

Squeaky Clean

Decontamination of Beta-Lactams in a production facility using chlorine dioxide gas

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In 2008, a leading pharmaceutical company was looking to renovate a Beta-Lactam production facility and turn it into a training facility space. The 33-room facility had been used for the production of an Imipenem based product, which was now being produced elsewhere. Beta-Lactam manufacturing facilities are often dedicated for the production of beta-lactam products for the facility's life and then demolished upon the cessation of production to limit cross contamination. Based on previous testing performed using chlorine dioxide gas to successfully inactivate various Beta-Lactams, ClorDiSys Solutions, Inc. was brought in to conduct the facility decontamination prior to renovation. A way to "recycle" the facility offered a large cost-savings opportunity to the company when compared to the alternative of demolition and reconstruction of a new facility.

BACKGROUND INFORMATION

In 2006, Clordisys Solutions, Inc. conducted testing to investigate the possibility of achieving a 3-log reduction (99.9% reduction) of eight beta-lactams, including Imipenem, Penicillin G and Penicillin V on various surfaces. The goal of a 3-log reduction was based off of previous studies done which showed that a 3-log reduction is the maximum level of CI inactivation that can be verified for some beta-lactams. This inactivation level is also consistent with the level of inactivation deemed suitable for other chemical inactivation, such as for the inactivation of endotoxins.

Testing was done using chemical indicators (CI) of various materials impregnated with eight types of beta-lactams. Three carrier materials were selected for testing, based on their prev-



The Minidox - M Decontamination System provides a rapid and highly effective method to decontaminate a target chamber. The system features a sophisticated sterilant concentration monitoring system to assure a tightly controlled decontamination process.

alence in the manufacturing and laboratory workplace.

The candidate carrier materials evaluated in the study were:

1. Lexan or Plexiglas (Polycarbonate Plastic)
2. Stainless Steel (304L, passivated)
3. Aluminum (Non-Anodized)

The carriers were approximately 15mm long by 5mm wide by 2mm thick. A single square-profiled groove or channel approximately 0.5-1.0mm deep and wide was machined along the center of the long dimension of one side of each coupon to simulate the presence of residues in cracks and crevices. Each CI was spiked with a cocktail of the eight beta-lactams. The beta-lactam cocktail consisted of beta-lactams from the Penicillin, Cephalosporin, and Carbapenem groups. From the penicillin group, Penicillin G, Penicillin V, Ampicillin, and Amoxicillin were included into the cocktail. From the Cephalosporin group, Cefadroxil, Cefazolin and Cephalexin were incorporated

into the cocktail. Imipenem, of the Carbapenem group, was also inside the cocktail. The inoculums were dried on the carriers prior to treatment with Chlorine Dioxide gas.

An outside laboratory was commissioned for recovery testing of the beta-lactams after exposure to chlorine dioxide gas. Liquid Chromatography and Mass Spectrometry were used during recovery testing for the presence of the beta-lactams. Results of the recovery testing proved that chlorine dioxide was effective against beta-lactams. Various decontamination cycles proved successful in attaining the goal of a 3-log reduction. Out of the nine inactivation cycles run, under various concentrations and exposure times, five of them achieved a 3-log reduction of beta-lactams on every CI, proving to be effective cycles under the test protocol.

Each inactivation cycle was performed under 75% Rh and held for 30 minutes prior to the introduction of CD gas.

Calculating the parts per million-hours for each cycle gives an added depth to the results. For gaseous chlorine dioxide, 1 mg/L is equal to 362 parts chlorine dioxide gas per million parts (ppm) of air. A ppm-hour is a measure of exposure, with one ppm-hour representing the exposure of 1ppm of chlorine dioxide gas for one hour. Determining the ppm-hours for Chlorine Dioxide Gas for each cycle consists of multiplying the gas concentration (in mg/L) by 362 and then multiplying that number by the exposure time (in hours). Table 1 shows the cumulative ppm-hours for each cycle. The successful inactivation cycles are shown in green.

