

ASEPTIC TECHNOLOGIES

FILLING SOLUTIONS – SAFER & EASIER

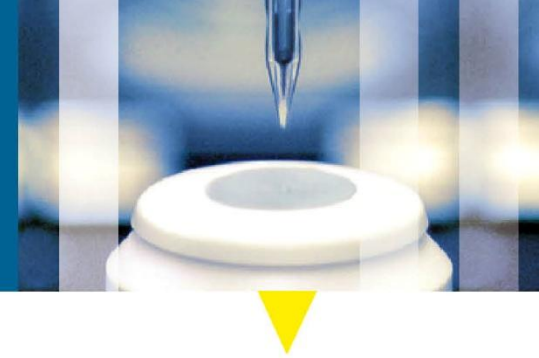
Overall Introduction

January 2013



NEW CONCEPT OF ASEPTIC FILLING

DESCRIPTION



***Crystal*[®] CLOSED VIALS**

- Vial body is made of COC polymer and stopper of a thermoplastic elastomer
- Vials are produced and stoppered in ISO5 clean room to ensure cleanness
- Vials are sterilized by gamma-irradiation before delivery to pharmaceutical users



***Crystal*[®] CLOSED VIAL FILLING LINES**

- Filling is performed by a special needle piercing the stopper
- The stopper is immediately re-sealed by laser
- Capping is done in the ISO5 area according to new authority requirements



ASEPTIC FILLING

NEW CONCEPT OF CRYSTAL[®] | PROCESS ON 3 SITES



PLASTIC MOLDER



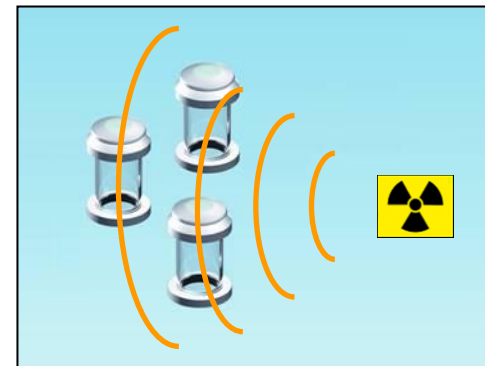
Molding & Closing (ISO 5)



Assembly (ISO 8)



IRRADIATION UNIT



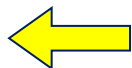
Sterilization
(Gamma irradiation)



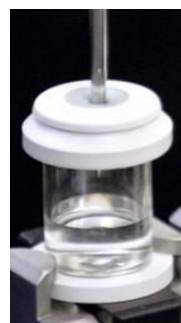
Filling line under barrier (ISO 5)



