Connecting People, Science and Regulation

Glass Delamination: Risks, Reality and Regulatories.

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AGENDA

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- Introduction to glass delamination mechanism
- SG Delamination studies & results
- Protocol for early delamination prediction
- Vials vs. Syringes
- Regulatory aspects

GLASS DELAMINATION

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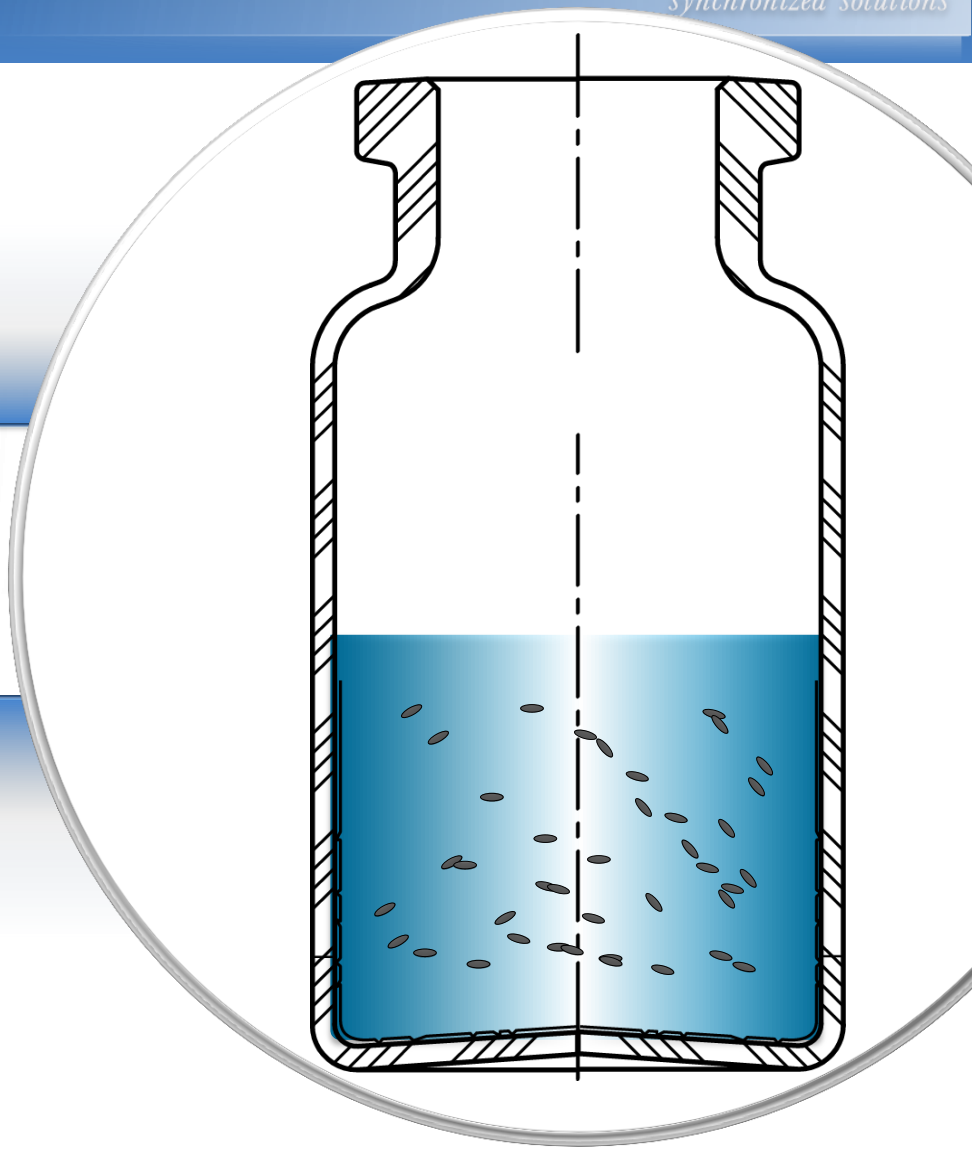
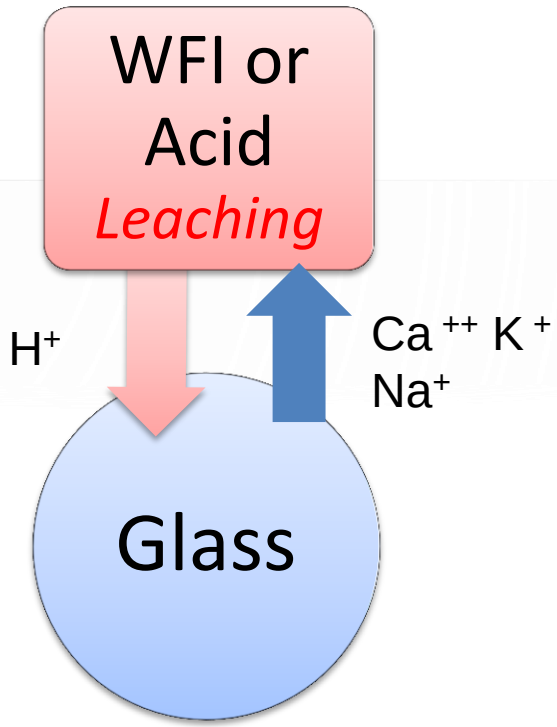
Separation of thin glass layers (lamellae) that appear as shiny, needle shaped particles floating in the contact liquid

The formation of a silica-rich layer poorly bonded to the substrate is the first stage of an extended delamination

