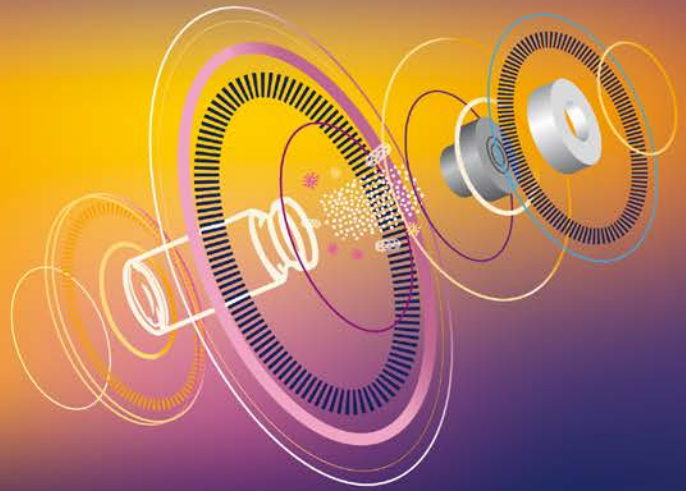
Robotic Tub Decontamination System - RTDS



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PDA Parenteral Drug Association
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Parenteral Packaging

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1. Background of the Project

The application of Ready to Use (RTU) container for fill finish technologies in the pharmaceutical industry increased in the recent years.

- Easy to use for smaller batch sizes
- Easy to perform frequent product/container changes
- Increasing availability of RTU container

Steriline, manufacturer of aseptic fillers, was looking to a simple and safe way of TUB decontamination

1. Background of the Project

Challenges of current decontamination processes

Robotic Tub Decontamination System RTDS

- Suitable for high output 2 to 4 tubs/min
- No decontamination step after un-packing
- Possible contamination through pin-holes not covered

→ **Unpacking devices with no-touch transfer**

- Suitable for high output 2 to 3 tubs/min
- Batch process
- Residual VHP content in containers possible

→ **Decontamination with gases : VHP, NO2**

- Suitable for high output up to 6 tubs/min
- Cost intensive
- High weight

→ **E-Beam Technology**

1. Background of the Project

Project triggered and conducted by 2 companies

- **Steriline**, manufacturer of aseptic filling lines for the pharma industry
- **Claranor**, manufacturer of Pulsed Light Decontamination equipments in the food industry

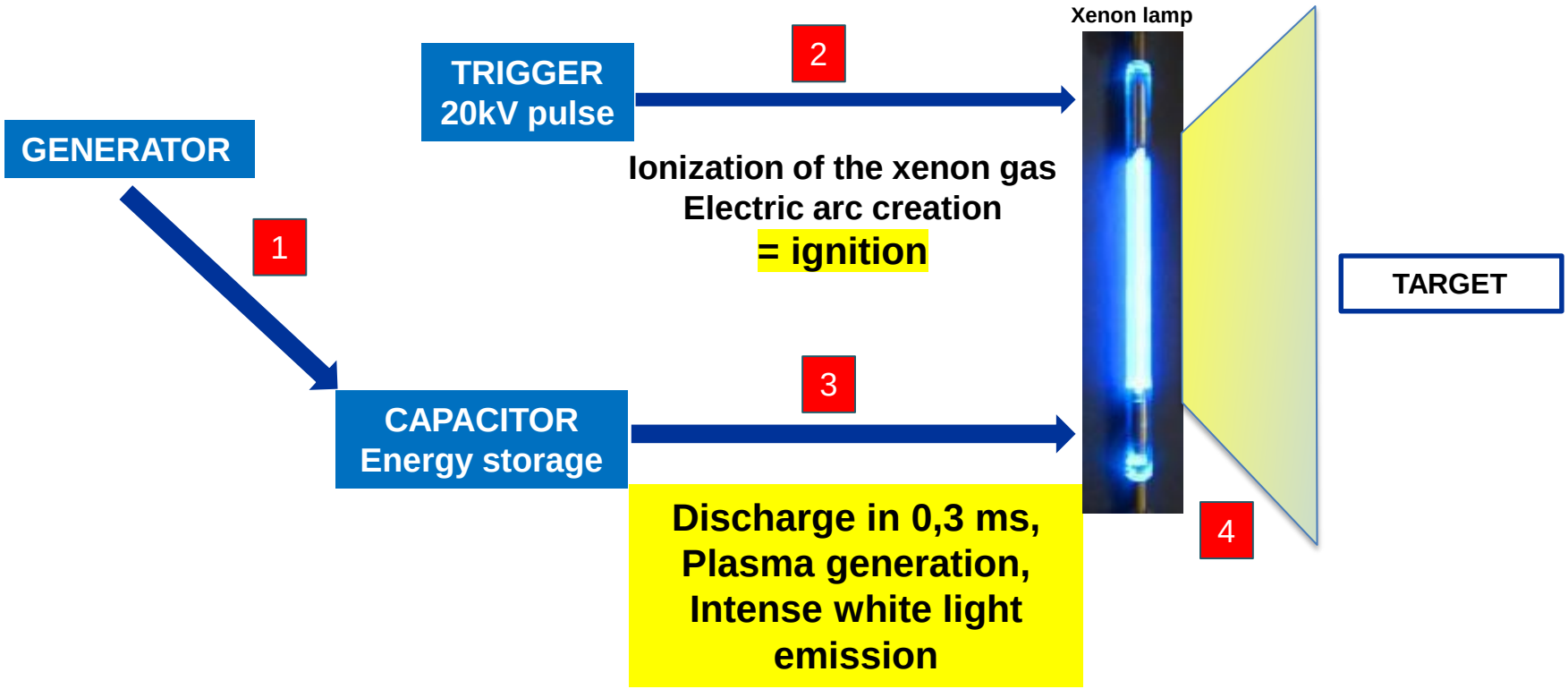
2009 : first ideas about tub decontamination with pulsed light, attempt to start with a global pharma company
2015 : Steriline introduced the idea of manipulating the tub with a robot
2017 : internal validation at 6log on a prototype, and start of a joint project with pharma expert, potential customer, manufacturer of BI's, Steriline, Claranor
2018 : first order of RTDS by a European pharmacy company
2020 : January : FAT with 4log BIs, May: delivery