Capping



Laser re-sealing



Filling



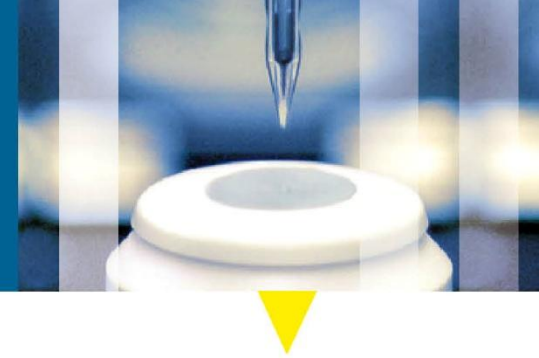
PHARMACEUTICAL SITE

**Clean & Sterile
ready-to-fill vial**



FILL AND CLOSE

NEW CONCEPT OF CRYSTAL® | KEY STEPS SUMMARY



1

**SUPPLIED CLEAN,
CLOSED & STERILE**

2

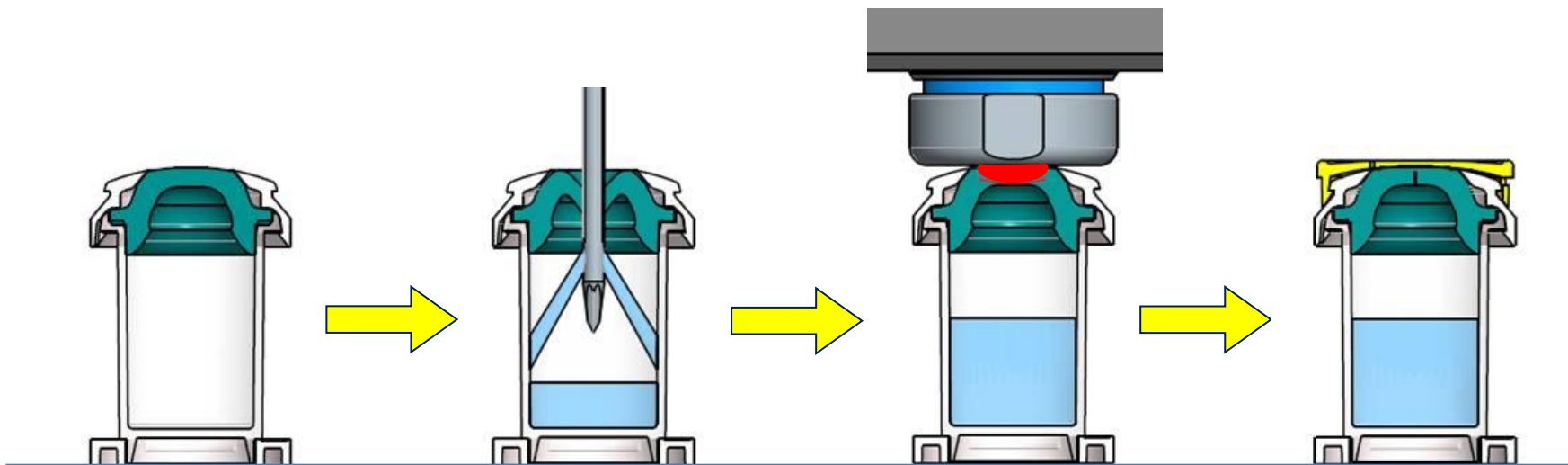
**FILLING THROUGH
THE STOPPER**

3

**LASER RE-SEALING
OF THE STOPPER**

4

**CAPPING
BY SNAP-FIT**

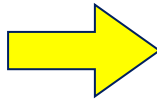
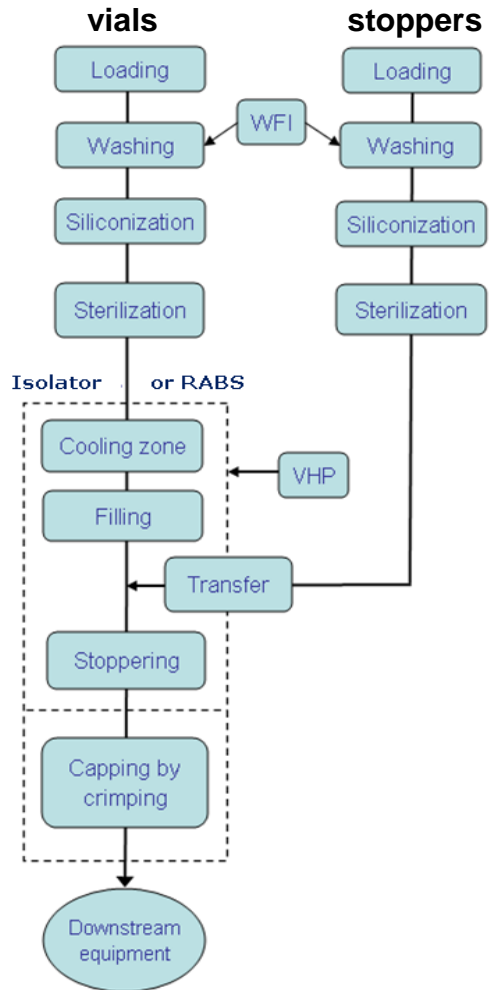


ASEPTIC FILLING

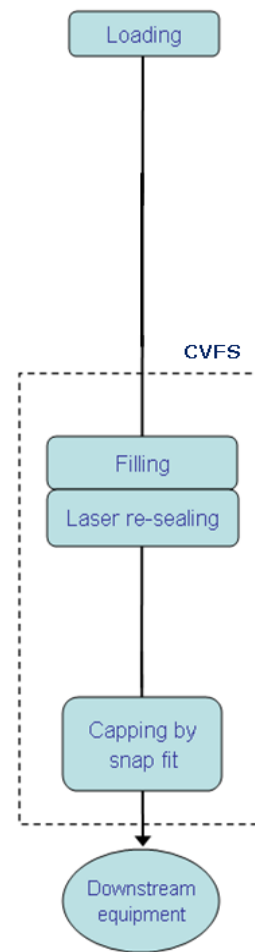
SIMPLIFIED PROCESS



GLASS VIAL FILLING



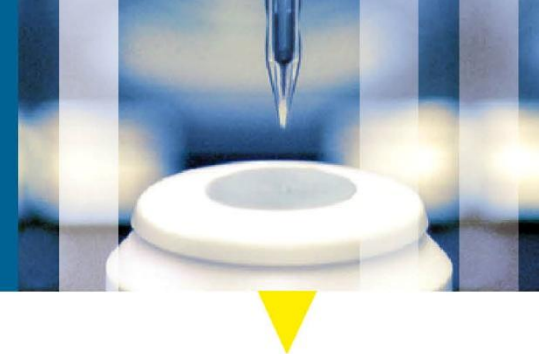
Crystal® FILLING



Lean manufacturing with elimination of:

- WFI
- Vial and stopper washing
- Vial and stopper siliconization
- Vial and stopper sterilization
- Stoppering
- Capping by crimping

CRYSTAL[®] VIAL DESCRIPTION



FLIP AWAY CAP Ensures sterility assurance level of the piercing area

TOP RING Ensures closure integrity

STOPPER Made of Thermoplastic Elastomer (TPE) Allows laser resealing after filling

VIAL BODY Made of Cyclo-olefin co-polymer (COC)
Contains volume from 0.2 to 50ml

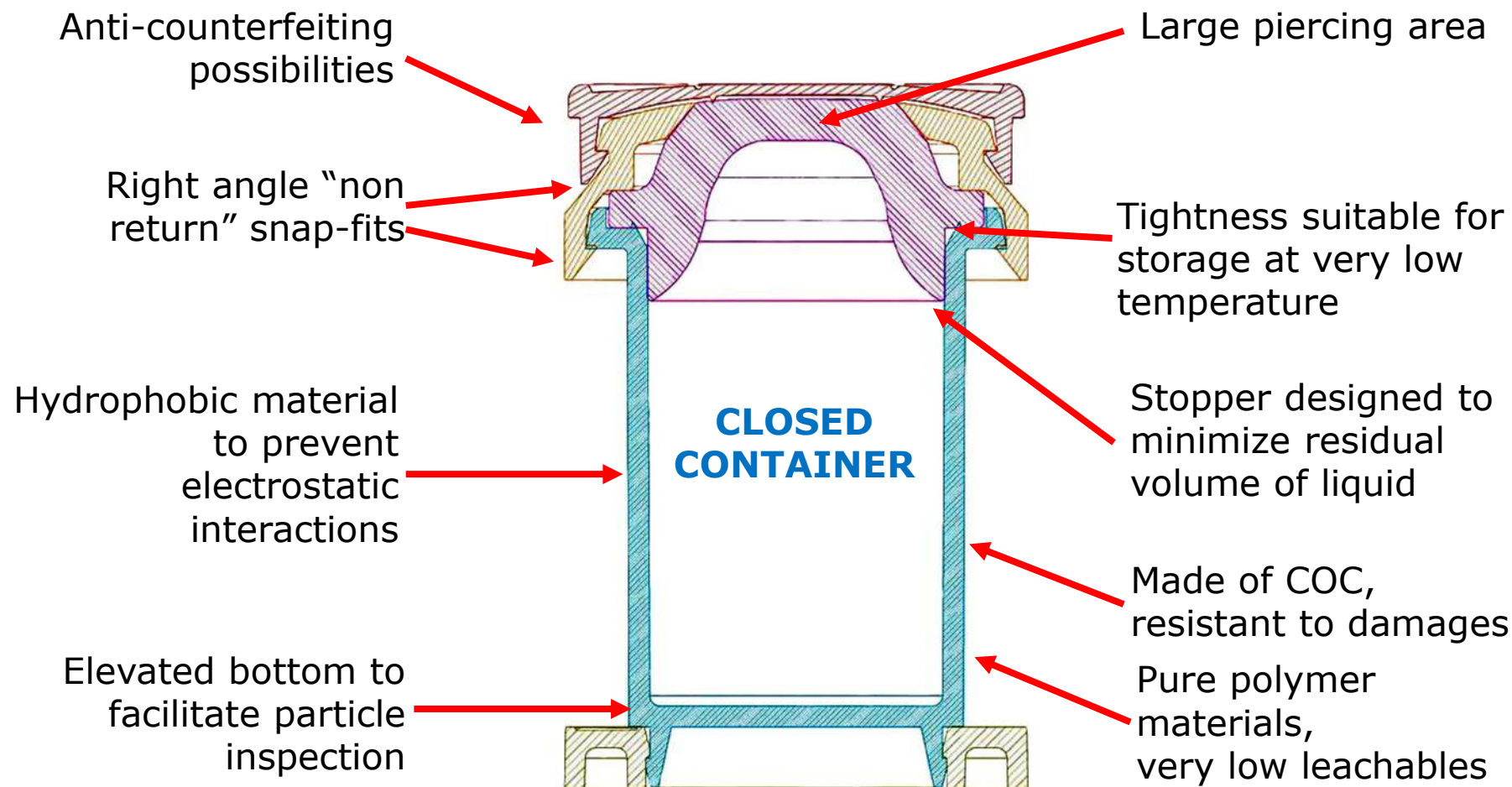
BOTTOM RING Ensures mechanical stability of small vials