Glass-liquid interactions are responsible for the formation of an altered layer



GLASS – LIQUID INTERACTIONS



Formation of a alkali depleted layer

Increasing of the layer thickness

Cracking

Detachment of scales

TYPICAL FLAKES ASPECT

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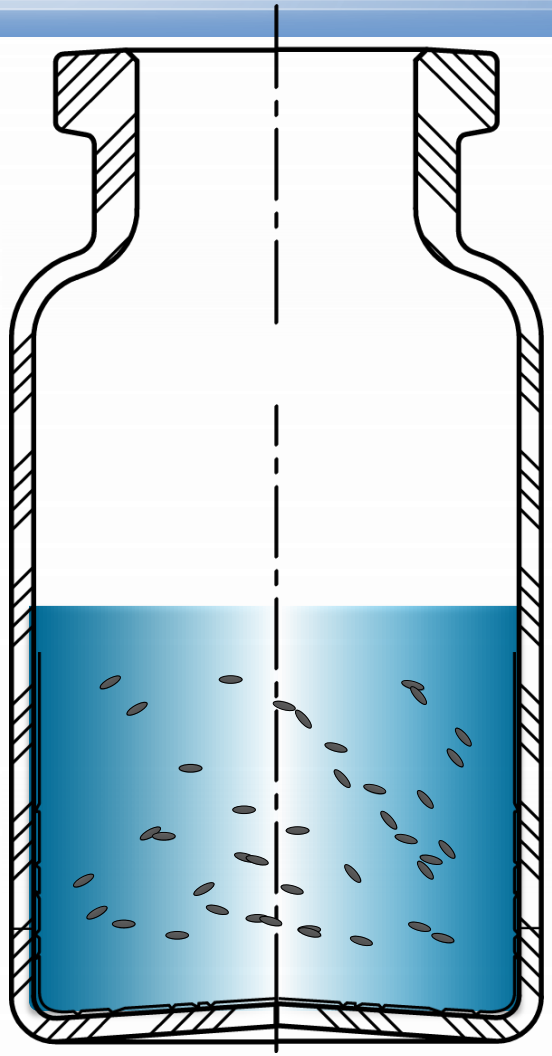

DELAMINATION OF PHARMACEUTICAL GLASS

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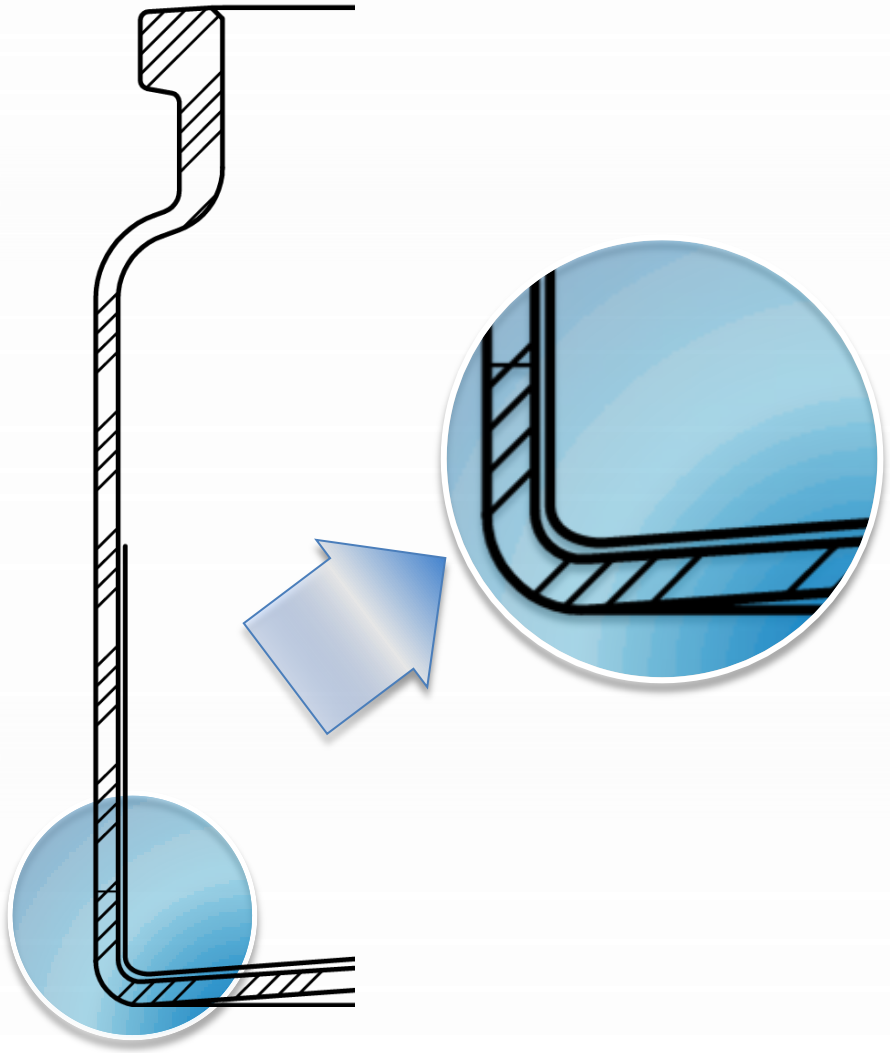

The first stage is always the formation of an altered layer

When vials are filled with the liquid preparation, this layer is subject to a strong re-hydration and swelling

DELAMINATION OF PHARMACEUTICAL GLASS

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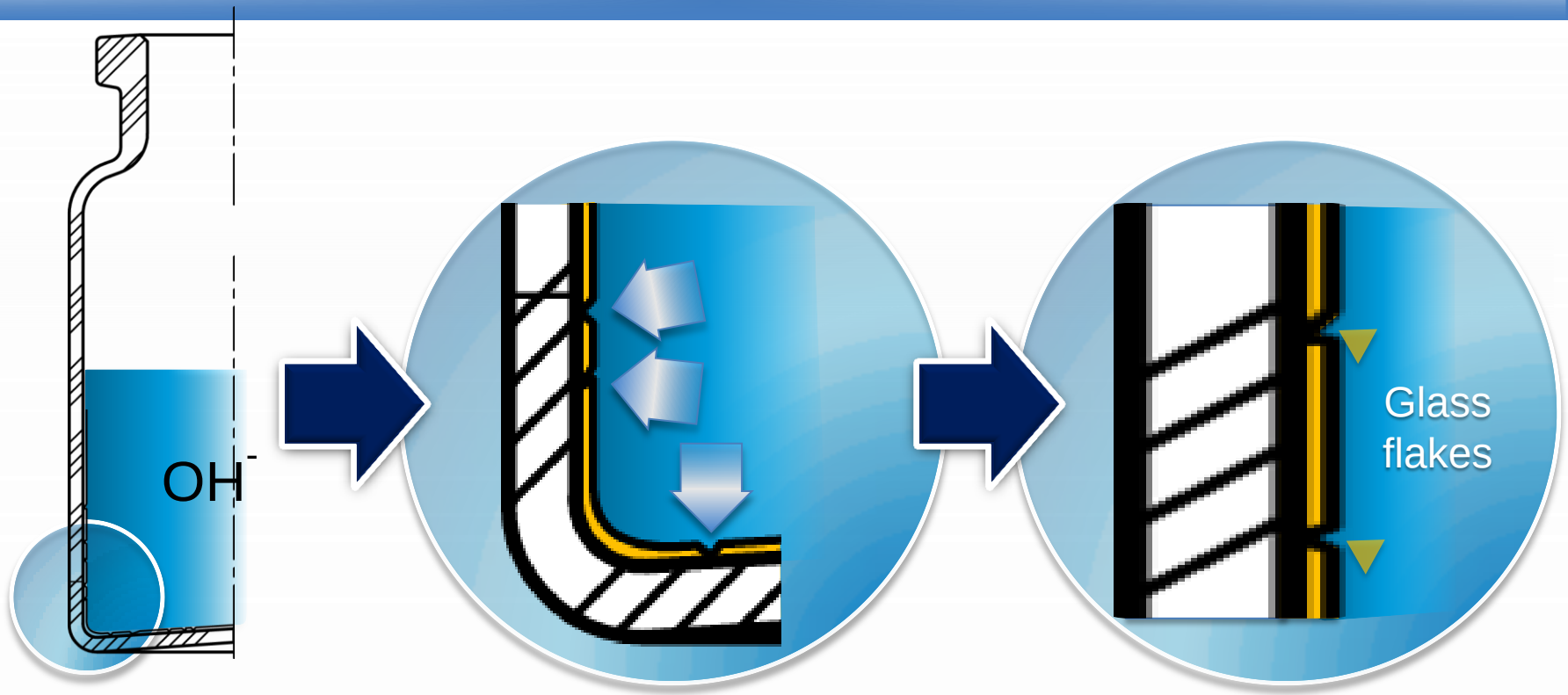