2. Pulsed Light Technology

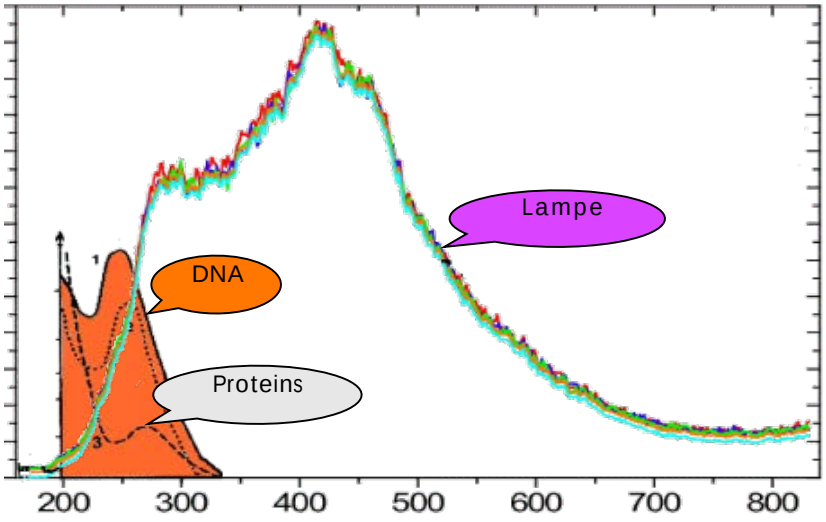
The pulsed light process consists in producing short duration emissions of intense, broad-spectrum white light from a Xenon lamp to sterilize surfaces.

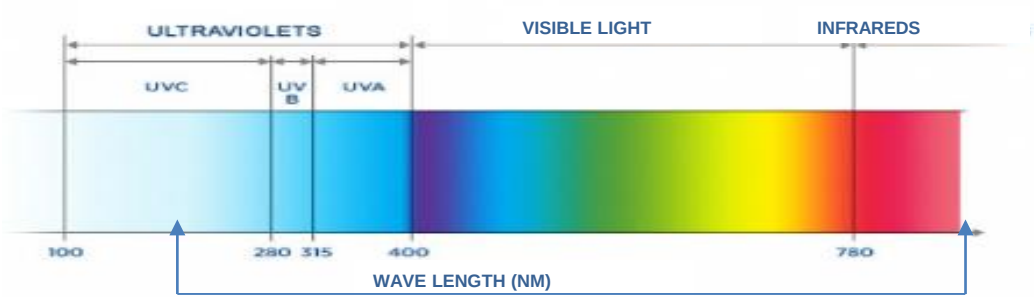
- The sterilizing effect was discovered first in Japan 1970
- Developed in the US by Pure Pulse 1985-2000
- Approved by FDA for food decontamination in 1996
- Industrially developed:
  - At low power and with UVB for hair removal by many companies
  - At high power and with UVC for packaging decontamination in the food and beverage industry first by Claranor since 2004

2. How to produce Pulsed Light (“flashes”)



2. Pulsed Light : A technology with power





- Very short flash: 300 micro-second
- Intensity: 50,000 x solar intensity on earth
- Spectrum between 200 and 1100 nm

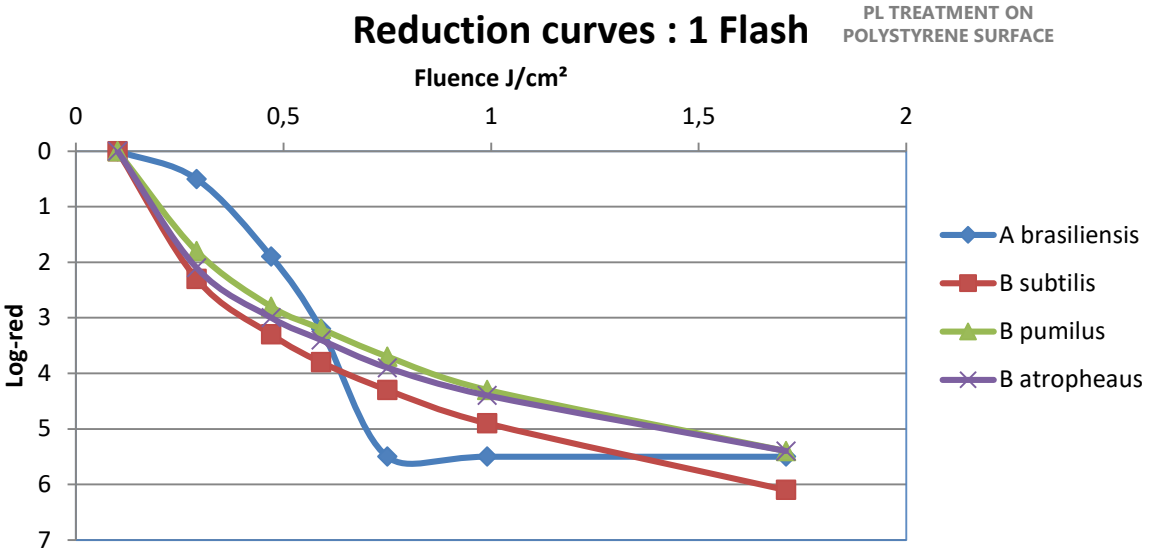
  15% UV rich in UVC
  50% visible
  35% near IR

$$\frac{\text{Lamp energy}}{\text{Flash time}} = \frac{300\ \text{J}}{0{,}3\ \text{ms}} = \mathbf{1\ MW}$$