FROM 1 TO 50 ML



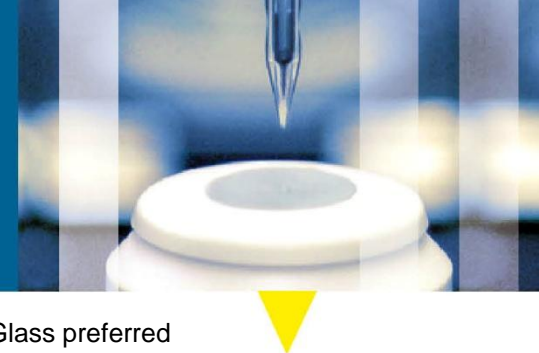
CRYSTAL[®] VIAL PROPERTIES

POLYMER MOLDING



CRYSTAL[®] VIAL ACCEPTANCE

MARKET RESEARCH RESULTS | CRYSTAL[®] vs. GLASS VIAL



Crystal[®] preferred



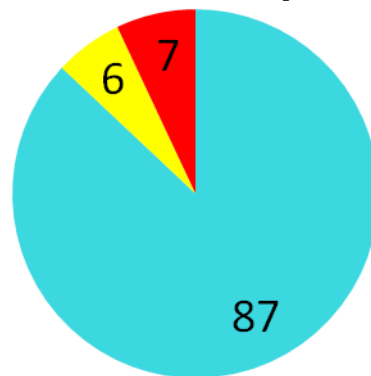
No preference



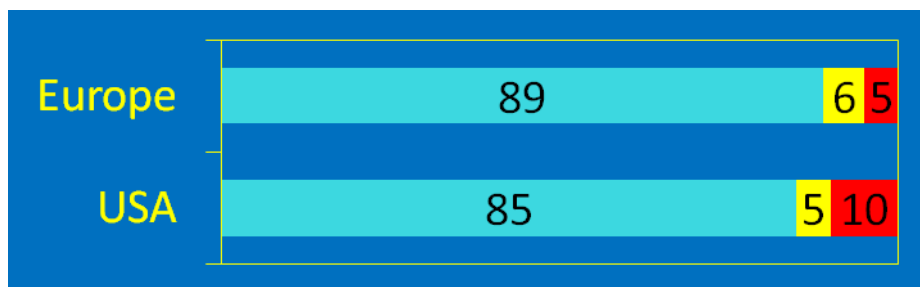
Glass preferred

- 246 healthcare professionals from hospital settings interviewed
- 71 doctors, 161 nurses and 14 hospital pharmacists
- 134 in Europe (F, B) and 110 in the US (West and East Coasts)

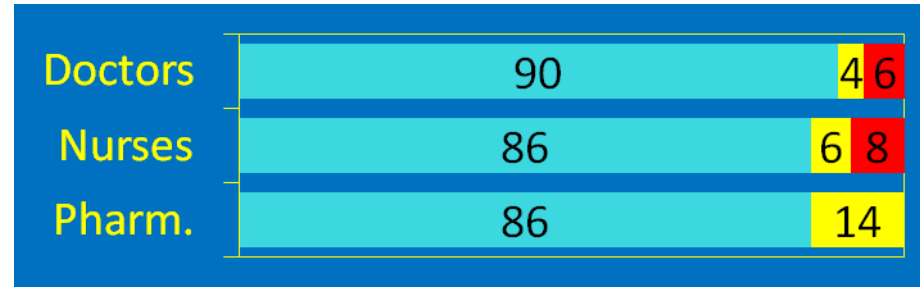
87% of professionals prefer *Crystal*[®]



In each region

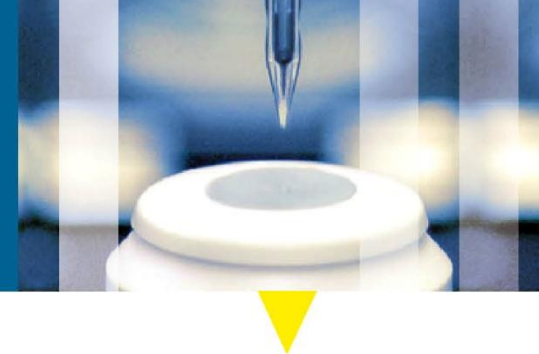


By each professional



CRYSTAL[®] CLOSED VIAL FILLING LINE

LABORATORY LINES



Crystal[®] M1 FILLING STATION



- Independent tools with manual transfer operations
- Capacity up to 2,000 vials per shift (about 150 vials/hour)
- Able to handle all formats of *Crystal[®]* vials (1 to 50 ml)
- To be installed in existing environment (LAF)
- Designed to fill very small batch filling (<2,000 vials) or lab operation
- Space needed: a cabinet of ~1 m² dimension

Crystal[®] L1 ROBOT LINE



- Designed to fill small batches (<5,000 vials)
- Capacity: about 600 vials/hour*
- Able to handle all formats of *Crystal[®]* vials (1 to 50 ml) and glass vials
- Robot line with all tools on robot head (needle, laser and capping)
- Space needed: ~10 m² (footprint: 1 m²)
- Suitable for installation in various containment (isolator,...)

