Microbiological Results

The initial count, 1,6 10E8, was calculated as average of count on the positive samples.
The decontamination rate of each sample was calculated by difference between average initial count and end count on treated sample.

A 6,7 log and 7,1 log reduction were achieved for the lower and the higher number of flashes.

Microbiological Validation

The pharmacy industry needs bio-indicators to perform regular qualifications. Steriline and Claranor are already collaborating with an industrial lab specialized in pharma process validation, having all quality certifications. This lab delivers an industrial BI adapted to a surface decontamination with pulsed light at 6log. This BI has adapted handling procedures, and is deliverable worldwide.

Steriline RTDS2

Designed to decontaminate tubs, before entering the de-lid / de-liner station

Features

- Up to 2 tubs per minute
- Also suitable for all kind of trays
- No format change
- 6-log reduction
- Tubs handling with anthropomorphic vaporized H_2O_2® compatible STAUBLI robot
- Vaporized H_2O_2® decontaminable Isolator
- Suitable to be installed in ISO8 environment
- Completely airtight

Benefits

- Compact & Light weight
- Cost-efficient:
  - investment cost proportional to low speed filling lines
  - low maintenance costs
  - Instant treatment, Instant restart
- Sustainable: no hazardous waste, reduced footprint

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www.steriline.it

www.claranor.com

PULSED LIGHT IN PHARMA INDUSTRY

State of the art

Secondary packaging decontamination

ROBOTIC TUB DECONTAMINATION SYSTEM

Steriline, an expanding European manufacturer highly specialized in the production of complete lines for the aseptic processing of injectable products, supplying pharmaceutical companies worldwide, teamed up with Claranor, pioneer of pulsed light in-line packaging decontamination to bring the benefits of pulsed light technology to the pharmaceutical sector.

New drivers in the pharmaceutical industry

Small series

A decade ago, the pharmaceutical industry's primary goal was to operate larger production lines and reach high productivity and product throughput. The actual trend is to install smaller, more modular and flexible lines, with shorter lead times. The primary industry drivers for this move away from the large factory model has been the growth of personalized medicines, the need for smaller batches, and the increase in regionalized manufacturing markets.
For payers, personalized medicine is attractive as a mechanism to control usage of expensive drugs and avoid wasteful expenditure on treatments that are ineffective. For the medicine, it means challenges and opportunities. Most importantly, the drug developer must be able to achieve the requisite return on investment despite the restricted market size. An evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient. By combining the data from those tests with an individual's medical history, circumstances and values, healthcare providers can develop targeted treatments and prevention plans.

Sustainability

A new challenge pharma manufacturers are facing is to minimize their impact on the environment. Key components of this green manufacturing program are reducing waste, energy and water use.

Ready-to-use pharma containers growing market

In this context of short series of injectable products and differentiated packaging, the large and high-speed lines are not any more efficient, as format change becomes a severe handicap. Simultaneously, the development of robotic technologies enables for low and middle speed lines (up to 600/min) a high flexibility for various formats of vials or syringes. Pre-sterilized RTU containers become more and more THE solution for the pharma industry, as washing and depyrogenation become too expensive at low speed, and remain not flexible. The last technical challenge for these lines is how to decontaminate the tubs before transfer to the sterile filling area, as chemical solutions are not safe, not sustainable, have a high footprint, and e-beam is too expensive and complex for smaller and slower lines.

In 2017, Steriline introduced to the pharma market a new Robotic Tub Decontamination System, integrating 2 innovations: robotic and pulsed light technologies.