UV emission in the range of 1 kW / cm²

2. Pulsed Light Decontamination Efficiency

Microbiological decontamination of surfaces:
Up to 6 log reduction on the most resistant microorganisms (bacteria, mold, spore)



Inactivation profiles of A. brasiliensis, B. subtilis, B. pumilus, B. atrophaeus depending on medium Fluence
Results obtained by C. Levy, PhD student, on Claranor 3 lamp pilot equipment, 2012

2. Pulsed Light Decontamination of Packaging

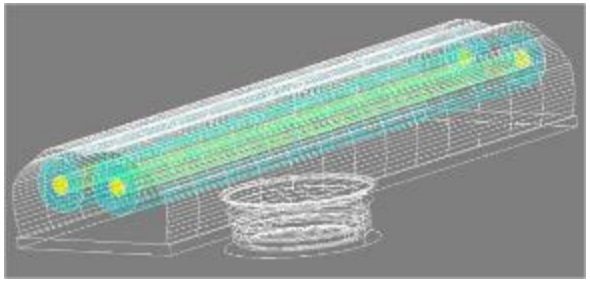
Cap decontamination: 3-4 log on Aspergillus *brasiliensis* or Bacillus *atrophaeus*, currently up to 82,000 caps/hour

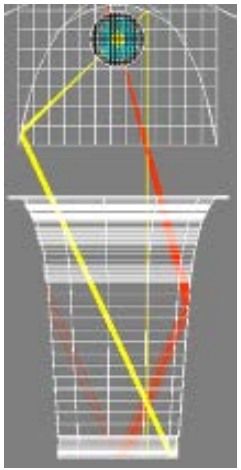
Cup decontamination: 3-5 log in < 0.5s

400 units operating worldwide

Hard operating conditions :

- High intensive industry (>6000h production per year)
- Humidity, vibrations…
- Low educated personnel

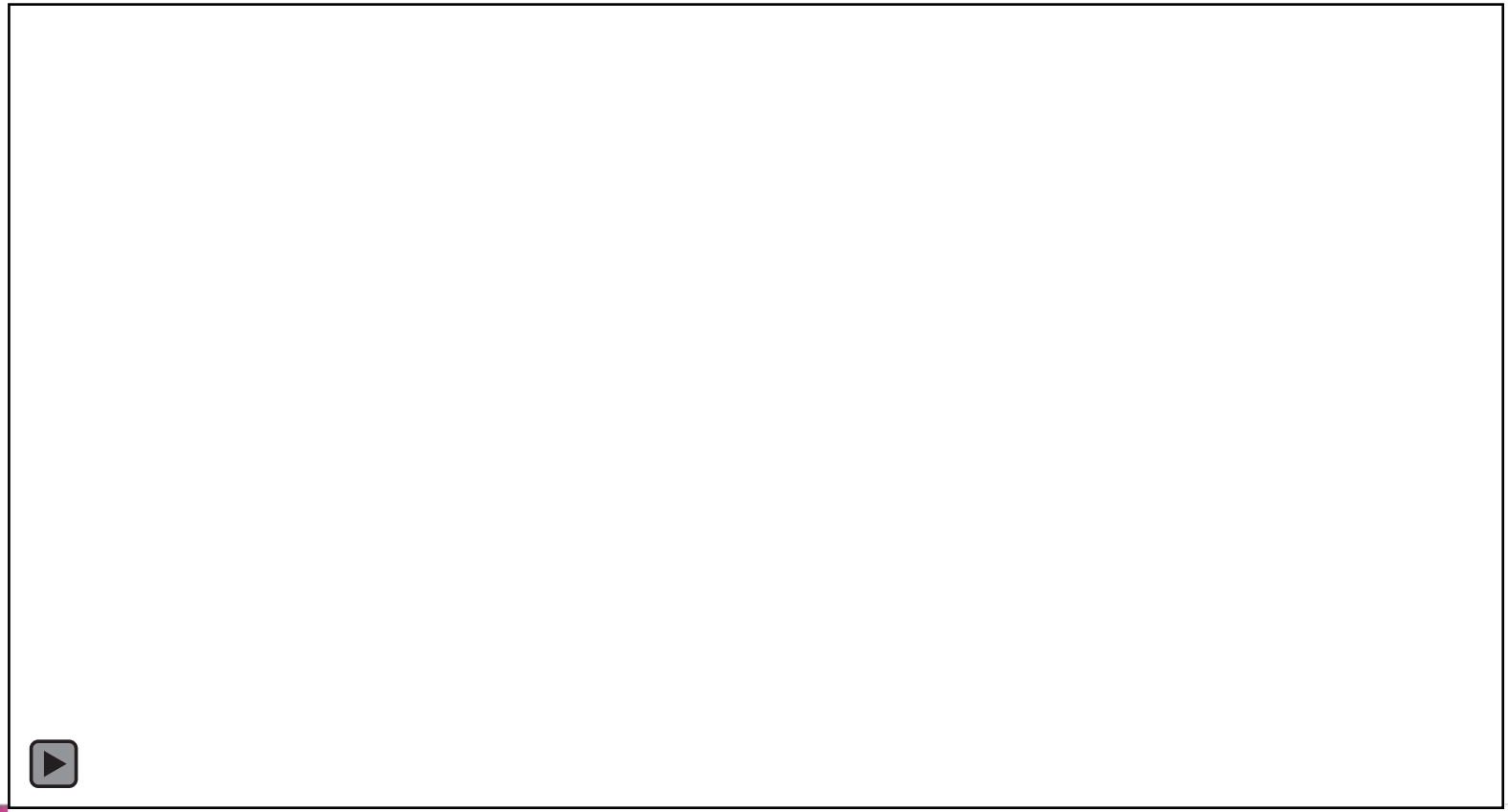




2. Pulsed Light Decontamination

Cup decontamination on a low-fat maragarine filling line (2013)
3log decontamination (Aspergillus brasiliensis) in 2 flashes at 60 strokes/min