* 1 ml vials

CRYSTAL[®] CLOSED VIAL FILLING LINE

PRODUCTION LINES

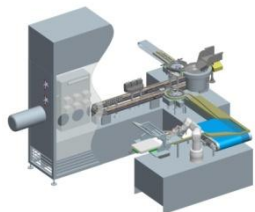


Crystal[®] CX FILLING LINE



- Designed to fill medium scale commercial batches: up to 100 vials/min*
- Able to handle all formats of *Crystal[®]* vials (1 to 50 ml)
- Equipped with up to 4 needles and lasers (C4)
- Space needed: 40 m² (footprint: 10 m²)
- Suitable for installation in various containment (isolator,...)

Crystal[®] PX FILLING LINE



- Designed to fill commercial batches: up to 200 vials/min*
- Able to handle all formats of *Crystal[®]* vials (1 to 50 ml)
- Equipped with up to 8 needles and lasers (P8)
- Space needed: 50 m² (footprint: 11 m²)
- Suitable for installation in various containment (isolator,...)

Crystal[®] Pxx FILLING LINE

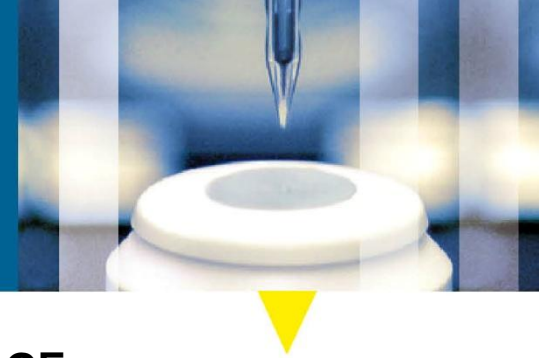


- Designed to fill very large commercial batches: up to 600 vials/min*
- Monoformat equipment able to handle all formats of *Crystal[®]* vials (1 to 50 ml)
- Equipped with up to 24 needles and lasers (P24)
- Space needed: 100 m² (footprint: 44 m²)
- Capacity increase is feasible by adding filling heads and lasers

* 1 ml vials

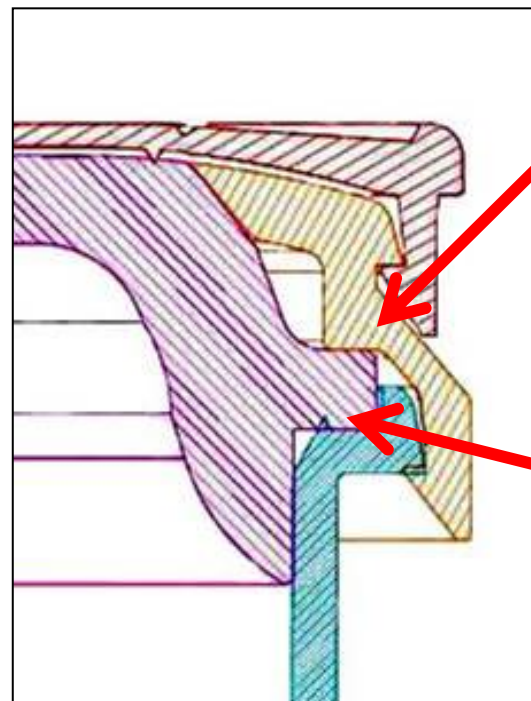
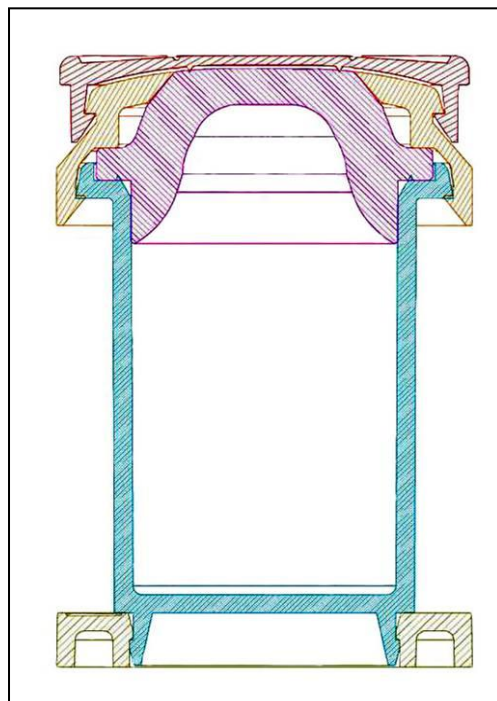
ADVANTAGES OF VIAL DESIGN

