



Introduction to the *Crystal*[®] Closed Vial Technology



**A Safe & Easy Solution
for BioPharmaceutical Aseptic Filling Operations**



**Aseptic
Technologies**

- **Developed a revolutionary vial for aseptic filling based on the closed vial technology**
- **Developed the filling line (CVFL or closed vial filling line) able to process the closed vial. Three formats available from 600 up to 36,000 vials/hour**
- **Launched a Validation Master Plan to support approval of the lines and the vials**
- **Provides key advantages to patients, manufacturing teams and healthcare clients**



***Crystal*[®]
Technology**

- **Is a ready-to-fill Closed Vial**
- **A fill and finish equipment (filling, laser re-sealing and capping)**
- **Has been fully validated for filling of aseptic drugs**
- **Offers key advantages:**
 - **SAFER for the patient**
 - **EASIER for the manufacturer**

➤ **Introduction**

➤ **Company**

➤ **Vials**

➤ **Filling Lines**

➤ **Validation Master Plan**

➤ **Freeze Drying**

➤ **Services**

➤ **Contact**

Introduction





200,000 infections by contaminated drugs are yearly reported worldwide, representing 1/100,000 injection



Centers for Disease Control and Prevention
Your Online Source for Credible Health Information



Clinical Sepsis and Death in a Newborn Nursery Associated with Contaminated Parenteral Medications -- Brazil, 1996

In October 1996, a total of 35 newborn infants died in a 26-bed nursery of a 200-bed hospital in Roraima, Brazil.

Authorities decided to reduce the use of preservatives in aseptic parenteral drugs



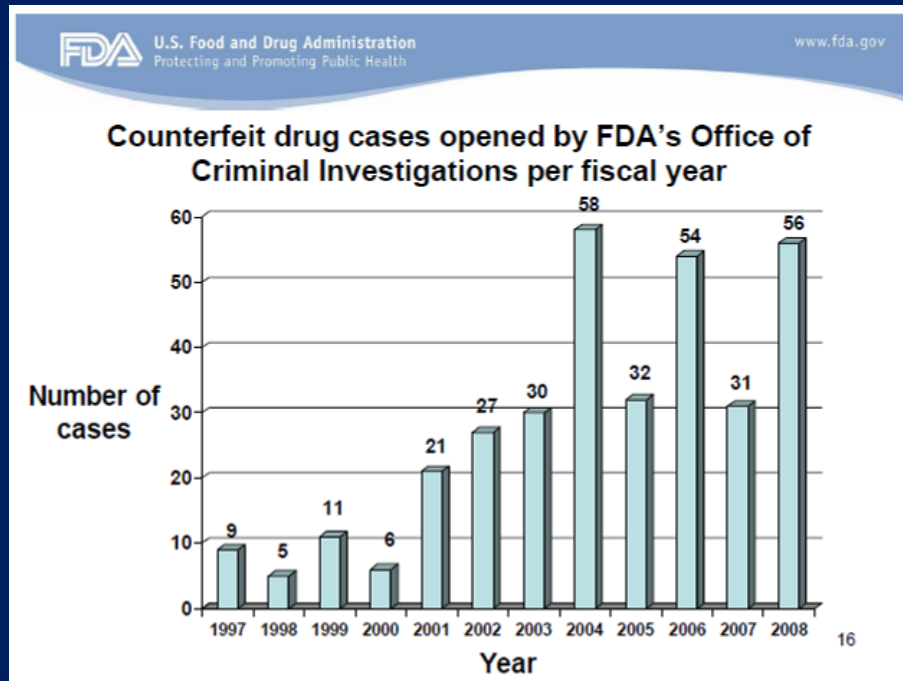
U.S. Food and Drug Administration



As a precautionary measure, the **Public Health Service** (FDA, NIH, CDC, HRSA) and the American Academy of Pediatrics issued two Joint Statements, **urging vaccine manufacturers** to reduce or **eliminate thimerosal** in vaccines as soon as possible (CDC 1999) and (CDC 2000).



New requirements on traceability and anti-counterfeiting of vials



Source: U.S. Food and Drug Administration
USPHS Scientific and Training Symposium, June 2 2009

Examples of companies facing counterfeited injectables (FDA report)

- Serono: Serostim
- Genentech: Nutropin
- Amgen: Neupogen
- Amgen: Epogen → Tim Fagan's law

Counterfeiting has dramatic effect: 2,500 people died in Nigeria when vaccinated with fake vaccines during meningitis epidemic

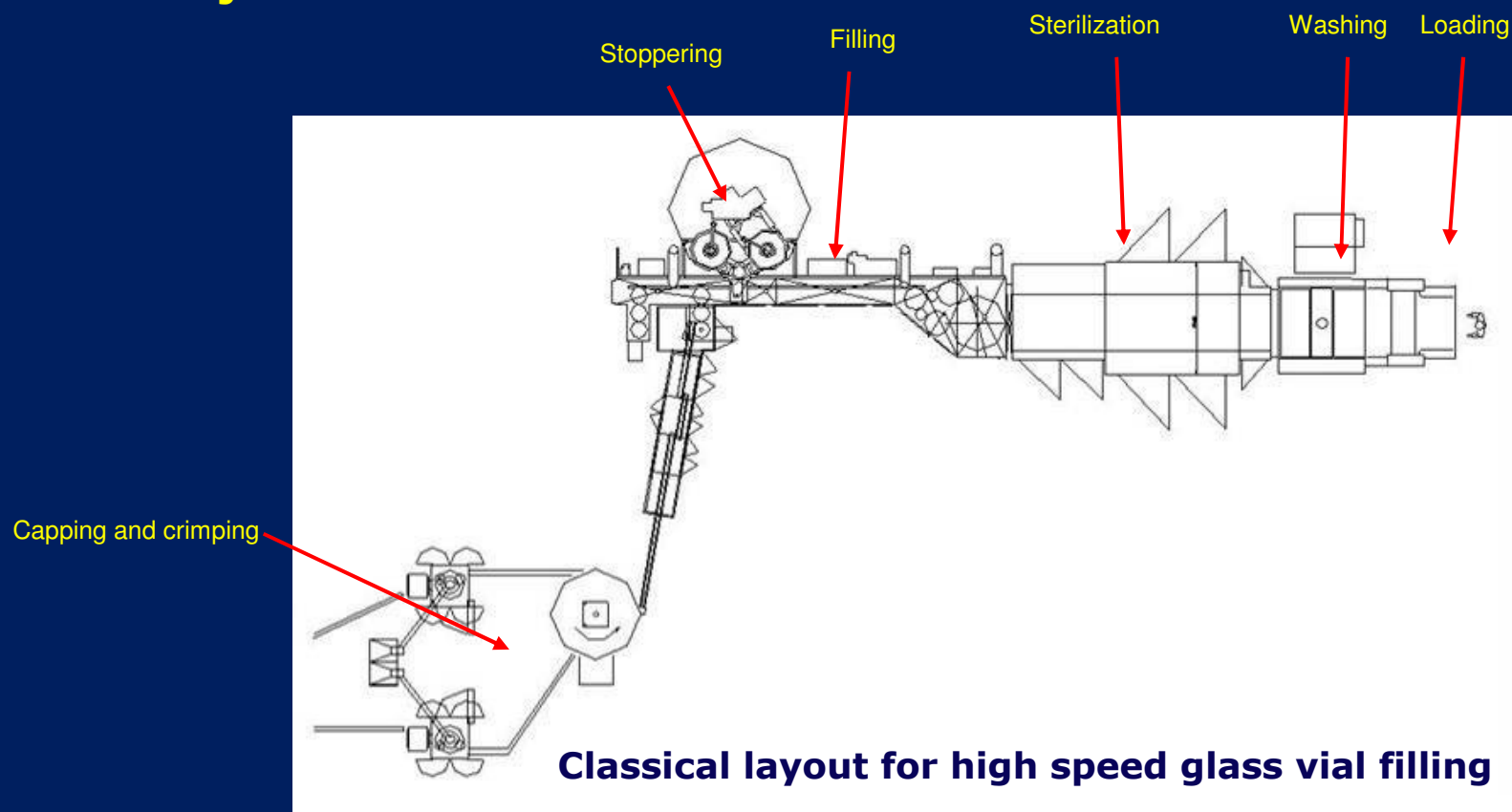
WHO data on counterfeiting:

- 32 USD Bio loss
- 10% of worldwide drugs
- Up to 50% in some countries



Manufacturing and QA/QC issues

- Huge investment costs
- Long delivery delays
- Extensive QA/QC validation work and follow up
- Complexity of production
- Risk on batch rejection due to deviations





Description

CLOSED VIALS

- Produced with the closing stopper installed (in ISO5 room) and secured;
- Sterilized through gamma irradiation before delivery to users.