3. Presentation of the RTDS



4. RTDS Validation Procedure

a) First Validation Trial

b) Determination of a reference micro-organism

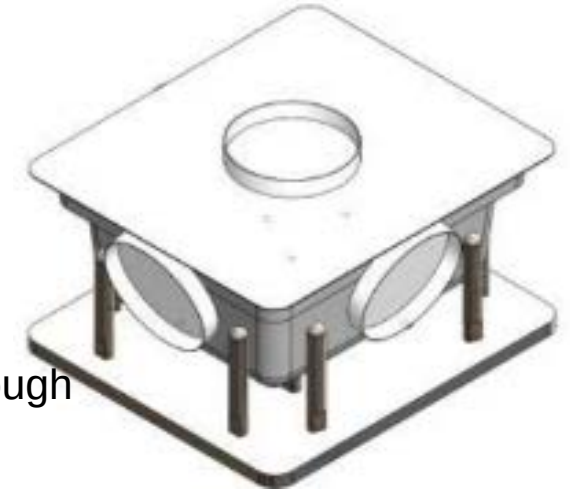
c) Why spray inoculation ?

d) Production of a bio-indicator

4.a. First Validation Trial

Qualification Protocol: Count Reduction Test

- Experimental microorganism: **Bacillus pumilus DSM 492**
- **Spray inoculation** of Petri dishes
- Dry overnight under laminar flow
- Average count of positive samples: **1,6.10^{E}8**
- Treatment of the tubs with Petri dishes stuck on 5 sides trough tunnel (transparent UV film protection on petri dishes)
- Recovery of surviving microorganism
- Calculation of the killing rate: **log (N / No)**



4.a. First Validation Trial

Attempt A: 8 flashes / side

LOG REDUCTION						
Investigated face	**1 st** Exp.	**2 nd** Exp.	**3 rd** Exp	**4 th** Exp	**5 th** Exp	**Mean Log-Red. (per side)**
Short side #1	6.7	6.2	6.4	6.1	6.7	**6.4**
Short side #2	6.6	7.5	6.2	6.7	6.5	**6.7**
Large side #3	7.0	7.2	6.3	7.0	6.5	**6.8**
Bottom #4	7.2	7.0	6.2	7.4	7.0	**7.0**
Top # 5	6.8	6.9	6.2	6.5	6.2	**6.5**
Mean	**6.9**	**7.0**	**6.3**	**6.7**	**6.6**	

4.a. First Validation Trial

Further points and questions

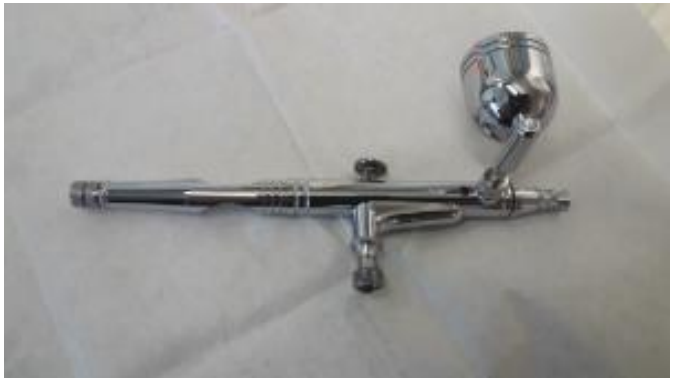
- **Results of first validation trial**
  - Test A: 6.7 log with 8 flashes
  - Test B: 7.1 log with 14 flashes
  - No sample < 6log (out of 50 in total)

- **Further steps with perspective of industrial validation**
  - Confirmation of reference micro-organism, use of spray inoculation
  - Development of a BI with the French laboratory Icare for industrial use for end-point test at 6log.
  - FAT

4.b. Why spray Inoculation

Efficiency assessment

- **Spray inoculation on Petri dish**
  - Monolayer of spores
  - Homogeneous spore distribution
- **Drying overnight**
- **Pulsed Light treatment 1,1J/cm²**
  - Lamps at end of lifetime
  - 1 to X flashes
  - 5 samples for each modality
- **Recovery** of survivors (count reduction test or end-point test)



4.b. Why spray inoculation

Contents lists available at ScienceDirect

Journal of Microbiological Methods

journal homepage: www.elsevier.com/locate/jmicmeth

Deposition of *Bacillus subtilis* spores using an airbrush-spray or spots to study surface decontamination by pulsed light

