Site remediation of a penicillin production facility using Chlorine dioxide gas as a sterilant

Brett Cole, B.Sc (Hons) M. Occ. Hyg. & Tox. And **Joseph Maté,** PhD

Edith Cowan University, School of Exercise and Health Sciences
Joondalup Campus, Joondalup Western Australia
Contact: Brett Cole – bfcole@our.ecu.edu.au or 0401 060 615

ABSTRACT

The manufacture of Beta-lactam (penicillin) based pharmaceutical products poses several public health risks to people due to allergies to beta-lactams. This health risk to both workers at Beta-lactam production facilities and the public at large has led to Pharmaceutical industry requiring purpose built facilities for the manufacture of Beta-lactam products separate to their main production facilities or buildings.

A Pharmaceutical company had such a facility where, due to high production costs in Australia, production of Beta-Lactams was moved off-shore. The facility had laid dormant since 2009 and the company wished to re-purpose the building for warehousing and re-use equipment inside the facility for non-Beta-lactam production elsewhere in their plant. This poses several Biosafety concerns as penicillin is difficult to decontaminate due to it's inherent high resistance to most disinfectants and sterilants. However, Chlorine dioxide gas has been shown to successfully inactivate major penicillin strains and Chlorine dioxide gas technology was employed to decontamination the 2000 m^2 facility.

Using similar sampling techniques to those used in previous successful studies, chlorine dioxide gas was used to decontaminate the facility for two strains of Penicillin manufactured there. The two strains were Penicillin-V and Amoxicillin. Successful decontamination was achieved with concentration levels of Chlorine dioxide of 7200 ppm-hrs (5mg/L for 10 hours) and the chemical indicator coupon analysis penicillin concentration was below 50ppb (EEC, 1990). The facility has been reused for a different application.

INTRODUCTION

Penicillin and other β-lactams (the core structure of many antibiotic families) have been used in clinical treatment of virus and other infections in patients for over half a century (Aldeman, 1991). However, the use of penicillin and other β-lactam strains has been limited in the clinical treatment of infectious diseases by the number of cases of allergy or hypersensitivity to these antibiotics (Chang *et al*, 2013). In some case studies, hypersensitivity has been observed in 10-20% of cases resulting in diarrhea, rash, urticaria, and superinfection such as candidiasis (Chang *et al*, 2013). Inflammation and pain at the injection site are also common for intravenously administered penicillin with less common adverse reactions such as fever, vomiting, erythema, dermatitis, angioedema and seizures (Romano *et al*, 2001). In some case studies, 0.01-0.04% of participants displayed anaphylaxis; a severe allergic reaction caused by the release of mediators from certain types of white blood cells triggered either by immunologic or non-immunologic mechanisms (Chang *et al*, 2013) and can be fatal in 0.0015% of cases or 1 in 50,000 (Chandra *et al*, 1980).

This health risk to both workers at Beta-lactam production facilities and the public at large has led to Pharmaceutical companies having purpose built facilities for the manufacture of Beta-lactam products separate to their main production facilities or buildings (Lorcheim, 2011). The production facilities are often dedicated to Beta-Lactam production for the life of the facility and then demolished at great cost at the end of production with little chance of re-use or re-purposing either the building or the equipment inside (Lorcheim, 2011).

Traditional methods of decontamination have involved manual wipe down of the facility and equipment using liquid disinfectants and sterilants, however this is subjective due to differing standards between workers (Takahashi, Sakai & Gold, 2008; Allan & Deeks, 1996). However, Chlorine dioxide gas has been shown to inactivate Beta-lactams by Lorcheim, Lorcheim and Czarneski (2009) and again by Lorcheim (2011) and this method was adopted for this project.

As there is no International Standard prescribing the minimum beta-lactam residue for re-purposing facilities, the European Regulation Standards EEC 2377/90 of beta-lactam residue in dairy products for safe consumption of less than 50ppb Maximum Residual Level (MRL) (50 ug/kg) (EEC, 1990) was adopted as the equivalent safe level for the purposes of this project.

Image 1 – The external façade of the penicillin manufacturing plant.

The aim of this research project was to decontaminate the facility and all equipment therein to levels of less than 50ppb Maximum Residual Level (MRL) of 50ppb (50 ug/kg) European Regulation Standards EEC 2377/90 for safe reuse or repurposing; for both Penicillin strains, Penicillin-V and Amoxicillin and to determine if there has been a significant reduction in residual penicillin concentration for both strains pre- and post-decontamination.

METHODS

The methodology for this research project followed those adopted by Lorcheim, Lorcheim and Czarneski (2009) and again by Lorcheim (2011). The method follows the standard ClorDiSys Solutions Inc (New Jersey, USA) Chlorine dioxide gas generation method whereby Chlorine dioxide gas is generated outside the target area (external of the building) and is then injected into the building until the internal Chlorine dioxide gas concentration reached 5mg/L required for Beta-lactam inactivation The gas level in the building was maintained until the exposure (concentration x time) is 7200 ppmhours at a relative humidity (RH) of 65-75%.

Humidity and chlorine dioxide gas concentrations were controlled throughout the entire cycle. During the charge and exposure steps, gas concentration was continuously monitored using a calibrated UV-VIS spectrophotometer within the Minidox to ensure that the required concentration was reached and maintained. Once the required exposure was reached in all 20 gas sample areas, the building Heating and ventilation (HVAC) systems was engaged to aerate the building and purge the space of Chlorine dioxide gas. Post aeration, the internal concentration was cleared to allow access and the chemical indicators were removed and returned to the laboratory for analysis. All other equipment was then removed from the site.