Steriline Vial Capping Machine

Pulsed Light : a technology for the pharma industry market

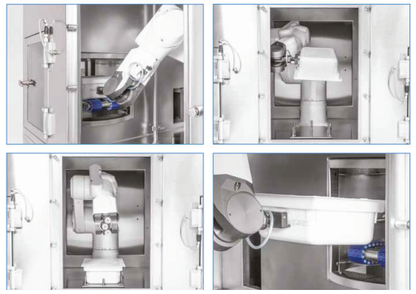
This machine combines the leading experience of robots in aseptic environment of Steriline to the expertise of Claranor, pioneer of pulsed light sterilization technology applied to surface decontamination.
This equipment was designed after several years of discussions, during which Claranor could build a strong experience of industrial machines, with now 300 units in operation throughout the world in the food and beverage industry. This experience was especially built in the field of microbiology, with several very strong assets: a team of microbiologists specialized in surface decontamination, an integrated microbiology laboratory, hundreds of tests together with the largest food & beverage companies, strong understanding of the various validation methods of the customers, and background of many onsite qualifications.

Steriline Robotic Tub Decontamination System

The Robotic Tub Decontamination System with pulsed light enables to decontaminate at 6-log reduction of Bacillus *subtilis* for 2 tubs/min in a vaporized H_2O_2 decontaminable Isolator. It brings to the industry a new reference in terms of low foot print, extremely short down times, easy maintenance, reduced capex and opex. Collaborating with Claranor, Steriline can offer the assurance of industrialized components and worldwide technical support.
A huge microbiology R&D programme was performed to be able to offer this optimized answer to pharmacy requirements and lead to the validation of the process.

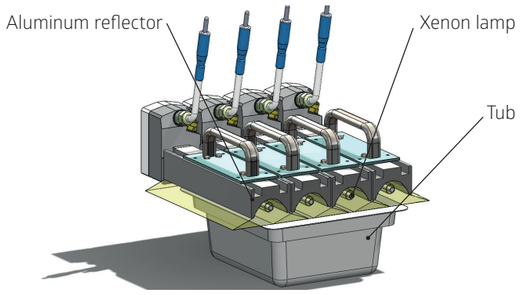
Steriline RTDS2

The Steriline RTDS2 is designed to decontaminate tubs, but is also suitable for all kind of trays, with flashes of Pulsed light, before entering the aseptic cabin.



Robotic arm presenting tub in front of the pulsed light unit

Tubs are first unwrapped in a clean environment and then move from the inlet to a small pass-through gate, and then to the isolated pulsed light chamber. The robotic arm's suction cups grip a side panel of the tub and present the panels successively in front of the pulsed light unit, in order to get a 6-log reduction.



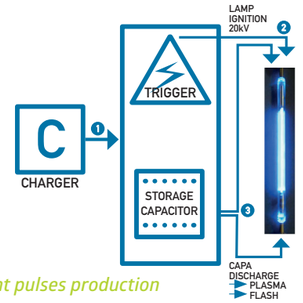
Principle of tub treatment - 4 x 1 lamp reflector

The untreated face of the tub is only exposed to the flash once the robot has released the tub on a sterile support, presented the cups to the flash to decontaminate them, and re-gripped the tub on a previously treated face. With all surfaces decontaminated, the arms releases the tub at the outlet gate of the machine.

Pulsed light decontamination

Physical principle

The flashes are produced by flash lamps, filled with Xenon gas, heaviest noble gas and giving the best UVC yield.
Electrical energy, typically 300J, is accumulated in a capacitor during fractions of a second and discharged in the lamp, where it ionizes the Xenon to create a plasma. It produces a very intense emission of white light, rich in UV, within a short time (300 µs). The result consists in a pulse of very high power with a very low of energy consumption, reaching 1 MW (300J/0,3ms). The process achieves a 6-log reduction with several flashes per side. Depending on the charging power, the capacitor is reloaded in about 0,2s.