CLOSED VIAL FILLING LINES

- Filling is performed by special needle piercing the stopper;
- The stopper is immediately re-sealed by laser;
- Capping done in the barrier, according to new authority expectations.



First ready-to-fill closed vial which minimizes the risk of contamination

||| New Concept of *Crystal*[®] | Process on 3 sites



MOLDING SITE

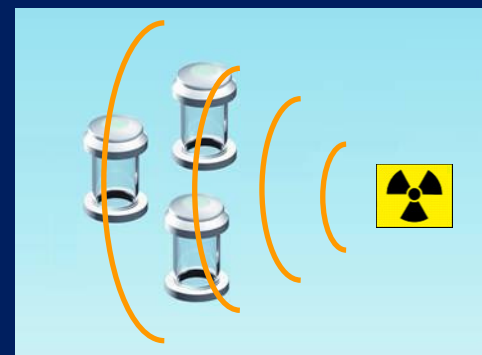


Molding & Closing
(Class ISO 5)



Assembly
(Class ISO 8)

IRRADIATION UNIT



Sterilization
(Gamma irradiation)

PHARMACEUTICAL SITE

Filling line under barrier (Class ISO 5)



Capping



Laser re-sealing



Filling

Clean & Sterile
ready-to-fill vial





Company





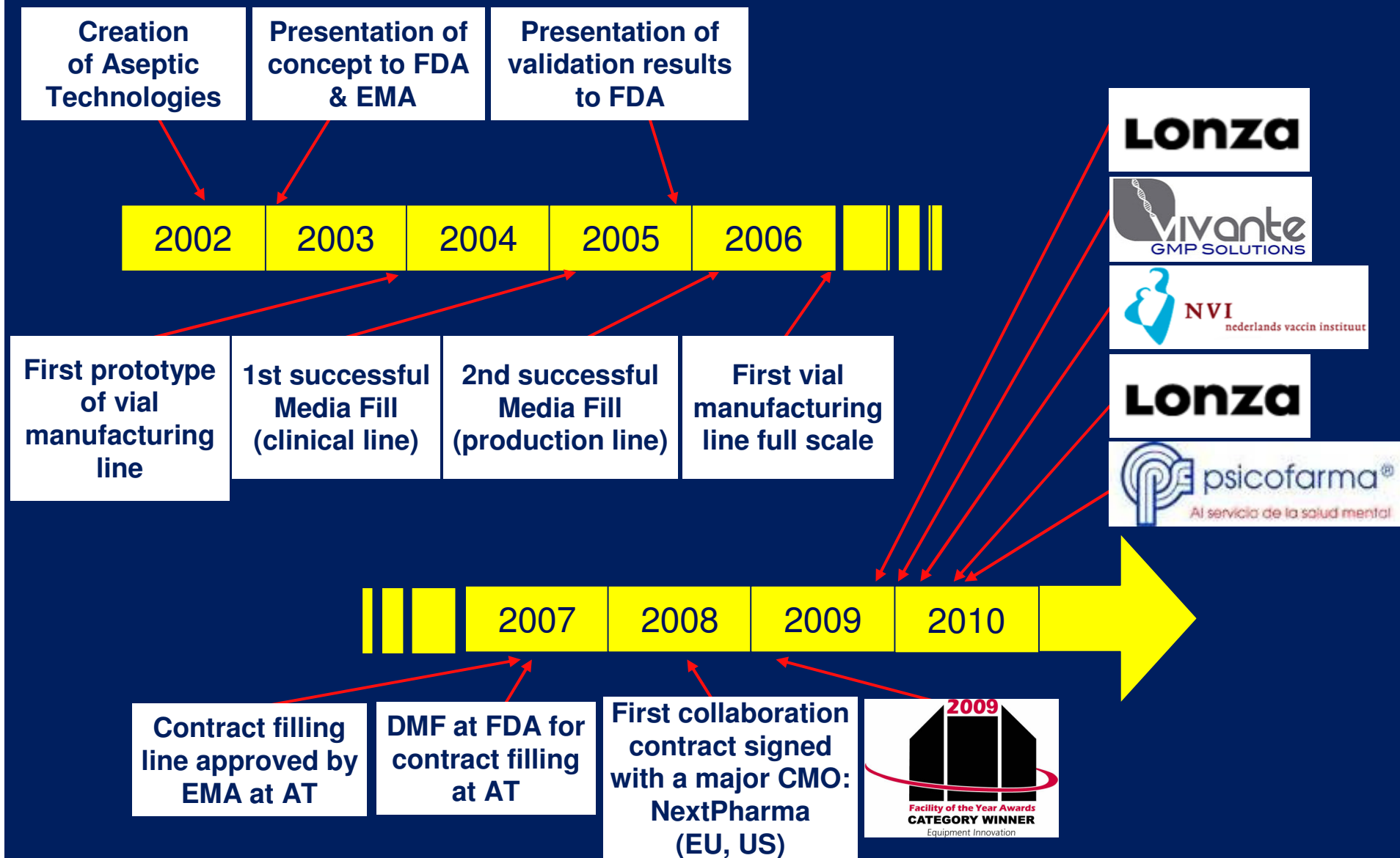
- Launched in June 2002 to develop the Closed Vial Technology
- Spin-out and affiliate of GlaxoSmithKline Biologicals
- Collaboration with several technical partners :
 - Technord: automation
 - IBA: mini e-beam
 - Lasea and Osysris : laser technology
 - Sirris: material studies
 - Rexam: vial manufacturing



- Core technology licensed by Medical Instill Technologies Inc.



The History of Aseptic Technologies



Vials





Key advantages

Body made of COC and stopper of thermoplastic elastomer:

- **Hydrophobic material to prevent electrostatic interaction with soluble proteins**
- **Unbreakable vial**
- **Glass-like transparency**
- **Specially designed stopper minimizing loss of residual volume**
- **Bio-compatible**
- **FDA approved material**
- **Ability to reduce oxygen concentration to 0.1%**

***Crystal*[®] Vial is particularly suitable for:**

- **Products sensitive to alkali and/or metal ions**
- **Toxic products**



See <http://www.aseptictech.com> for videos

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

Crystal[®] vial is closed in a class ISO5 room before being sterilized by gamma irradiation