Looking at the results in this way quantifies the results to better explain the differences between the successful and unsuccessful cycles. The successful inactivation cycles all had 7240 or more cumulative ppm-hours. Based on this, it can be concluded that in order to achieve a 3-log reduction of beta-lactams, an inactivation cycle starting with a 30 minute conditioning phase at 75% relative humidity, should be followed by exposure to chlorine dioxide gas for at least 7240 ppm-hours.

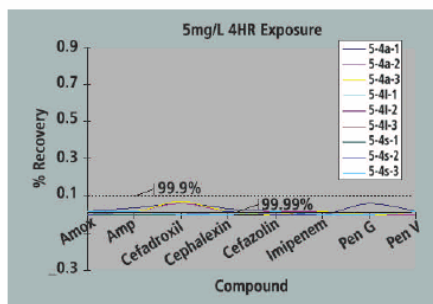
THE DECONTAMINATION EVENT

As a result of the test runs performed previously by Clordisys, the production facility decontamination was set to undergo a minimum of 7240 ppm-hours. The entire production facility along with its HVAC duct work was to be decontaminated. Positive samples for Beta Lactams were found in multiple rooms as well as inside the ductwork prior to decontamination. After decontamination, the facility was to be swabbed at various places, including inside the ductwork, to ensure that no beta-lactams were present.

In preparation for the decontamination, the entrances into the facility were sealed except for one doorway for personnel to use. The access points to the HVAC system in the mechanical area above the facility were also sealed to prevent any leakage. Fans and humidifiers were placed around the facility in order to raise the humidity level and to speed distribution of the

Inactivation Cycle	CD Concentration (mg/l)	Exposure Time (hours)	Cumulative ppm-hours
1	1	6	2172
2	3	6	6516
3	5	4	7240
4	5	6	10860
5	7	2	5068
6	7	4	10136
7	7.5	4	10860
8	9	2	6516
9	30	4	43440

Table 1: Cumulative ppm-hours per trial inactivation cycle. Successful inactivation cycles are shown in green.



Graph of inactivation cycle 3 recovery results.

gas. CD Gas Injection and sample tubing was run throughout the facility in order to spread and measure the gas. CD gas was to be injected into 24 locations and sampled from 12 locations throughout the facility to ensure fast and thorough distribution. CD gas has a yellow-green color, which makes it able to be accurately monitored in real-time using a UV-vis spectrophotometer. The concentration of gas within the facility could then be accurately measured during the whole decontamination, from start to finish. This allowed for the determination of whether the process parameter of attaining at least 7240 ppm-hours of CD gas exposure was met. The facility's exhaust system, as well as make-up air intakes, were shut down and capped on the roof to avoid any exhausting or leakage of CD during the decontamination. Humidifiers were then turned on throughout the facility in order to raise the building to 75% Rh, after which the humidity level was maintained

for 30 minutes as per the test cycles. The facility was then given a final check to make sure all penetrations were sealed and everything was in place. After the safety check, the remaining entryway was sealed. CD gas injection was then initiated to start the decontamination phase.

To ensure that gas was getting into the HVAC system, the recirculation blower for the facility was bumped throughout the decontamination. CD gas concentrations were taken every 30 minutes throughout the facility and

logged to calculate the progress of the decontamination. A hand held low-level CD gas sensor was used to check for any leakage from the facility, with safety checks made several times during the decontamination. After approximately 6.5 hours of injection and exposure, the correct process parameters for the decontamination were attained. The exhaust HVAC system was then uncapped and turned on, allowing the CD gas to be aerated from the facility. The facility was monitored using a low-level gas sensor and after the facility had been aerated to a safe level, the facility was entered to remove all auxiliary equipment. Upon completion of the decontamination, the area was swabbed for any beta-lactams by the pharmaceutical company. The HVAC system was also swabbed for remaining beta-lactams. The swabs came back negative proving that no beta-lactams were left within the facility, making the decontamination a success. The facility was now able to be safely renovated and used for training. ■