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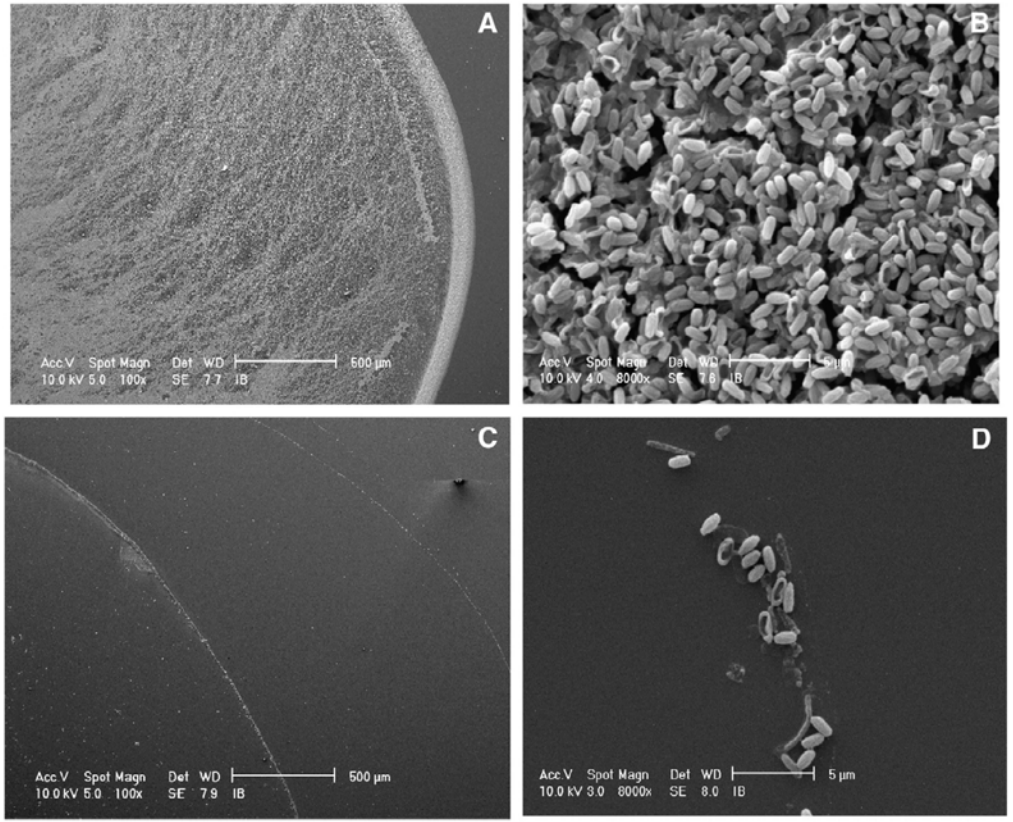


Fig. 2. Scanning Electron Microscopy pictures of 10 µL spots of a *B. subtilis* suspension in sterile distilled water containing 10^6 spores in a 10 µL spot at ×100 (A), and ×8000 (B) magnifications, and 10 µL spots containing 10^4 spores in a 10 µL spot at ×1000 (C) and ×8000 (D) magnifications.

4.b. Why spray inoculation

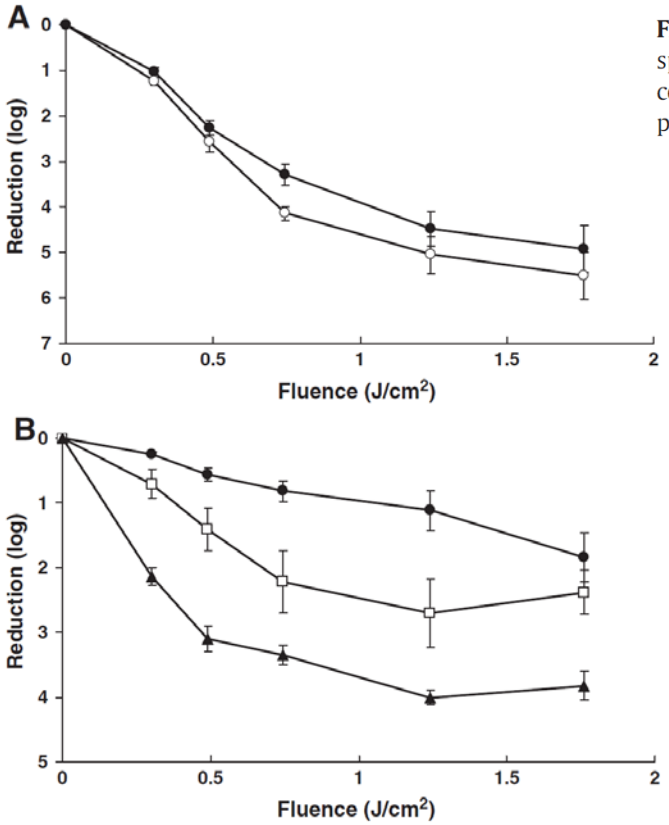


Fig. 4. Inactivation of spores of *B.subtilis* DSM 402 inoculated on LB Agar media with (A) spray (●) and with a manual spreading with rakes (○), and (B) inoculated by spot at concentrations of 3×10^6 (●), 3×10^5 (□) and 3×10^4 (▲) spores per 10 µl spot on a polystyrene surface, as a function of fluence (in J cm^{-2}). Bars represent standard error.

- Pulsed Light is efficient on spots up to 10^E4/10µl.
- Above 10^E4, reproducibility is reduced.
- No difficulty to spray 10^E8 spores on a petri dish