From 1ml to 50 ml

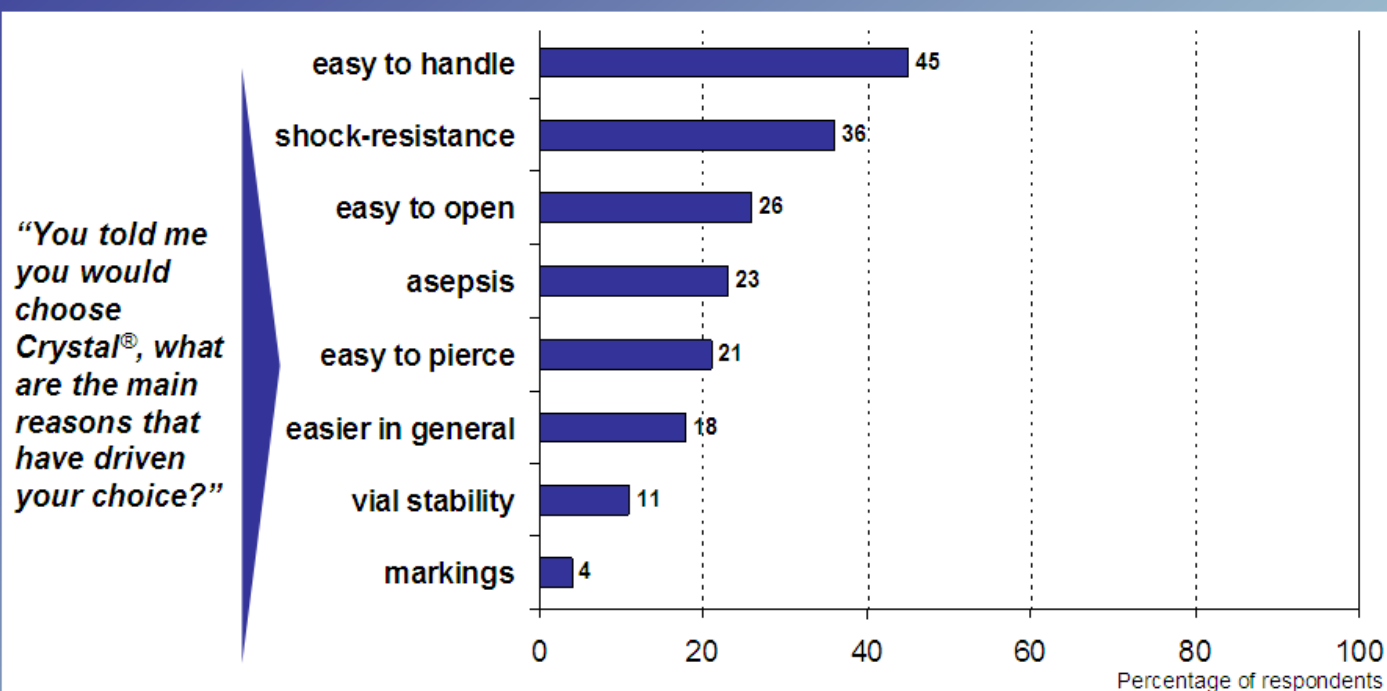




REASONS TO PREFER *Crystal*®



**EASY TO HANDLE AND SHOCK-RESISTANCE
ARE THE MAIN REASONS TO CHOOSE *Crystal*®**



Market Survey

Perception by Health Care Professionals

February – April 2007



Crystal®

Filling Lines



Four formats available



Manual line (Crystal® M1)

- Independent tools for manual operations
- To be installed in existing containment
- Designed to fill very small batches (<1,000 vials) or for research purposes



Laboratory line (Crystal® L1)

- Designed to fill batches of max. 5,000 vials
- Capacity: about 10 vials/min
- Space needed: ~8 m² (footprint: 2 m²)



Clinical line (Crystal® C2 or C3)

- Designed to fill clinical batches and small commercial batches
- Capacity: up to 75 vials/min
- Space needed: 40 m² (footprint: 9 m²)



Production line (Crystal® P6 to P24)

- Designed to fill large commercial batches
- Capacity: up to 600 vials/min
- Space needed: 100 m² (footprint: 44 m²)
- Capacity increase by adding filling heads and lasers





Key advantages

The Filling process

The *Crystal*[®] closed vial enables to:

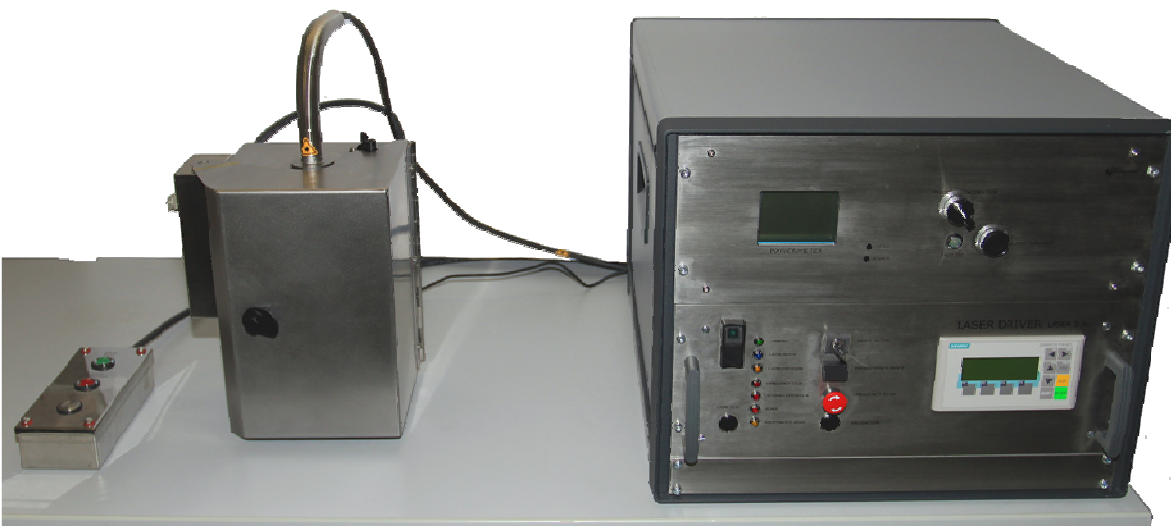
- **Eliminate most complex steps of aseptic filling**
 - no WFI washing
 - no hot-air tunnel
 - no siliconization
 - no stoppering
- **Limit risk of batch rejection thanks to process simplification**
- **Secure potent and high-value products**

***Crystal*[®] Technology drastically simplifies aseptic filling operations**



Manual kit M1

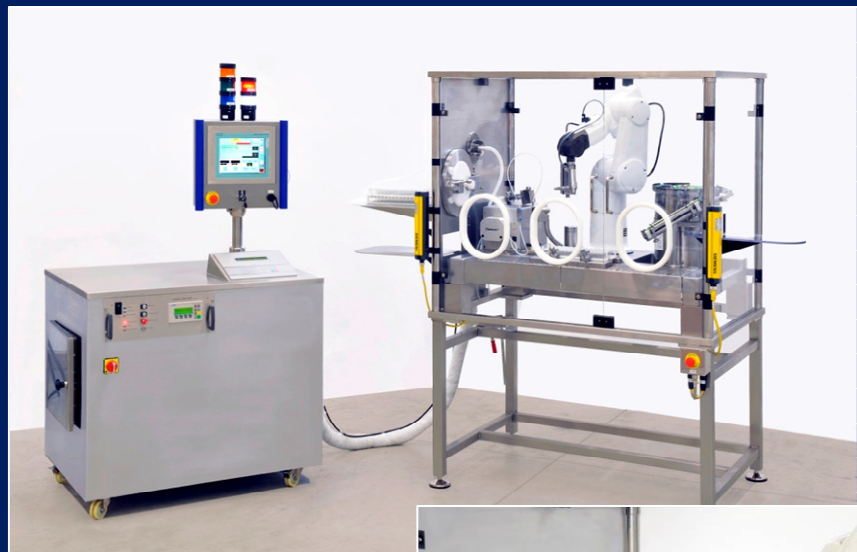
Delivered to Lonza (MD, USA)





Laboratory line L1

At Aseptic Technologies for trial testing, 10 vials/minute



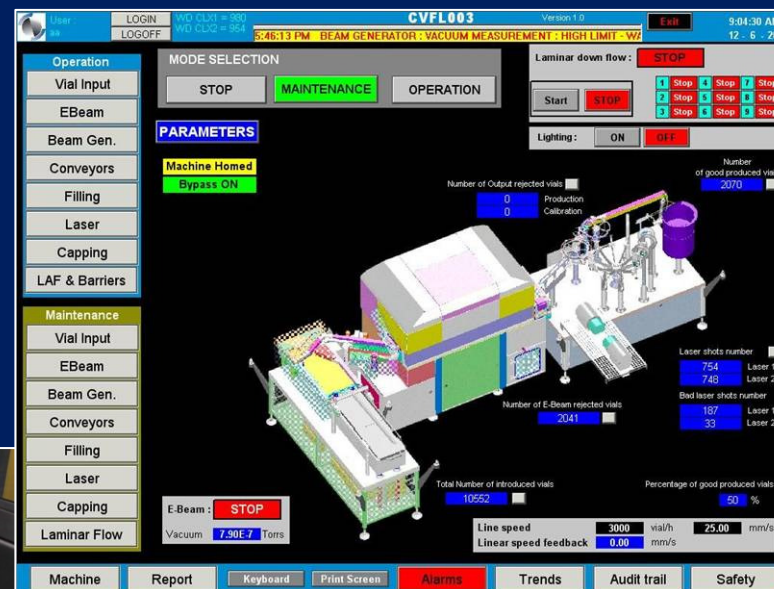
See <http://www.aseptictech.com> for videos