Light pulses production

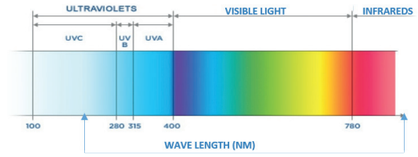
High flexibility of the process

A Pulsed light treatment may be adjusted depending on the decontamination target by:
- Number of flashes
- Distance between the reflector and the samples,
- Reflector optimization: the shape of the reflector around the lamp is key in order to optimize the light emission

In some cases the decontamination can take place through the material

Action on micro-organisms

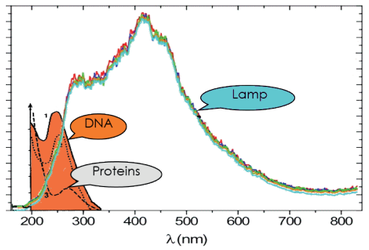
The cells are immediately killed due to a combined effect:
1. Broad spectrum emission affecting all capacities of molecular energy absorption especially in the UV range 200-400nm.



Xenon lamp spectrum

2. High power emission saturating immediately the capacity of absorbtion, leading to molecular break in DNA as well as in proteins, enzymes, and structural molecules.

A total and irreversible cell destruction
High log reduction levels are obtained within one flash (0,3ms), with all kinds of microorganisms like Aspergillus *brasiliensis* (mould), Bacillus *pumilus,* Bacillus *atrophaeus,* Geobacillus *stearothermophilus* (bacterial spores).



Xenon light and biomolecules absoption
The pulsed light (green curve) mainly interacts with biomolecules (orange curve) between 200 and 350 nm (UVC, UVB)

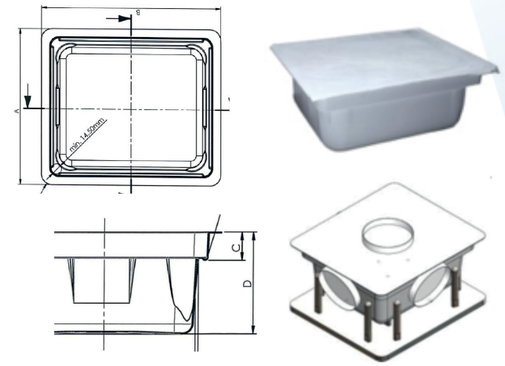
Looking for an appropriate reference germ for pharma applications of pulsed light, Bacillus *pumilus* DSM 492 emerged as the most resistant and was accordingly selected as the reference germ for validation of tub decontamination by PL treatment.

Tub decontamination : proof of concept

Prototype Qualification Procedure

The ability of the Claranor pulsed light unit installed on the Steriline RTDS2 to reach 6-log decontamination on the outer surface of prefilled syringes tubs was investigated with a « real-life » test in « dynamic mode ».
The unit uses specially designed reflectors, adapted to flat surfaces

Modality of the test:
- 4 x 1 lamp reflector.
- Input voltage: 3600 V
- 2 modalities: low and high number of flashes



Tub submitted to the test
Tub 3" BD Hypak SCF · length = 227 mm · width = 260 mm · height = 97 mm

5 sides of the tub were investigated by placing 1 inoculated Petri dish as bio-indicator on the middle of each side.

To perform the validation, bio-indicators were placed on 5 of the 6 faces of the tub. These BI's consisted in Petri-dishes spray inoculated, in order to get an homogeneous dispersion of spores, and avoid clusters. A count reduction test was preferred to an end point test in order to get information about the decontamination buffer. These Petri dishes were inoculated at 10E 8 with Bacillus *pumilus*, and covered with a UV transparent film, to avoid cross contamination in the chamber.
The movements of the robotic arm were set up to present each tub face in front of the reflectors with a 5 mm distance between the quartz window and Petri dish.
5 processed samples and 5 control samples were investigated.

After treatment, Petri dishes were investigated for surviving spores. The film was removed from each Petri dish of processed samples. The Petri dishes were filled with molten agar media and closed with a new sterile cover and incubated 5 days at 30°C. In parallel, control samples were placed into sterile bags that were filled with Ringer solution and shaken for 1mn. Different dilution series were prepared from the suspensions and the aliquots were investigated by pour plate method and incubated 5 days at 30°C.

Pulsed light decontamination of tubs - February 2019