- Some preparations may favour delamination
- Alkaline solutions strongly affect the dissolution of the silica layer. SiO_2 concentration in the extraction liquid increases steeply
- Flakes appearance

FACTORS AFFECTING DELAMINATION OF PHARMA GLASSES

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- sulfur treatment
- siliconization
- coating

→ Surface treatments

- speed of the transformation process
- burners flame temperature
- improper annealing stage, tensile stresses
- type of glass

→ Conversion process

- chemistry of the buffer supporting the active principle
- pH & ionic strength of the drug solution
- organic acids
- sterilization process
- storage conditions

→ Drug formulation & post-treatments

ORGANICS ACIDS

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«Neutral solutions of organic acids behave as strongly alkaline solutions favoring dissolution of silica»

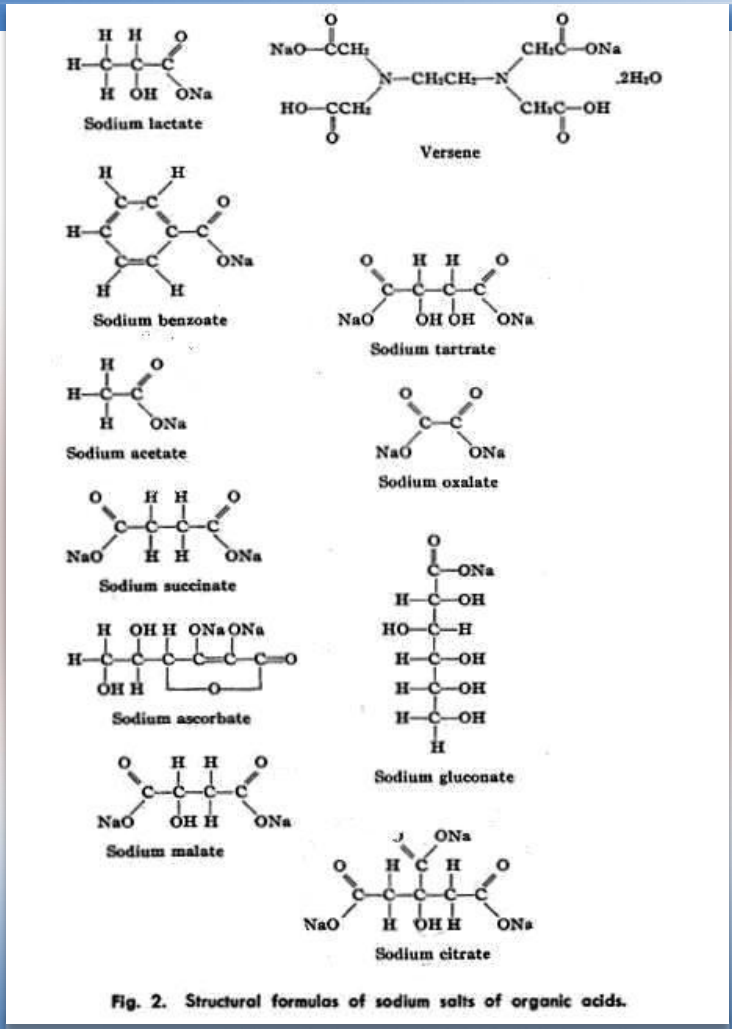

Fig. 2. Structural formulas of sodium salts of organic acids.

Frank R. Bacon and Frank C. Raggon, Journal of the American Ceramic Society, **42 [4] 199-205 (1959)**

OPEN QUESTIONS

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- How can delamination be predicted?
- What parameters can be used to investigate delamination propensity?
- Are EP values still a good indicator of delamination resistance?
- Which glass Type is more suitable to which preparation?

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SG DELAMINATION STUDY

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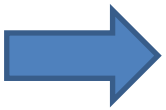
Investigation of:

- Two different Exp 51 glasses provided by different suppliers
- Exp 33 (“pyrex”) glass
- Exp 51 sulfur treated glass

Filled with:

- 0.9% KCl pH 6
- 0.9% KCl pH 8
- Citric and Glutaric acid



Autoclave
Treat.
1h+1h@121°C

SIO_2 IN NEUTRAL AQUEOUS SOLUTIONS: CORRELATION WITH EP VALUES

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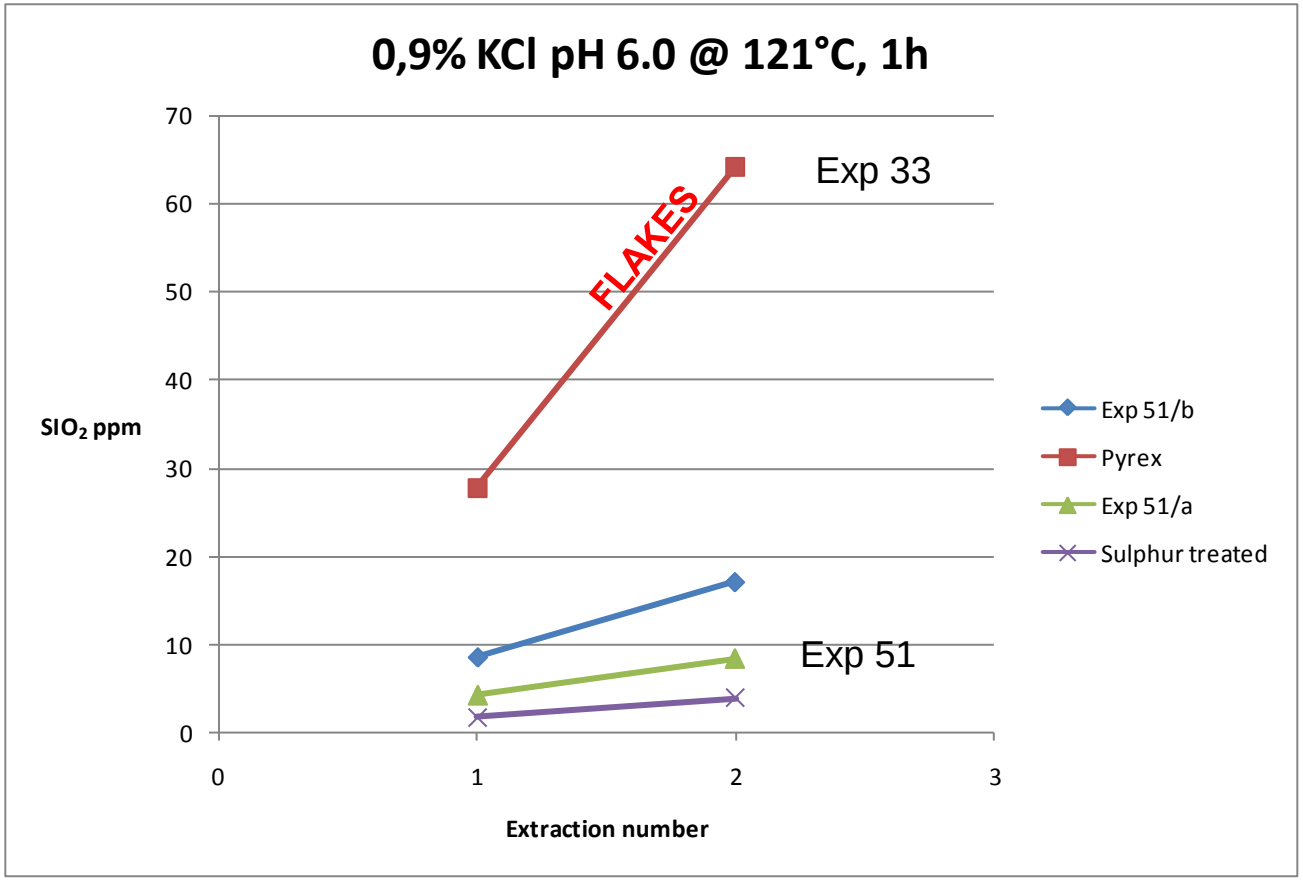

Glass Type	E.P. titration values
Exp 33	0.93
Exp 51/b	0.92
Exp 51/a	0.63
Exp 51 Sulfur treated	0.51

EXTRACTIONS WITH SLIGHTLY ALKALINE SOLUTIONS

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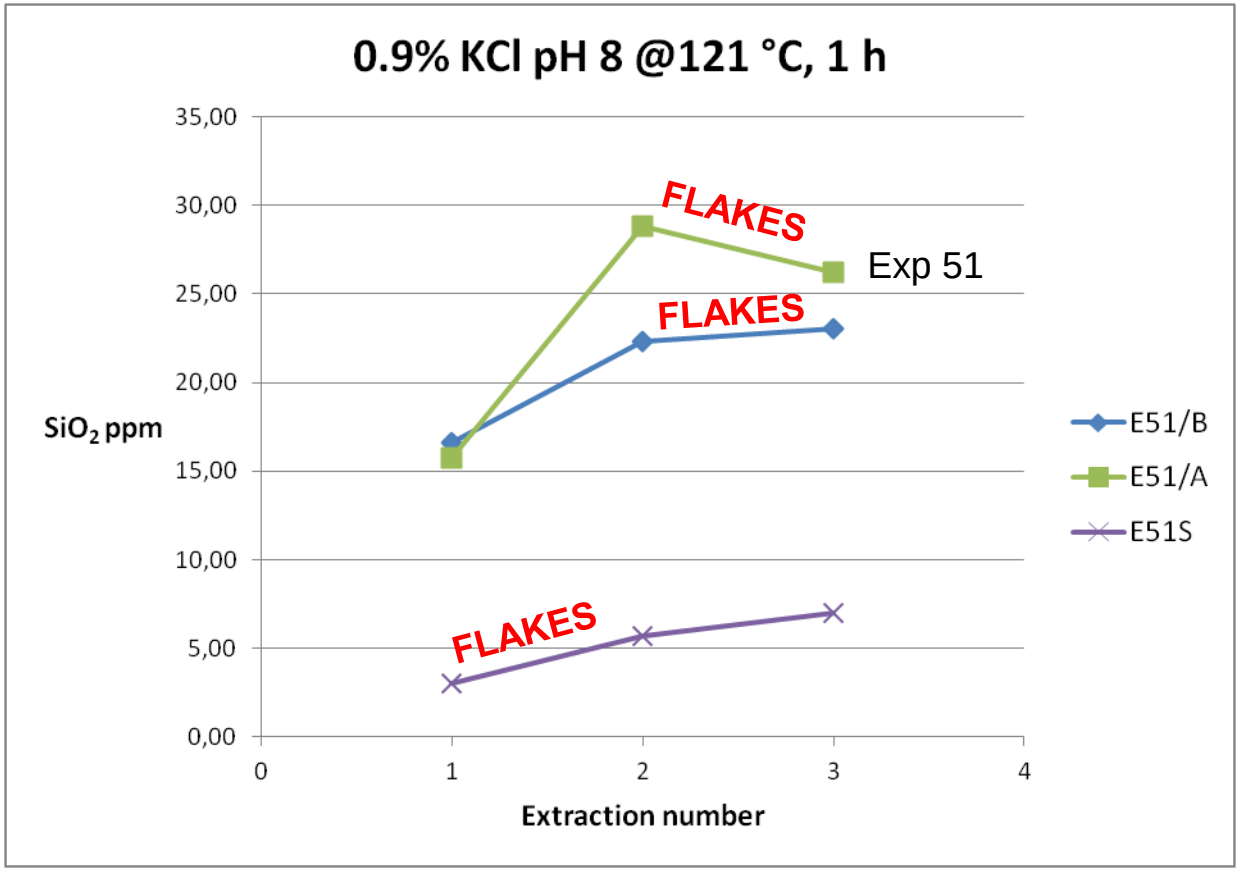