Crystal® Closed Vial Filling Line



Clinical line C2

Delivered to a US CMO, 50 vials/minute



Crystal® Closed Vial Filling Line



Production line P24

To be delivered to GSK Biologicals, 600 vials/minute



New equipment under development



✓ **Multi-purpose filling platform, suitable for liquid and freeze dried products**

✓ **Able to handle various categories of products:**

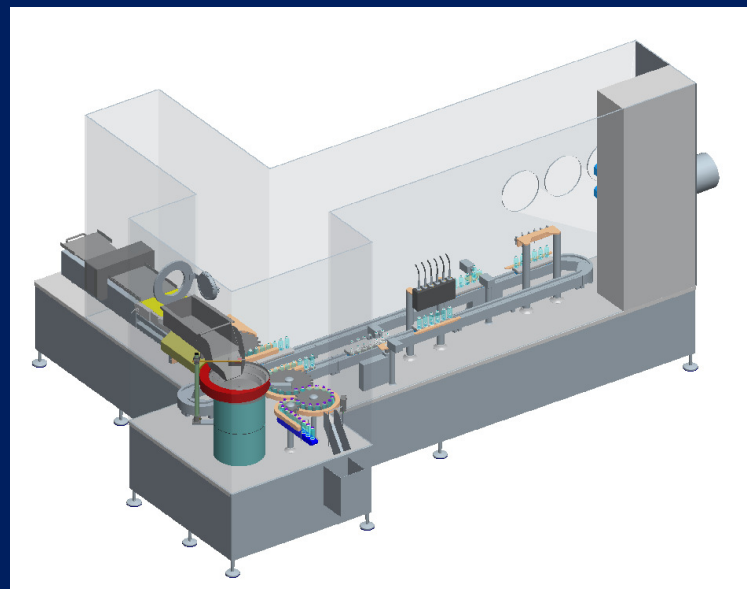
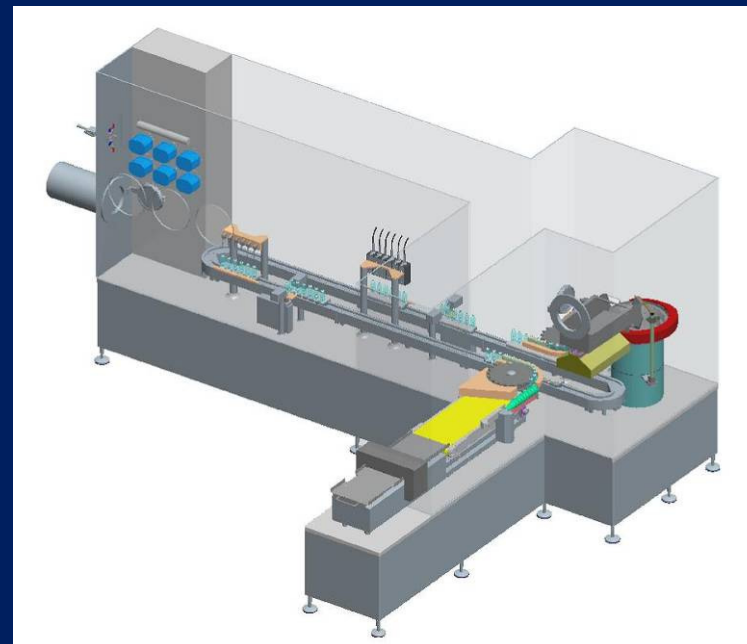
- aseptic
- aseptic toxic
- aseptic bio-hazard

✓ **Capacity from 50 to 150 vials / min**
(3.000 to 9.000 vials / h)

✓ **Multi-format by design**

✓ **Ready for different containments :**

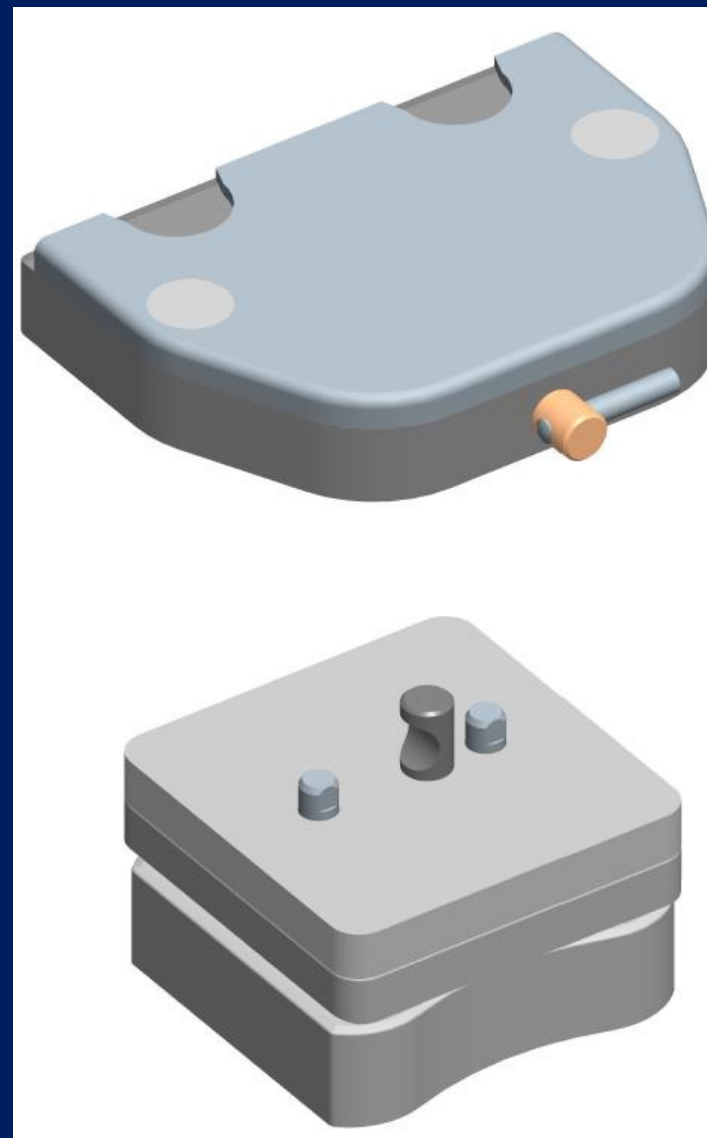
- clean room arrangement
- CVFS for Class ISO8 clean room
- Isolator for toxics





