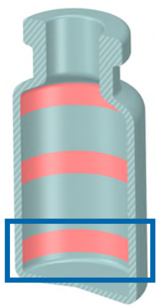
SEM



$Na_2{}^{10}BO_2$

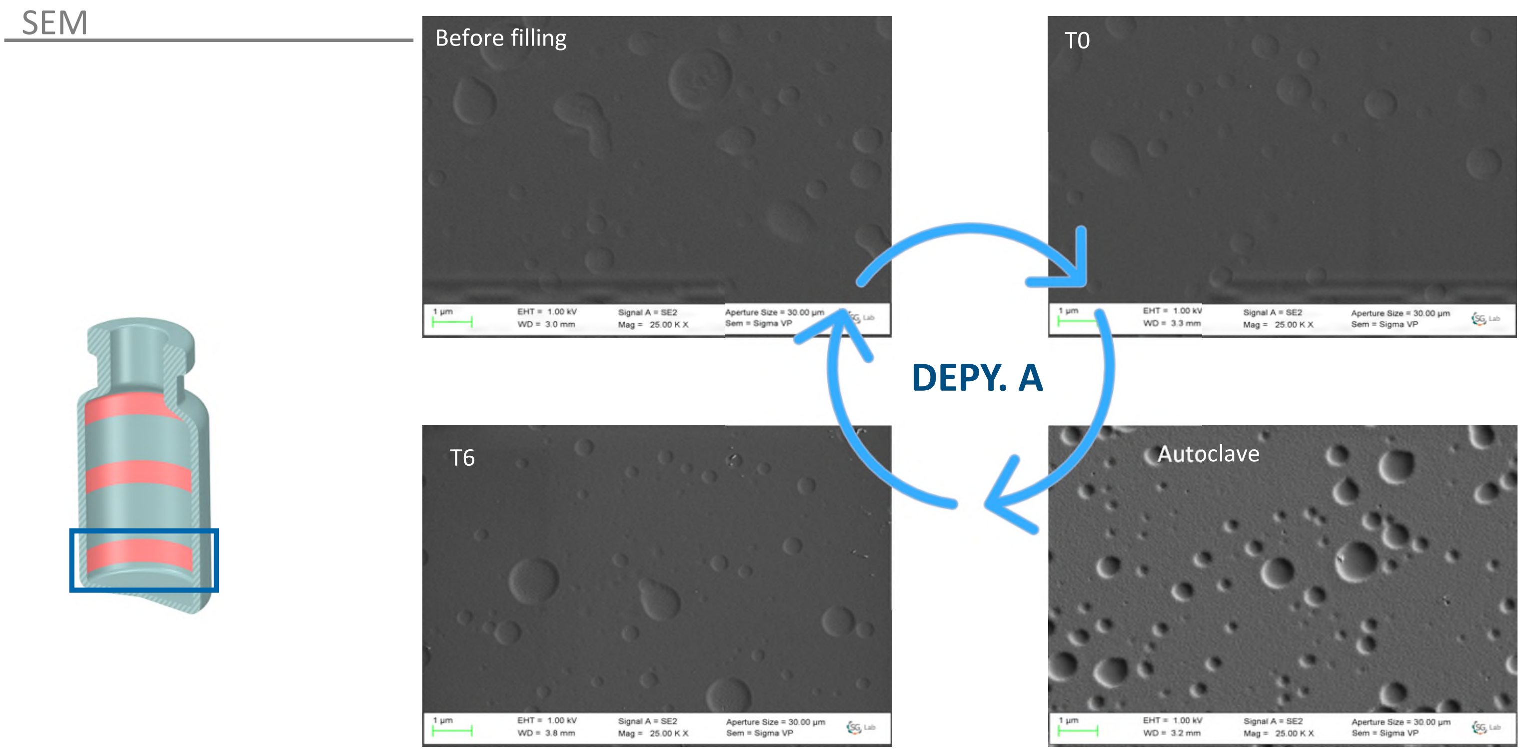
$Na_2{}^{11}BO_2$

From TOF-SIMS analysis



Case Study 2: Impact of processes and treatments

Morphological analysis



Case Study 2: Impact of processes and treatments

Goal achieved

Changes in process parameters do not affect glass durability

Take home messages

- **Screening method** can help to evaluate the impact of processes (e.g. sterilization, depyrogenation) on glass durability
- For this specific case, washing and depyrogenation **do not directly** affect glass durability
- **Risk assessment** process can be improved including glass durability attributes

Thank You!

For further information please contact

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or visit www.stevanatogroup.com