Glass Type	E.P. titration values
Exp51/b	0.92
Exp51/a	0.63
Exp 51 Sulfur treated	0.51

ORGANIC ACIDS EXTRACTIONS

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Glass	Treatment	3% Glutaric Acid + 1 % KCl pH=8.0		3% Citric Acid + 1% KCl pH=8.0	
		SiO_2	pH	SiO_2	pH
Exp 51/A	1 h121°C	16.78 F	8.14	36.36 F	8.54
	2 h121°C	28.15 F	8.31	49.20 F	8.68
Exp 51/B	1 h121°C	17.20 F	8.56	43.85 F	8.79
	2 h121°C	26.76 F	8.86	47.06 F	8.71
Sulf. treated	1 h121°C	10.56 F	8.54	47.70 F	8.51
	2 h121°C	19.42 F	8.91	31.87 F	7.97
Exp 33	1 h121°C	65.21 F	7.94	140.11 F	8.24
	2 h121°C	148.76 F	8.11	198.93 F	8.42

CONCLUSIONS

EP titration values are not always reliable indicators of delamination risk

SiO_2 in solution increases with increasing appearance of flakes

Sulfur treated glasses show strong propensity to delaminate vs alkaline solutions even at low SiO_2 values

Exp.33 glass is the most extensively corroded

RESULTS

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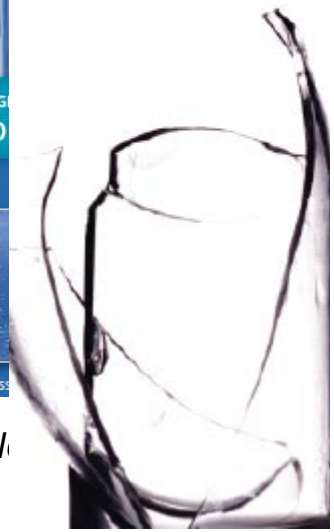
SG N

NEWS

Delamination Propensity of Pharmaceutical Glass Containers by Accelerate

Emanuel Guadagnino (ret.) a



Delamination Propensity of Pharmaceutical Glass Containers by Accelerated Testing with Different Extraction Media

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[1]Scientific Advisor for Stevanato Group, Via Molinella 17, Piombino Dese (PD) 35017—Italy and [2]Stevanato Group, R&D Glass Division, Via Molinella, 17, Piombino Dese (PD) 35017—Italy

ABSTRACT: The delamination of pharmaceutical glass is a serious issue, as it can cause glass particles to appear in vials, a problem that has forced a number of drug product recalls in recent years. In Type I pharmaceutical glass vials, delamination occurs generally at the bottom and shoulder, where extensive flaming during the conversion process can favor a strong evaporation of alkali and borate species and the formation of heavily enriched silica layers. The contact with parenteral preparations dissolved in an alkaline medium increases the rate of glass corrosion, while the differential hydration of these layers can cause the detachment of flakes. The purpose of this study was to investigate the effect of the pH and the composition of the extraction solutions on the propensity of different glass types to delaminate. Repeated autoclave extractions at 121 °C were carried out on different glass types with different extraction media, including organic extractants like citric and glutaric acid. When vials were in contact with alkaline solutions and similarly aggressive media, an increase in silica extraction values indicated glass corrosion and an increasing risk for further delamination. Under such conditions expansion 33 glass is extensively corroded, showing high silica concentration and heavy flaking as compared to other glass types. Sulfur-treated glass also showed early flaking, even if SiO_2 concentration was very low. A similar ranking was observed with extractions carried out with glutaric and citric acids, but at far much higher SiO_2 concentration levels. Extractions with 0.9% KCl solution can be used as an accelerated test to highlight the propensity of a glass to delaminate, but in no case it can be taken as a guarantee that the glass will not delaminate when exposed to the pharmaceutical drug, whose extraction ability requires case-by-case study.

KEYWORDS: Hydrolytic resistance, Delamination, Glass corrosion, ICP-OES, Accelerated extraction test, pH,

PDA J Pharm Sci and Tech , 2012 , 66 116-125

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Objective

Early prediction of delamination

TEST PROTOCOL

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Vial As received

Colorimetric test

Vial filled with the intended preparation 1h autoclave 121 °C

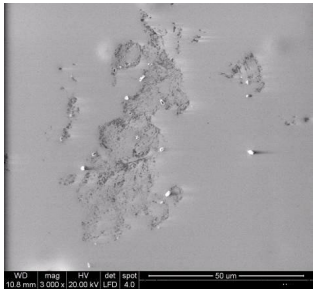
ICP-OES ppm SiO_2 in the extract	Visual inspection for particles presence	Colorimetric test

Vial filled with the intended preparation 1h autoclave 121 °C

ICP-OES ppm SiO_2 in the extract	Visual inspection for particles presence	Colorimetric test

SEM of selected vials

Confirmation of the results



COLORIMETRIC STAINING TEST

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Methylene Blue

Cup as received

Glass surface inhomogeneity due to corrosion

COLORIMETRIC TESTING

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Exp 51 vial, standard process, sample as received

COLORIMETRIC TESTING

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Exp 51 vial, standard process, sample after autoclaving

Flakes -
SiO_2 8.2 ppm

COLORIMETRIC TESTING

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Exp 51 vial, stressed process, sample as received

COLORIMETRIC TESTING

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Exp 51 vial, stressed process, samples after autoclaving

Flakes+
SiO_2 17.9 ppm

COLORIMETRIC TESTING

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Sulfur treated Exp 33 vial , sample as received

COLORIMETRIC TESTING

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Sulfur treated Exp 33 vial,after autoclaving