CLOSURE INTEGRITY AT VERY LOW TEMPERATURE



POLYMER VIAL BODY RESISTANT TO LOW TEMPERATURE STORAGE

Stopper crimped between vial body and top ring ensuring uncompromised closure integrity (no loss of closure integrity as with glass vial)

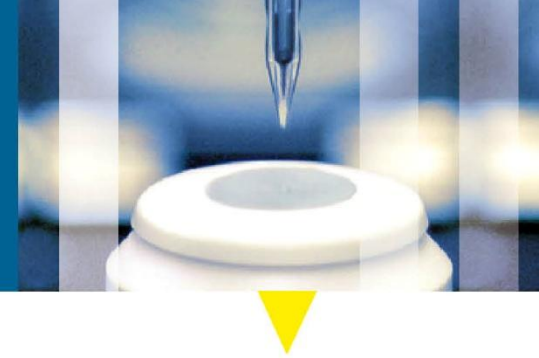


Stopper compression secured by snap-fit assembly

V-pressure rib hanging the stopper

CRYSTAL[®] CLOSED VIALS

BEHAVIOR AT VERY LOW TEMPERATURE



AT -80°C AND IN LIQUID NITROGEN

Closure integrity ✓

Weight variation ✓

Tightness ✓

Visual aspect ✓

Polymer vial body resistant to extremely low temperature storage
TPE stopper ensures uncompromised closure integrity

Crystal[®] Closed Vials particularly suitable and widely used for cryogenic storage of injectables

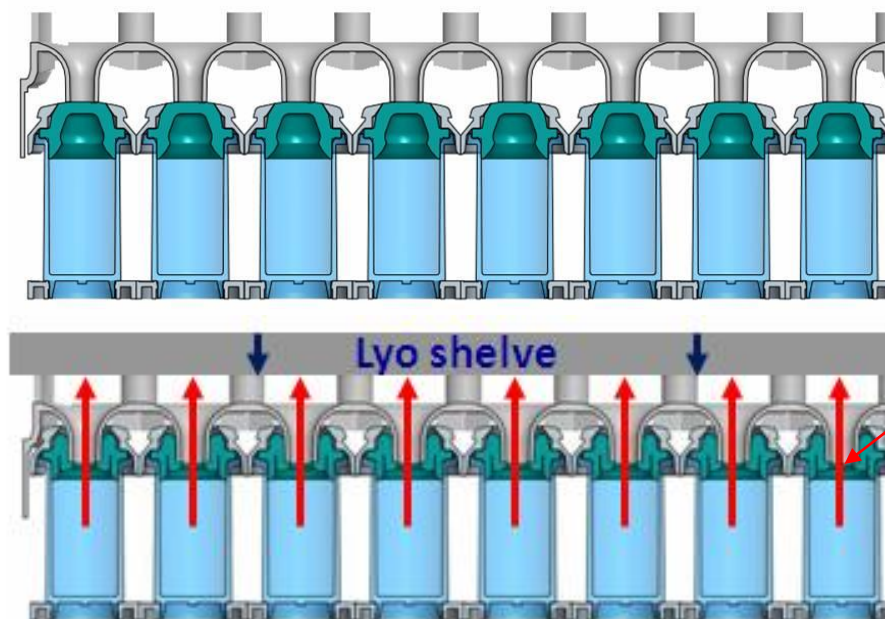


LYOPHILIZATION WITH CRYSTAL[®]

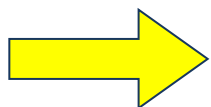
PROCESS



1. Normal vial filled but not laser re-sealed
2. Penetrator (funnel shape) placed in line on vial top
3. Lyo shelf moved down to push penetrator and re-open piercing trace
4. Lyophilization done through piercing trace
5. Penetrator withdrawn and vial laser re-sealed and capped



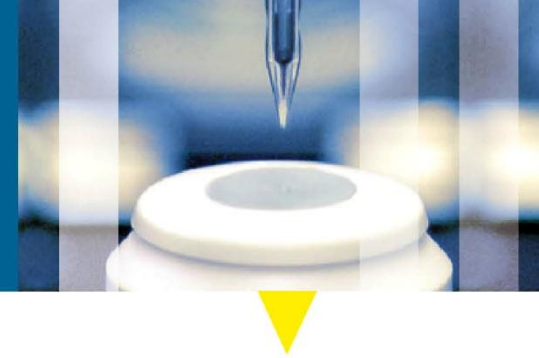
Piercing trace re-opened



- Lactose 5 % and 10% : successful
- Sucrose 5 % and 10% : successful
- Viruses: same titer as in glass vials
- Multiple formats of vials: successful



KEY ADVANTAGES



FOR WHOM?