4.b. Why spray inoculation

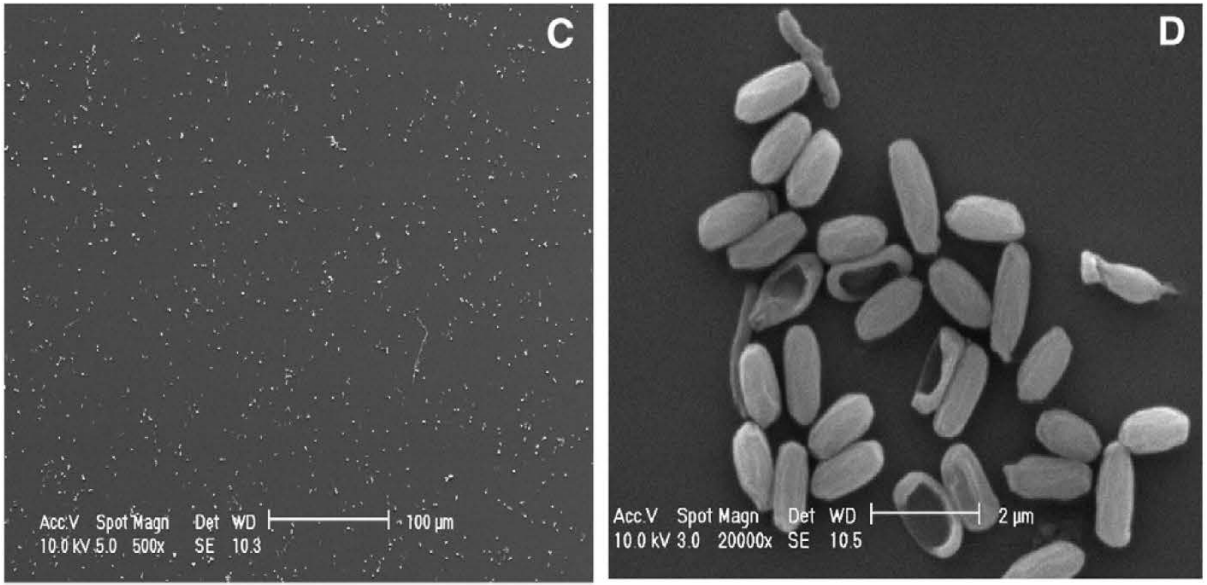


Fig. 1. Dispersion of spores of *B. subtilis* sprayed on polystyrene Petri dishes. Colonies were formed after 24 h incubation at 30 °C from a spore suspension sprayed on the dish, dried for 24 h, and covered with molten LB agar. Volumes of 100 µL of the 10^{-3} (A) and 10^{-4} (B) dilutions of a spore suspension containing 10^{8} *B. subtilis* spores mL^{-1} were sprayed. The pictures C and D show the Scanning Electron Microscopy of 100 µL of *B. subtilis* spores at a concentration of 10^{8} spores mL^{-1} sprayed on polystyrene surface at ×500 (C), and ×20,000 (D) magnifications.

4.b. Why spray inoculation

And what about real life contamination ?

Example from the dairy industry :

- Empty PP cup stored 3 days in our warehouse without protection
- 10 positive samples, with 160 to 880 cfu/cup, **in average 610 cfu/sample** (2,8log)
- Decontamination test with pulsed light and compared to a high output UVC lamp (100W/cm)

	Pulsed Light 1 flash	UVC 2sec	UVC 4sec
Log red	2,1	0,1	0,3

Pulsed Light is efficient against natural contamination

4.b. Why spray inoculation

- Pulsed light is efficient against **natural contamination**
- Inoculation in **spots** is not a regulatory requirement
- Spot inoculation does not give reproducible results above 10^E4 to 10^E5, because pulsed light is not efficient against **clusters** of micro-organisms for high concentrations.
- Spray inoculation enables to inoculate small surfaces with high quantities of spores, and to demonstrate in a reproducible way a local 6log reduction

Conclusion :

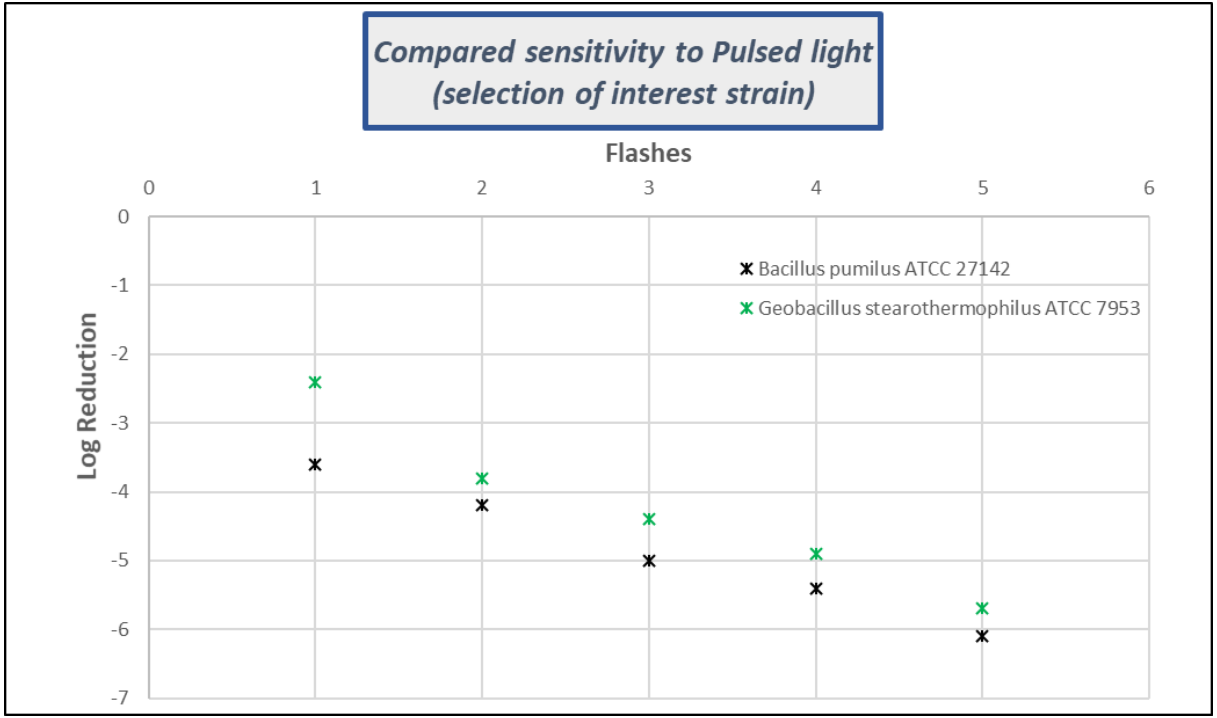
Spray inoculation can be considered as acceptable for BI's validating surface decontamination in the pharmacy industry.