Flakes +++
SiO_2 49.6 ppm

TEST PROTOCOL – SEM-EDS

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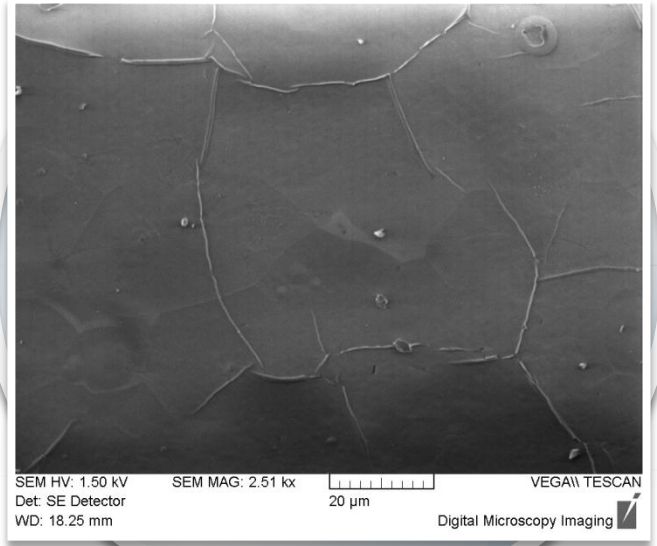
Vials from stressed production after autoclaving



SEM image of the bottom

- ✓Presence of crizzling
- ✓Signs of glass corrosion

TEST PROTOCOL – SEM-EDS

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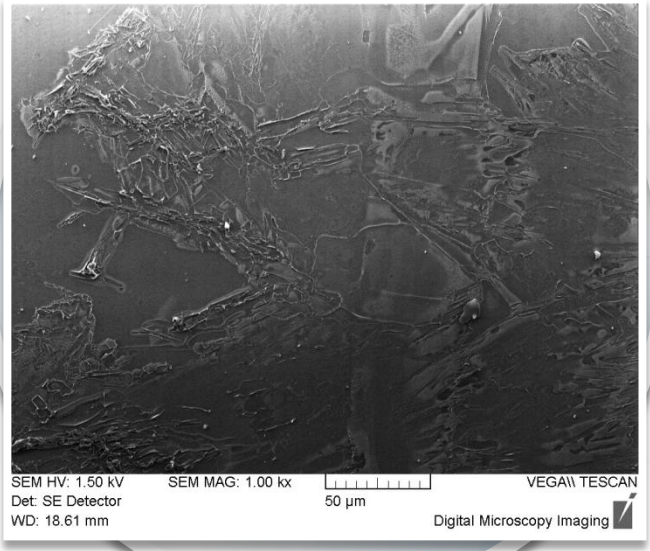

Vials from exp 33 sulfur treated glass after autoclave.

SEM image of the vial bottom

- ✓Extended corrosion occuring
- ✓Some scales detached

CONCLUSIONS

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1. E.P. do not always correlate with the delamination propensity
2. SiO_2 content of the actual preparation is the best indicator for glass corrosion
3. The colorimetric test correlates well with flakes and delamination propensity
4. SEM analysis confirms results

Delamination control from design to market

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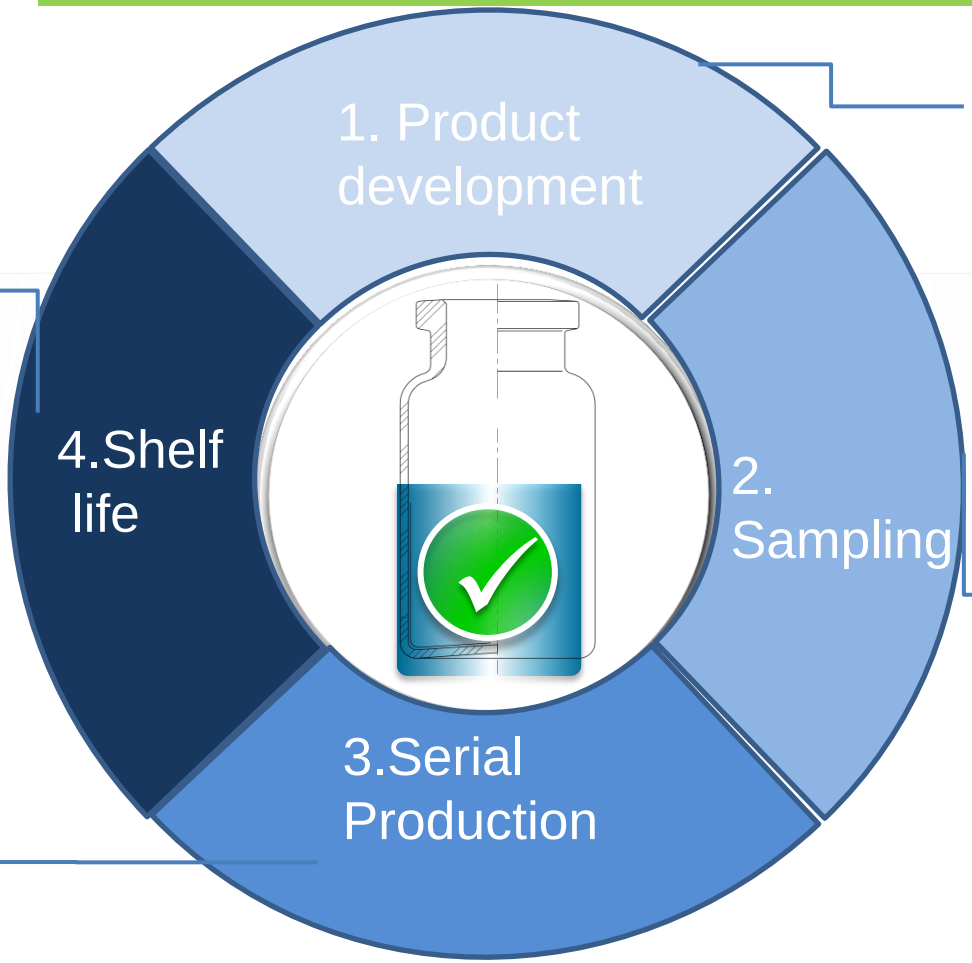
Delamination resistant containers

Statistical sampling and delamination testing

Raw material selection and design optimization



Freezed production conditions + colorimetric testing

Tuning of production parameters + testing

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SYRINGES vs VIALS
DELAMINATION RISK

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12 recalls (2010-today)

NO recalls

What are the reasons for such different behaviour?