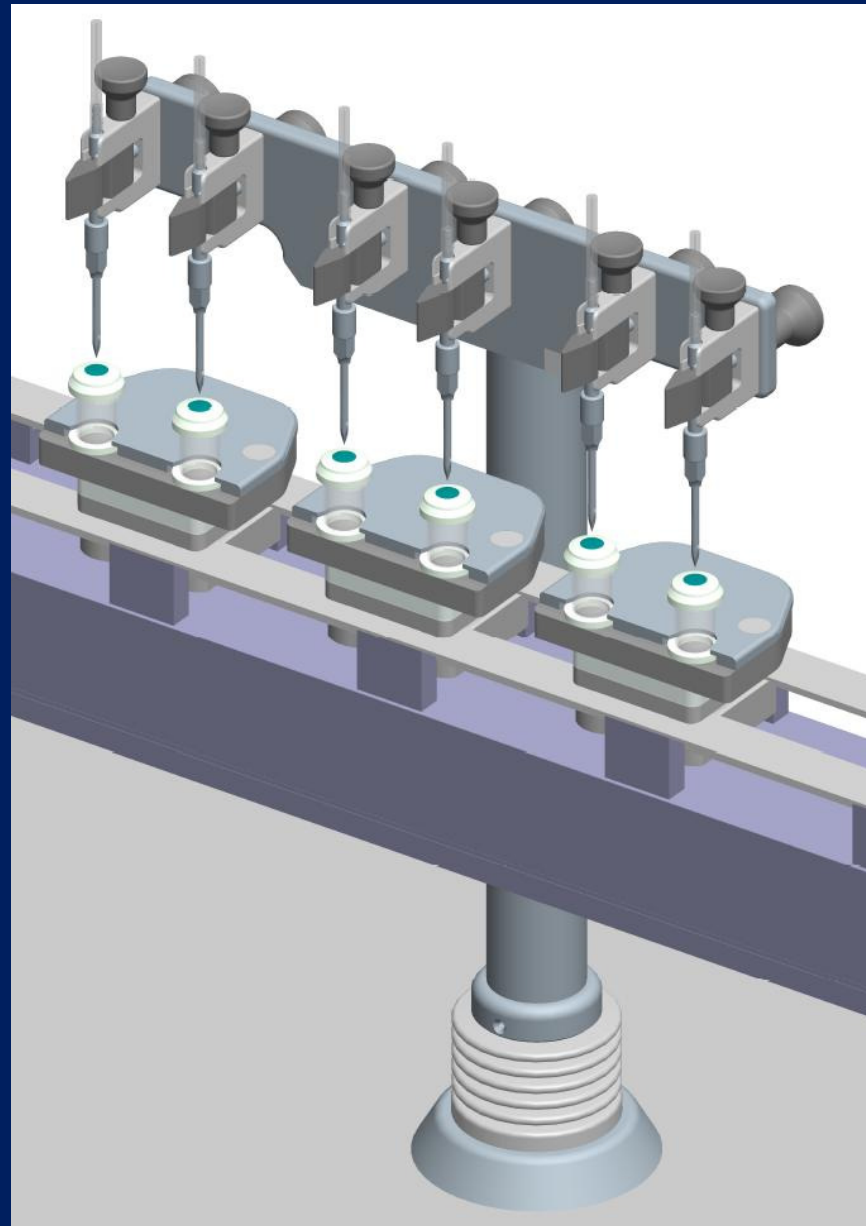
Conveying by independent wagons
(magnetic conveyor)

- Easy, tool-less format change (top piece removal with back handle);
- Easy to clean and sanitize.



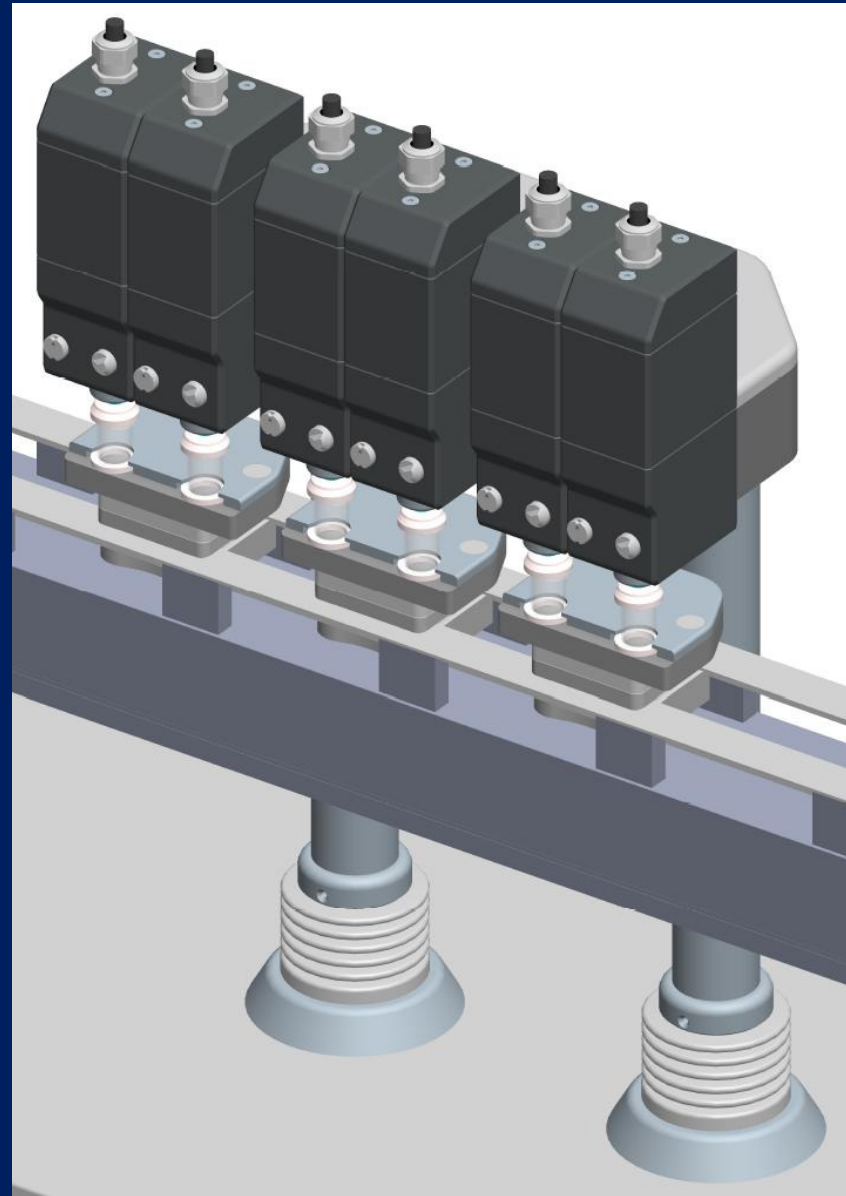


- Easy needle installation;
- Minimum hole size without coring;
- Low particle generation.