4.c. Determination of a reference micro-organism

Log10 reduction in spores after PL treatment at 3600 V (similar to industrial configuration)								
Strain	***Bacillus pumilus*** ATCC 27142				***Geobacillus stearothermophilus*** ATCC 7953			
Flash	Exp. 1	Exp. 2	Exp. 3	**Mean**	Exp. 1	Exp. 2	Exp. 3	**Mean**
1	3,1	3,9	3,8	**3,6**	2,4	1,9	2,9	**2,4**
2	3,7	4,2	4,8	**4,2**	4,1	3,5	3,8	**3,8**
3	4,7	>4,7	5,3	**5,0**	5,1	3,5	4,5	**4,4**
4	6,1	4,7	>5,4	**5,4**	> 5,3	> 5,1	4,4	**4,9**
5	6,4	5,7	>6,0	**6,1**	6,0	> 5,9	> 5,3	**5,7**

The study was conducted with 4 microorganisms : *A. brasiliensis, B. atrophaeus, G. stearothermophilus, B. pumilus* ***Bacillus pumilus*** **ATCC 27142** *and* ***Geobacillus stearothermophilus*** **ATCC 7953** emerged as the two more resistant

4.c. Determination of a reference micro-organism

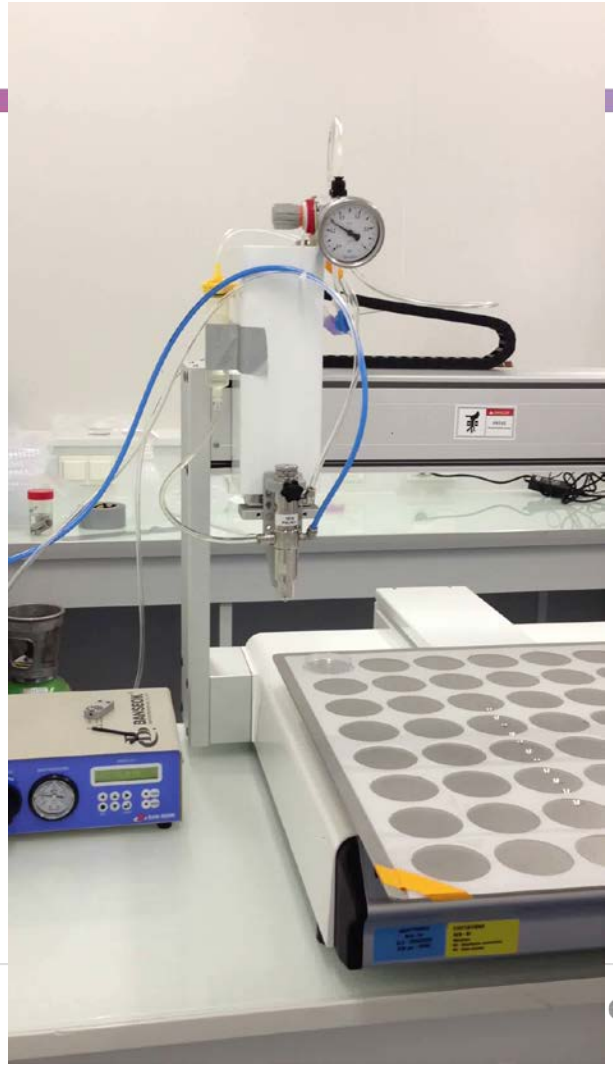


Geobacillus stearothermophilus ATCC 7953 was chosen because having a comparable sensitivity, and easier lab handling.

4.d. BI development

- Definition of shape, packaging, handling: BI in a UV-transparent film
- Stability of micro-organism resistence to pulsed light
- Reproducibility of spray inoculation
- Stability during storage and transport

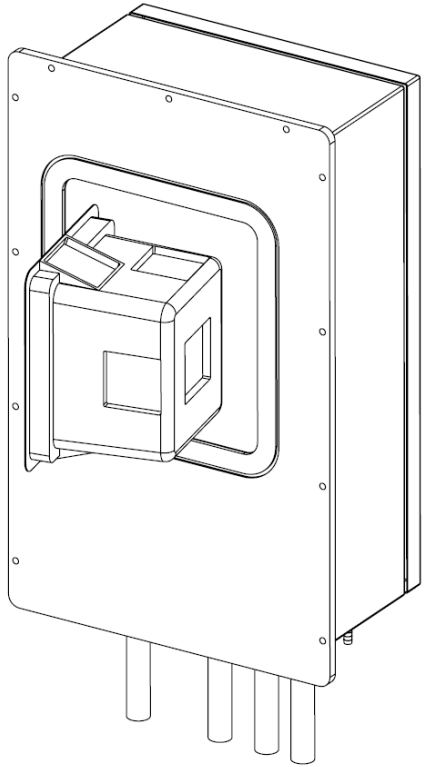
- Already validated at 4log
- Ongoing validation at 6log