Delamination areas at risk due to the forming process

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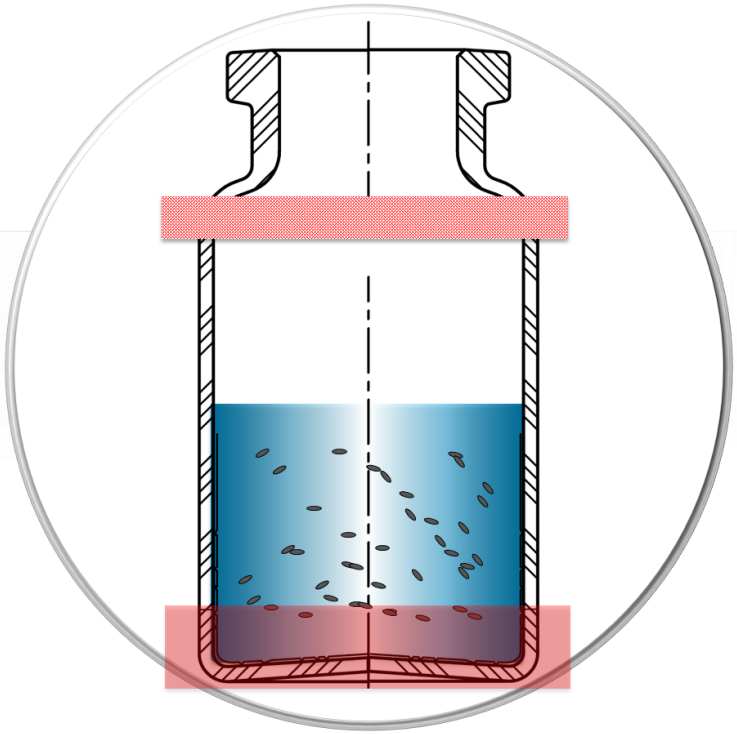
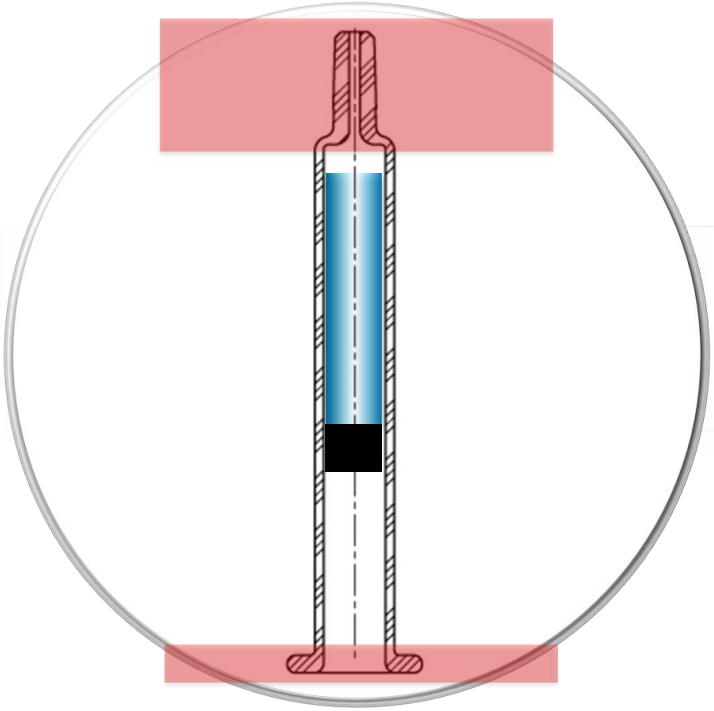


Syringes are formed using a low heating process



The use of high temperature burners is restricted to areas (flange, cone) not in contact with the pharmaceutical preparation

SYRINGES vs VIALS

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Previous studies on a similar transformation process (cartridges) showed that the contribution of the forming process has a low impact

Glass Technol.: Eur. J. Glass Sci. Technol. A, December 2011, **52** (6), xxx–yyy

An improved method to evaluate the quality of glass tubing as a raw material for pharmaceutical articles

Emanuel Guadagnino,[1] *Daniele Zuccato,*[2] *Chiara Gloder*[2] *& Diego Mason*[2]

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Manuscript received 8 May 2011
Revision received 21 June 2011
Manuscript accepted 21 June 2011

The transformation process used to turn glass tubing into a finished article, causes an inevitable increase of surface alkalinity. A study was designed to quantify and distinguish the endogenous contribution of the tubing from other contributions arising from the conversion process. A representative sample was selected from a segregated pallet provided by one supplier, tubing was cut into pieces of suitable length in a way that their surface to volume ratio was of the same order as the cartridges obtained from the same tubing. One end of the pieces were closed with stoppers, the pieces were subject to suitable testing to identify the alkali and other water soluble glass species which are readily available on the inner surface of the raw tubing. Other tests were carried out to isolate the contribution of the autoclaving process and