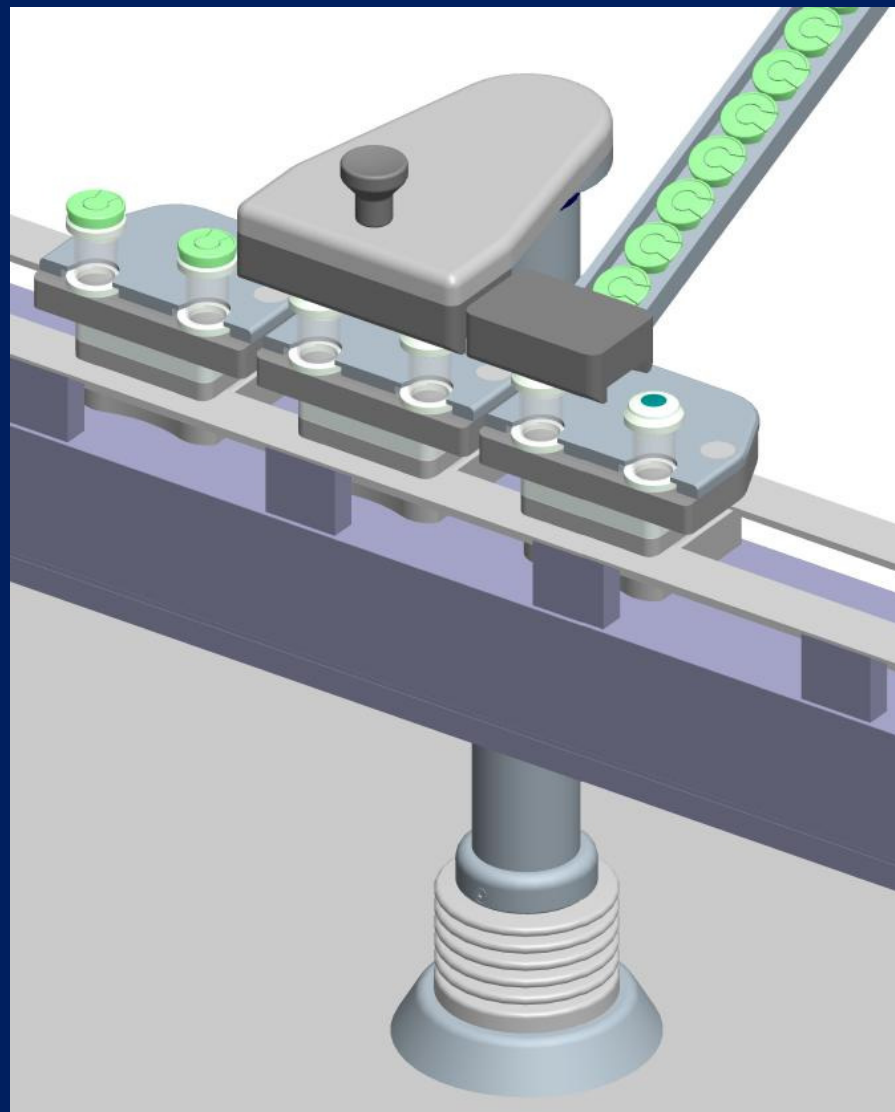
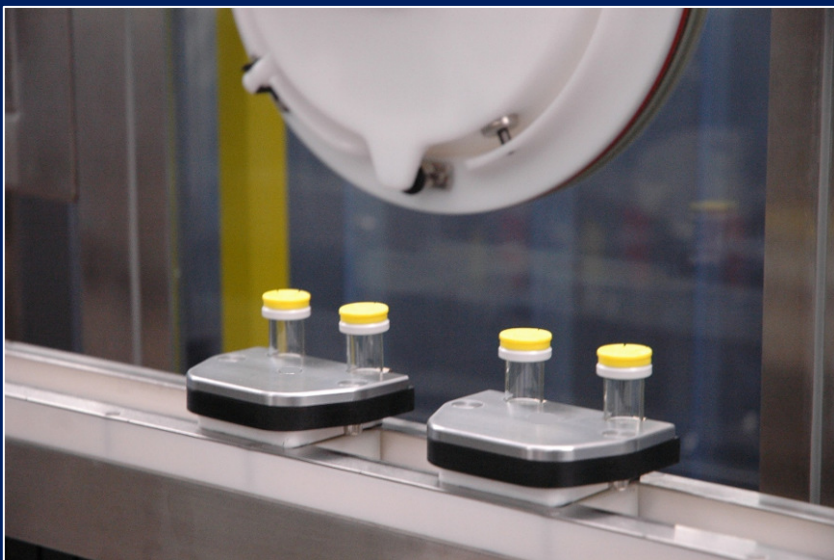


- Laser wing;
- 2 laser heads per carrier.



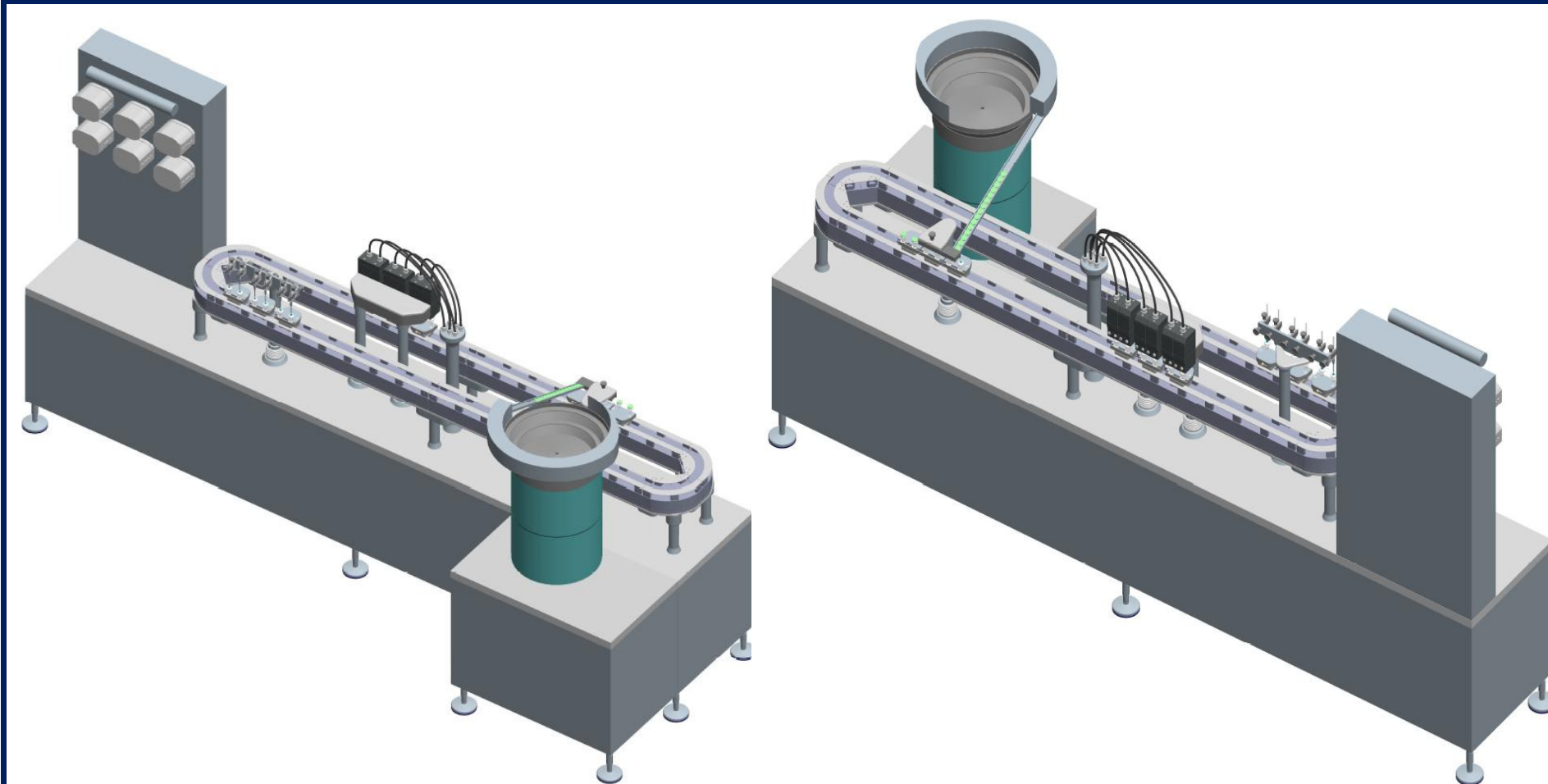


- Flip away cap installed by snap fit.