WHY?

SAFER

- For your regulatory
- For your supply chain
- **Top-class sterility** assurance level thanks to a closed ready-to-fill vial
- Product secured inside an **unbreakable** and unique container

EASIER

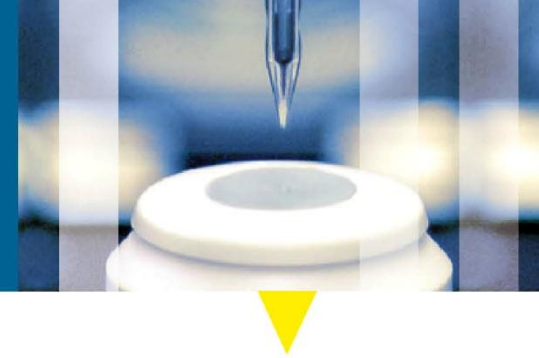
- For your manufacturing
- For your QA/QC
- For your marketing
- **Lean manufacturing** leading to lower investment and operating costs
- **Simple and dry** process reducing initial and regular validation work
- **Appreciated** by practitioners
=> sales booster

CRYSTAL[®] VIAL SUITABLE FOR



- Potent and hazardous drugs (cytotoxics, radiolabeled, immuno-modulating drugs, recombinant viruses,...)
 - Unbreakable container
 - No spillage outside during filling inside a closed container
- Frozen products (-20°C, -80°C and in liquid nitrogen)
 - No loss of closure integrity (no stopper retraction)
 - Container remains resistant
 - No damages during thawing
- Expensive drugs (antibodies, recombinant proteins,...)
 - Lower risk of batch rejection thanks to simple process
 - Residual volume minimized
- Soluble products at risk of adsorption
 - Hydrophobic material
 - No ion inducing electro-static interaction
- All aseptically filled products
 - Ready-to-fill container, ensuring lean and safe process
 - Improved quality thanks to a container permanently closed