Chemical indicators (CI) of various materials (316L Stainless Steel, Aluminium and Perspex (Acrylic) were used to vaildate successful inactivation. The CI's were impregnated with two strains of beta-lactams manufactured in the facility (1 mL of 500 ppb Amoxicillin and Penicillin V (each) in methanol). The three carrier materials were selected for testing based on their prevalence in the manufacturing workplace. The carriers were approximately 100 mm long by 100mm wide by 5-mm thick. Validation of recovery was completed on control samples (n=8). Prior to deploying the CI's into the facility, each sample was labelled with a location number and material number. The site locations for each set of chemical indicators are shown in Figure 1. In total, there were 80 samples of each material used with a total number of 240 samples.

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Figure 1: Chemical Indicator locations for each of 240 samples (80 locations x 3 materials; 316L Stainless Steel, Perspex (Acrylic) and Aluminium.

RESULTS

The following results were obtained from the chemical indicator data and concentration of chlorine dioxide (CD) gas from the study. Table 2a shows the mean post decontamination concentrations of the two beta-lactams. Figure 2 (b & c) shows the concentration of chlorine dioxide (CD) gas from each of the twenty gas sampling points and it can be seen that in all locations that the minimum exposure of 7200 ppm-hrs was achieved

Penicillin Type – Test Material	Number of samples	Mean (ppb)	Geometric Standard Deviation (GSD) (ppb)	Max Residue Level (MRL) (ppb)	Distribution fit (LogNormal, Normal, Both, Neither)	95th percentile Upper Confidence Limit (UCL95)	Mean Variance Unbiased Estimate (MVUE)	Percent of samples above the adjusted MRL (%)
Amoxicillin – Acrylic (ppb)	79	1.353	3.173	50	Neither	N/A	N/A	0
Amoxicillin – Stainless Steel (ppb)	79	1.170	3.012	50	Neither	N/A	N/A	0
Amoxicillin - Aluminium (ppm)	80	0.809	2.384	50	Neither	N/A	N/A	0
Penicillin – Acrylic (ppb)	79	0.270	1.831	50	Neither	N/A	N/A	0
Penicillin – Stainless Steel (ppb)	79	0.260	1.778	50	Neither	N/A	N/A	0
Penicillin - Aluminium (ppm)	80	0.284	1.982	50	Neither	N/A	N/A	0

Figure 2a shows statistical analysis from results for the three materials

DISCUSSION

At all gas sample locations, a minimum of 7200 ppm-hrs exposure to Chlorine dioxide gas was achieved. In fact, in most locations, the exposure of Chlorine dioxide gas was greater than 10,000 ppm-hrs. In all chemical indicator samples, the post-decontamination penicillin concentration was well below the 50ppb adopted EEC standard level for acceptance. Whilst there was variability in the data, all individual and mean concentrations for both strains were well below 50ppb which would suggest that the decontamination using Chlorine dioxide was successful. This is synonymous with Lorcheim (2011) who showed a similar level of inactivation of penicillin strains

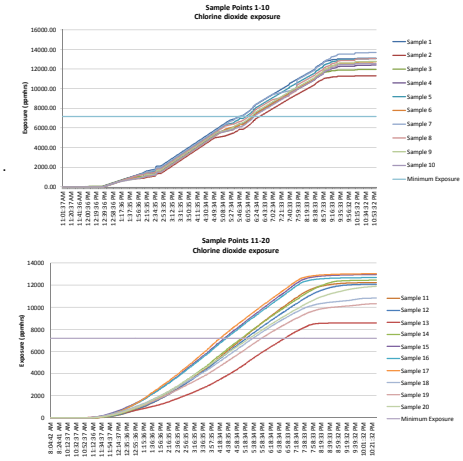

Figure 2 (b & c) shows the concentration of chlorine dioxide (CD) gas from each of the twenty gas sampling points

There was a statistically significant difference between the pre- and post-decontamination swabs (p>0.05 – t-test Excel) for both penicillin strains. The reduction in concentration to low levels (<50ppb) was significant from a pre-decontamination control mean of 129.82 and 317.24ppb for Amoxicillin and Penicillin-V respectively to a mean range of 0.05-1.47ppb for both which suggests that the Chlorine dioxide is effective at inactivating these two strains. An area of further investigation may be to determine if there is any statistical difference between the three materials used as the carrier for the penicillin strains and to determine if there are any material compatibility differences on Chlorine dioxide's ability to inactivate on different materials.

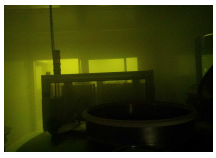

Image 2a&b – The Chlorine dioxide gas inside the penicillin manufacturing plant during remediation.

CONCLUSION

From the data obtained from this study, the Chlorine dioxide gas concentrations in the monitored areas all exceeded the minimum level of 7200ppm-hrs required to successfully inactivate penicillin. The mean post-decontamination concentrations for both Amoxicillin and Penicillin-V in all samples were well below the adopted EEC level of acceptance of 50ppb.

Given that all Chlorine dioxide gas concentrations were above 7200ppm-hrs, all chemical indicators showed concentrations less than 50ppb and there was a significant difference between the pre- and post-decontamination results, it is feasible to assume that the decontamination of the Pharmaceutical Facility was successful and may now be repurposed, reused or demolished.

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