Glass Technol.: Eur. J. Glass Sci. Technol. A, December 2011, 52 (6), 203–209

SYRINGES vs VIALS
Silica extraction results with 0.9% KCl pH 6.3

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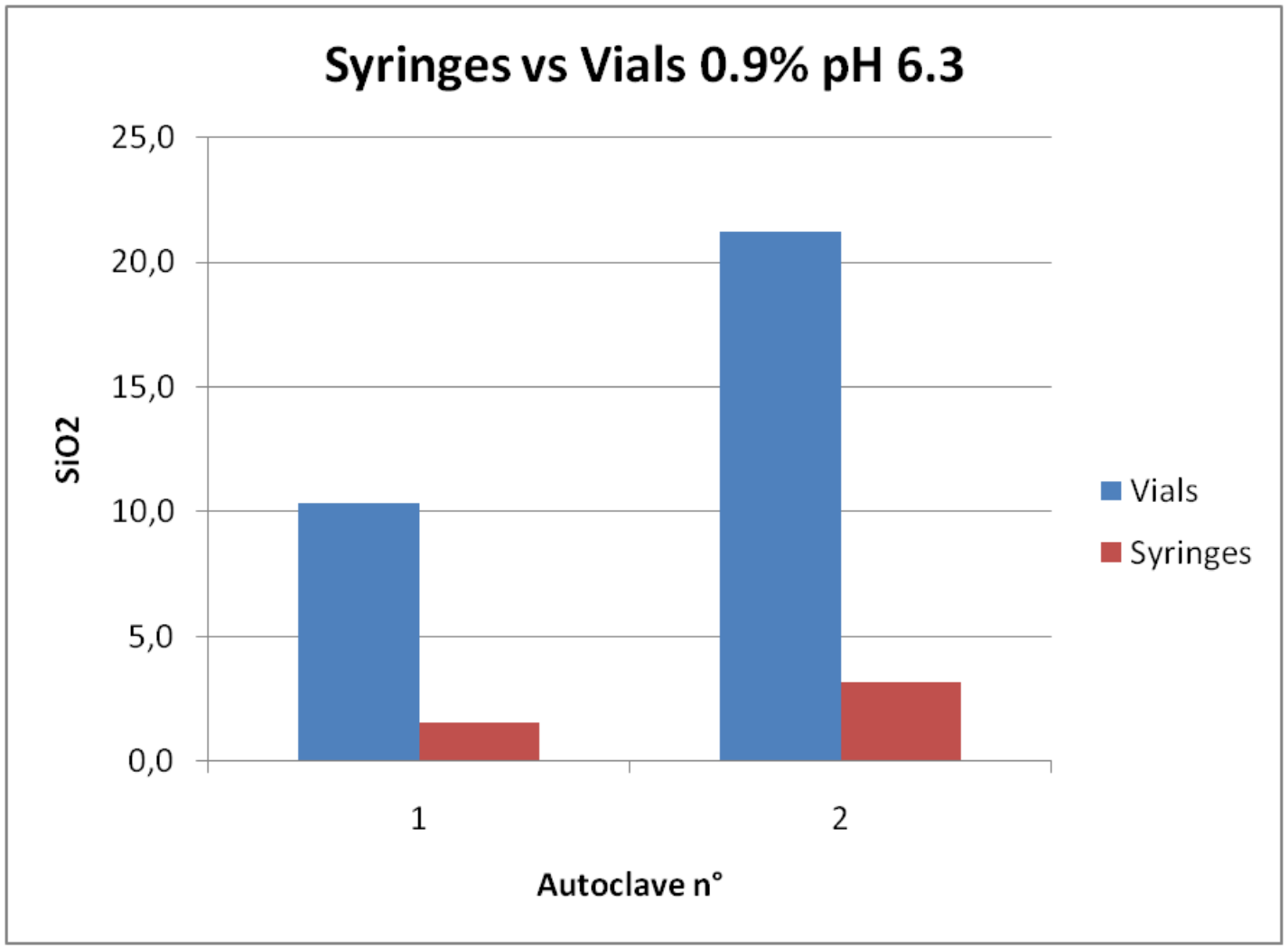

Significantly different SiO_2 release from vials and syringes with comparable S/V ratio after multiple autoclave cycles

SYRINGES vs VIALS – Methylene blue testing

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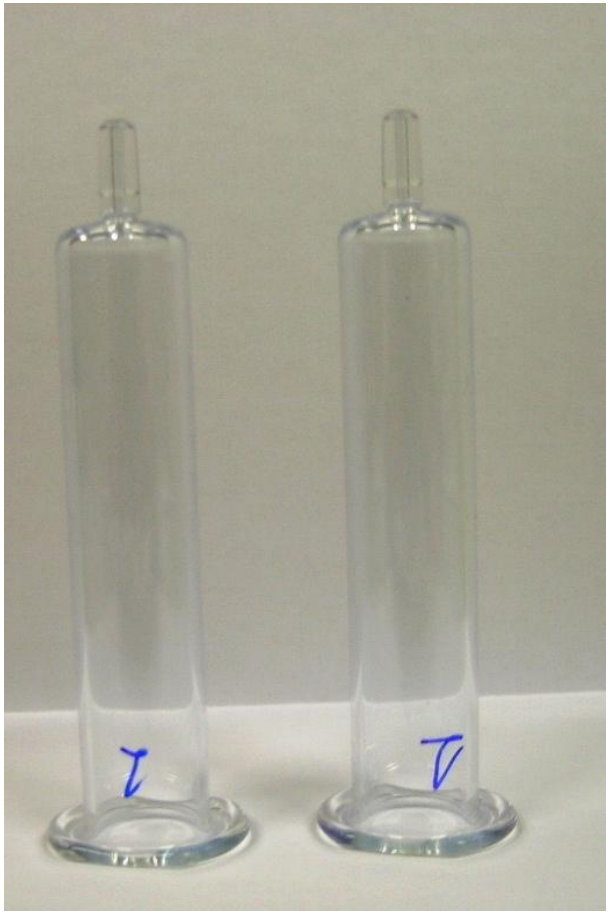

No coloration and absence of visible flakes

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U.S.P. Guidance

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BRIEFING

〈1660〉 **Evaluation of the Inner Surface Durability of Glass Containers.** In response to the recent product recalls that have further increased the pharmaceutical industry's heightened awareness of glass quality and glass delamination (i.e., the formation of glass flakes in a vial), USP proposes a new general information chapter to recommend approaches to predict potential formation of glass particles and delamination.

(PSD: D. Hunt.) Correspondence Number—C115672

Add the following:

▪〈1660〉 EVALUATION OF THE INNER SURFACE DURABILITY OF GLASS CONTAINERS

PURPOSE

This general information chapter provides information about factors that affect the durability of the inner surface of glass containers and recommends approaches to predict the potential of a drug product to cause formation of glass particles and delamination and to detect their occurrence. Useful procedures are listed and can be applied for both characterization and control tests.

<1660> Chapter Structure

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- Glass Container Manufacture & Processing
  - Molded and Tubing containers
- Glass Surface Chemistry
- Factors Influencing Glass Inner Surface Durability
  - Container manufacture, processing & storage
  - Drug Product formulation, processing & storage
- Screening Analytical Techniques
  - Techniques to examine inner glass surface, extracted elements, lamellae and sub-visible and visible glass particles
- Screening Strategies
  - Use of aggressive model systems, drug product and water control to assess the chemical durability of the inner surface using screening analytical techniques

<1660> Evaluation of Inner Surface Durability of Glass Containers

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- General Information Chapter <1660> = Guidance
- Published in USP's Pharmacopeial Forum Volume 38 (4), July-August, 2012
- Comment period ended September 31, 2012
- Comments received from glass industry and pharmaceutical companies
- USP's Packaging Storage & Distribution Expert Committee is revising the chapter taking into account the comments received
- It is estimated that the revised chapter will be published in the USP36-NF31 Second Supplement

Thanks for your attention…

Questions?

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