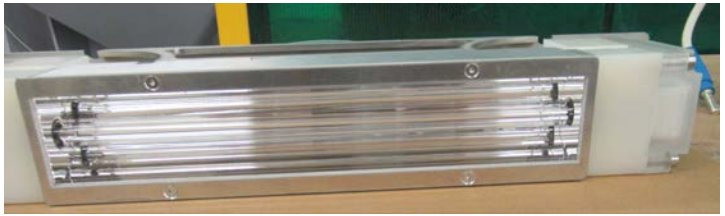
4.d. BI Development

Handling of the BI's

- A dummy Tub was 3D printed with spaces available for BI's.
- This Tub should be used for any qualification



5. Features of the RTDS



5. Features of the RTDS

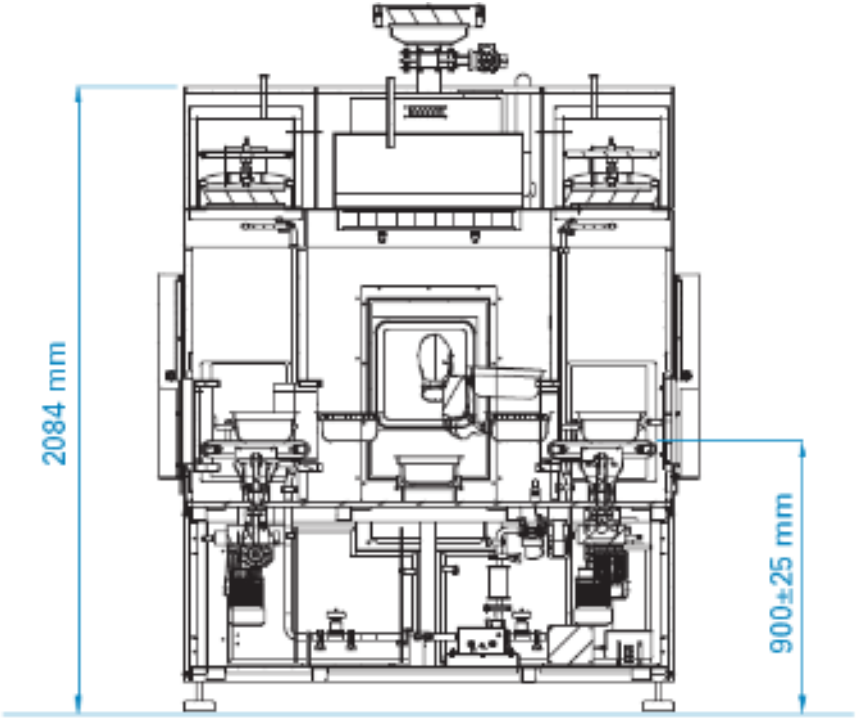
- Lamp change every 100,000 tubs
- Energy consumption <3kW
- Traceability on flashes
- Light intensity measurement
- Access to reflectors and lamps from outside, enabling intervention on lamps without breaking sterility of the chamber
- Simple lamp change by user
- Power electronics in changeable racks
- Low maintenance

5. Features of RTDS

- Isolator
- AirTight System
- 6-log Reduction with VHP
- Short VHP Decontamination Cycle

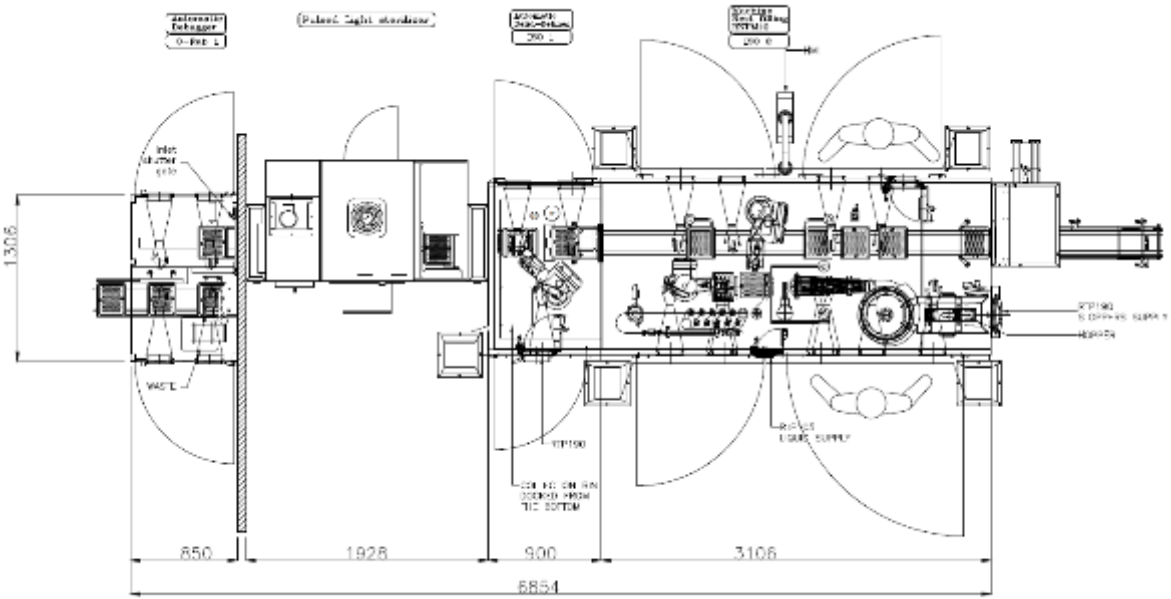
5. Features of the RTDS

- 3-Chamber-System:
  - Inlet Chamber
  - Decontamination Chamber
  - Outlet Chamber
- Uni-directional airflow through HEPA-Filter
- Airflow 0,45 m/s
- Pressure difference of 2 Pa between chambers



6. Integration in a Filling Line

- Automatic De-Bagging System
- Pulsed-Light Decontamination
- Automatic De-Liner
- Filling Machine for 360 Syringes/min under Isolator



Questions ?