PRODUCT TESTING

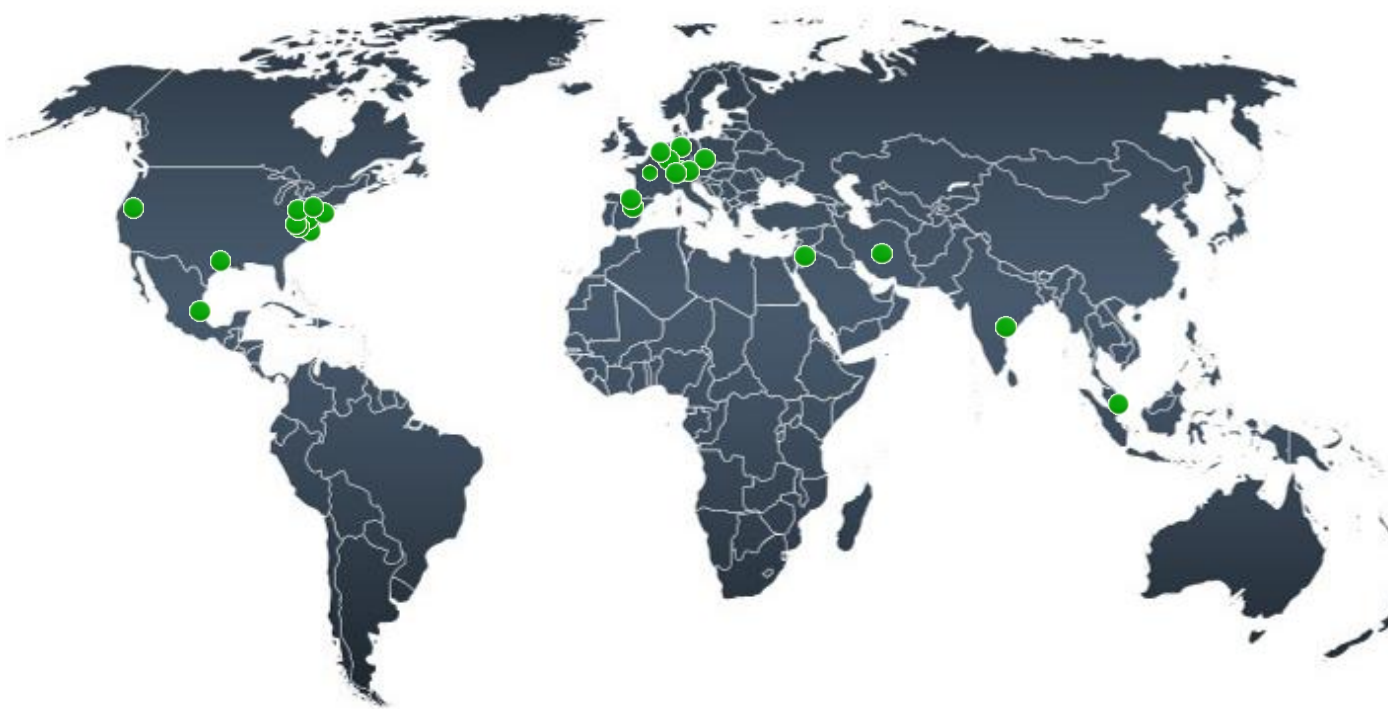


97 PRODUCTS FILLED IN CRYSTAL[®] VIAL

- Various categories tested, including
 - 64 biological products (vaccines, antibodies, proteins, cells, viruses, mRNA,...)
 - 7 cytotoxic products
 - 7 lyophilized products
- 61 different companies, including
 - 5 top 10 pharma
 - 5 top 10 biotechs
- Currently 78 results obtained
 - 31 products with better stability than with other containers
 - 10 products with lack of stability*
 - 37 products with good stability

* 3 are unstable in glass as well, one unbuffered product was sensitive to acid, two are degraded due to oxygen ingress without protective packaging, two are hydrophobic, one is more absorbed than in PP but less than in glass and one is adsorbed

CRYSTAL[®] TECHNOLOGY INSTALLATIONS



Bilthoven, Netherlands



San Carlos, CA, USA



Geneva, Switzerland



Chennai, India



Walkersville, MD, USA
Visp, Switzerland
Singapore



Martinsried, Germany



Mexico D.F., Mexico



Allendale, NJ, USA



Brussels, Belgium



SYNFLORIX[™] pediatric vaccine is approved by EMA
in the Closed Vial for all European countries

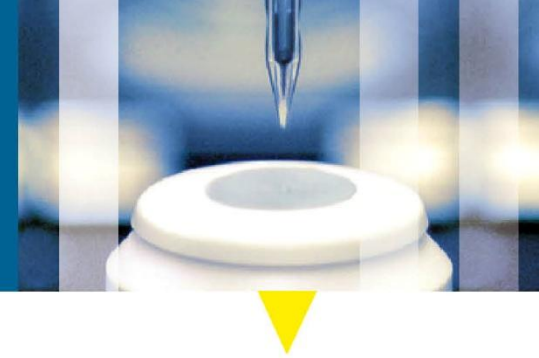
Several other users under confidentiality agreement



36 equipments installed/ordered so far

FIRST PRODUCT APPROVED

SYNFLORIX® FROM GSK BIOLOGICALS

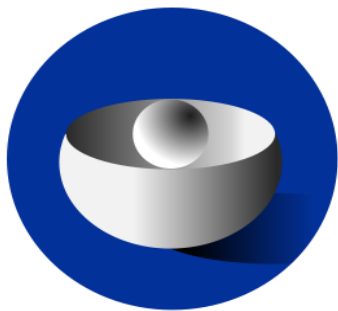


SYNFLORIX®

Pneumococcal polysaccharide conjugate vaccine, 10 valent adsorbed



- Product filled in late 2007 in AT facility (filling line in CVFS, located in ISO8 clean room)
- Two years of stability obtained in early 2010, all data within specifications
- Data submitted to EMA in January 2011, CHMP recommended approval in May 2011 with sentences such as "...very interesting innovative technique...", approval granted by EMA in July 2011



Decision C(2009)2563 is amended as follows:

1) The following number is added to Article 1 and entered in the Community register of medicinal products:

EU/1/09/508/011 Synflorix - Suspension for injection - Intramuscular use - Vial (polymer) - 0.5 ml - 1 vial

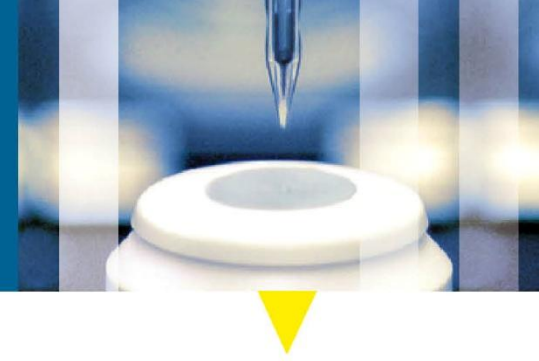
CONCLUSIONS

- Offer SAFER and EASIER solution for your injectable products
- Has a proven track record of product stability
- Is fully validated to meet authority requirements and the Validation Master File was used to get SYNFLORIX™ approval by EMA



Filling suite in our facility to support your stability studies in our **Crystal®** vials

CRYSTAL[®] CLOSED VIAL TECHNOLOGY



CONCLUSIONS



+



SAFER

EASIER

Simply Safer !

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