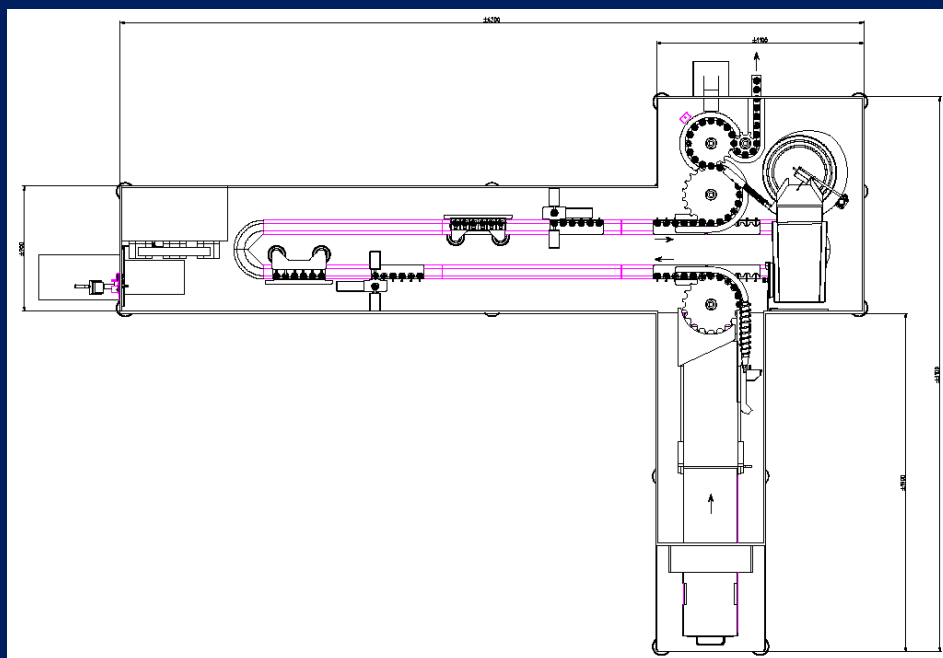


Example of 3D view of the main process part

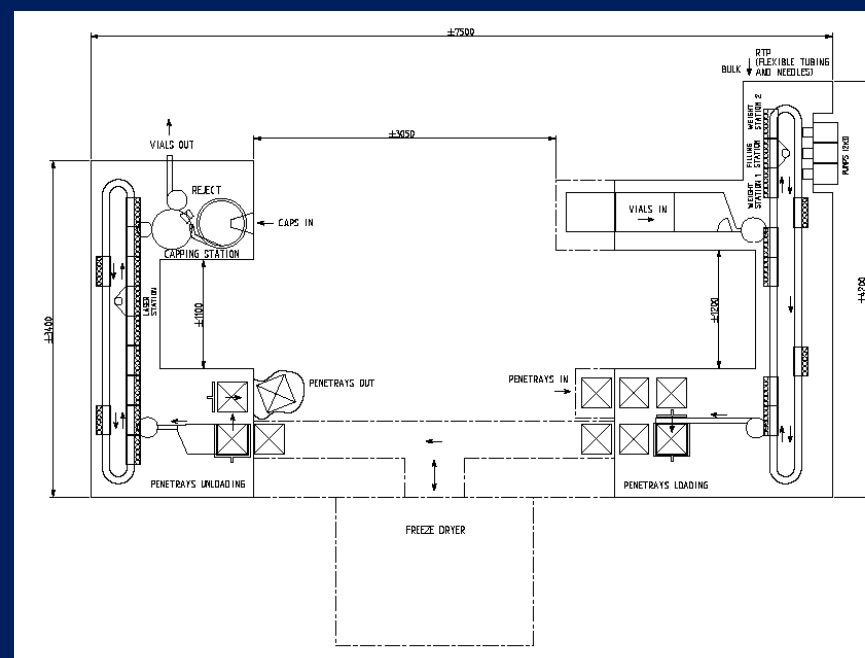




Different configurations

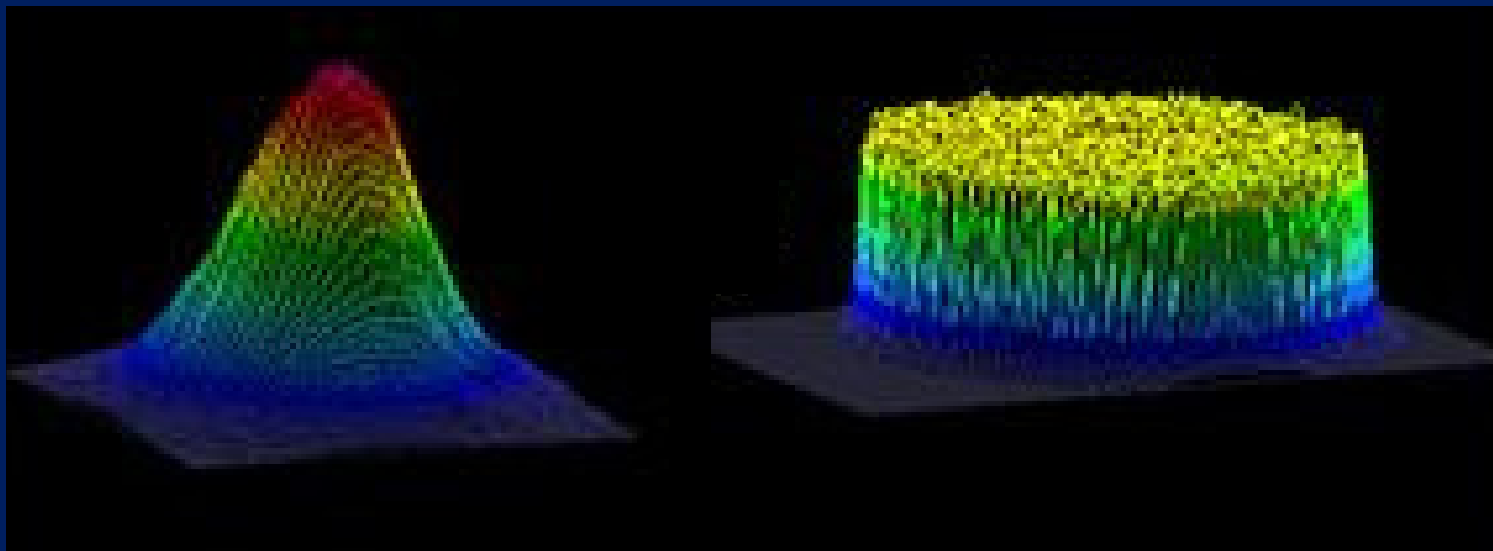


Aseptic liquid



Aseptic freeze-dried

The Validation Master Plan





TOPICS	VALIDATION STUDIES	STATUS
▪ Container materials	▪ USP and EP tests (class VI, biological and physicochemical, olefin, elastomeric closure)	Pass
▪ Assembled vial	▪ Particle test	Pass
	▪ Container closure integrity (vial and cap)	Pass
	▪ Endotoxin contamination and bioburden	Pass
	▪ Permeability	Done
	▪ Extractable	Done
	▪ Aging in ICH condition	On-going
	▪ Low temperature resistance	Pass
	▪ Gamma irradiation	Pass
▪ Filling line	▪ E-beam	Pass
	▪ Laser	Pass
	▪ Filling accuracy	Pass
▪ Simulation	▪ Media fill in unclassified area	Pass

All data are available to support approval of your products



- Media fill performed in unclassified workshop;
- TSB transferred inside the filling area through a circulation loop with two connectors;
- All operation performed as it would be in a clean room

	<u>MEDIA FILL #1</u>	<u>MEDIA FILL #2</u>	<u>MEDIA FILL #3</u>
▪ Date	March 2, 2005	March 8, 2005	March 16, 2005
▪ Vials			
–Vials filled	6,162	6,552	6,302
–Contaminated vials	0	0	0

Currently over 100,000 vials filled without contamination



Leachables in WFI

RANGE	T= 3 MONTHS	T= 6 MONTHS	T = 12 MONTHS
Concentration \geq 10 ppm	none	none	Acetic acid
From 5 to 10 ppm	Acetic acid	Acetic acid, Formic acid	Formic acid
From 1 to 5 ppm	Formic acid, t-butanol	t-butanol	t-butanol
Less than 1 ppm	Very few products. No concern with toxicity and carcigenocyt	Very few products. No concern with toxicity and carcigenocyt	Very few products. No concern with toxicity and carcigenocyt

Very few leachables.
No toxicity concern, according to FDA recommended expert

**Moreover, Crystal[®] vials are - latex free
 - silicone free**

Similar results obtained in ethanol 10%, PBS, NaCl 0.9% and 2-phenoxyethanol 0.5%

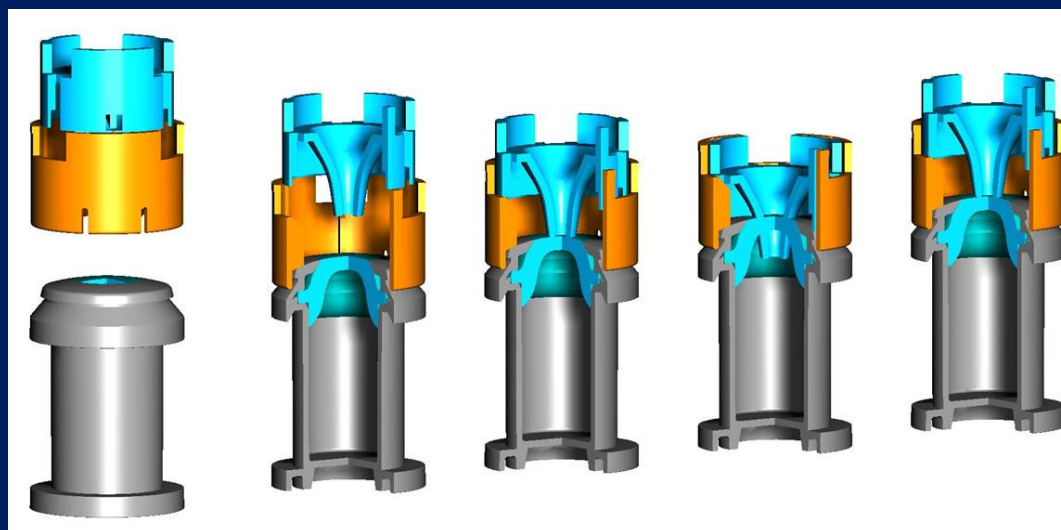
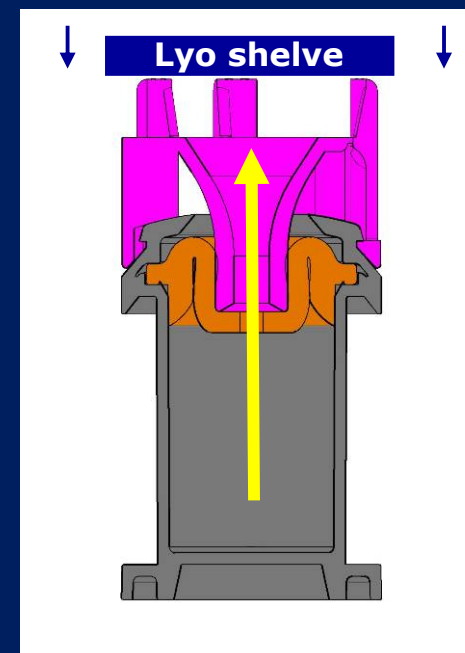
The Freeze Drying





Process

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





Tests performed

Lactose 5 % : ✓

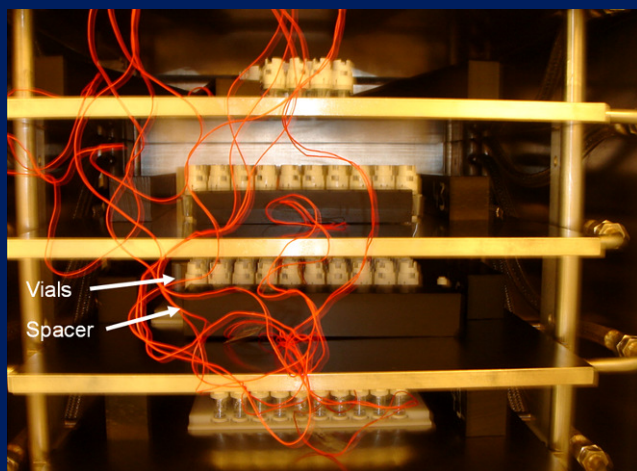
Lactose 10 % : ✓

Sucrose 5 % : ✓

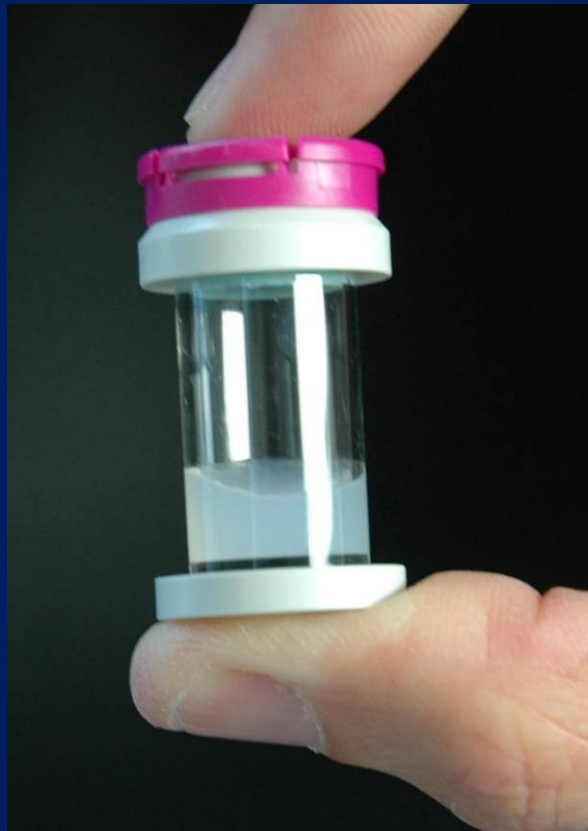
Sucrose 10% : ✓

Three viruses : ✓

- Lyophilization done with the same cycle as for glass vials
- Very high quality of cakes
- No stopper sticking on shelves
- Better vial stability during loading/unloading
- No vial breakage



Services





To facilitate your evaluation of the *Crystal*® Closed Vial technology, three options are offered:

- **Filling in your own facility;**
- **Aseptic filling in our facility in a non-classified environment;**
- **Aseptic filling in our facility in our GMP approved filling suite.**

Currently, 60+ products tested in the *Crystal*® Closed Vials, including:

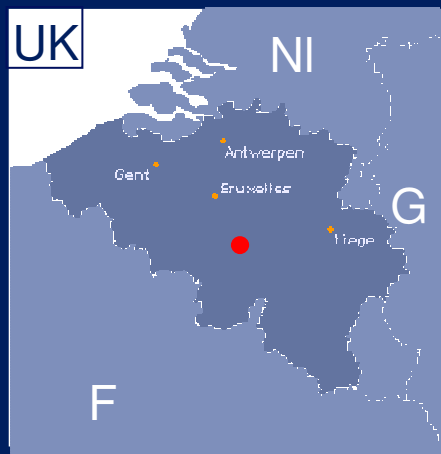
- **41 biological products (vaccines, antibodies, proteins, cells, viruses, mRNA);**
- **7 cytotoxics;**
- **5 lyophilized products.**

From 31 different companies.



Crystal® C1 filling line in Class ISO 8 clean room in our facility, GMP approved filling suite for stability batches filling

✓ **EMA approved**
✓ **2 DMF filed at FDA**



- Head-quarter in Belgium, Gembloux, 40 km in the south of Brussels, capital of Europe.
- Central location, between France, Germany, the Netherlands and UK.
- Easy access by plane, train and road.

- GMP approved *Crystal*® Filling Suite
- Development lab for filling and freeze drying

4,000 m² facilities
(3 levels) including
400 m² of clean room





Material path





Clinical line

Mio EUR

Sources of investment	Total cost
• Building including HVAC	1.82
• Filling line (complete line, including IQ/OQ)	3.06
• WFI generation system	0.03
• Double door autoclave	0.10
• Various equipment	0.18

• Total	5.19
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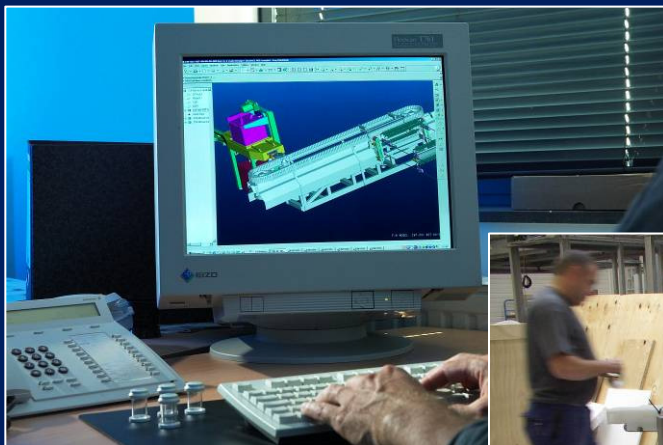
• Timing:

- Start from greenfield
- Inspection by EMEA

March 05
June 06



From Equipment Design to After Sale Service



**Providing SAFER & EASIER Aseptic Filling operations
to the BioPharmaceutical Industry**



RISE WITH US

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