

Chlorine Dioxide Gas Inactivation of Beta-Lactams

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Abstract

Allergic reactions to beta-lactams, such as penicillin, can be life-threatening. Due to the large number of individuals allergic to beta-lactams, a method for their inactivation was explored such that a contaminated area could be treated and re-used. The goal was to validate a cycle that could be used to treat a pharmaceutical manufacturer's beta-lactam manufacturing equipment for the future production of non-beta-lactam compounds. Testing was conducted using chlorine dioxide gas at various concentrations and exposure times in an effort to achieve the pharmaceutical manufacturer's required 3-log (99.9%) reduction of eight different beta-lactams on various surfaces. After a period of cycle development, multiple chlorine dioxide gas cycles at various concentrations and exposure lengths were shown effective in inactivating the eight beta-lactam compounds to a successful degree.

Introduction

Beta-lactam antibiotics are by definition a class of antibiotics which contain a beta-lactam ring in their structure. They work by inhibiting the formation of bacterial cell walls by blocking peptidoglycan synthesis (Pratt, 1983). Beta-lactam antibiotics are split into various groups depending upon their base structure, with the main groups being penicillins, carbapenems, cephalosporins, and monobactams. These antibiotics are used to treat a variety of gram-positive and gram-negative bacteria but can also cause adverse effects on patients and those who come in contact with them. Allergic reactions to beta-lactams are the most common cause of adverse drug reactions mediated by specific immunological mechanisms (Torres et al., 2003). According to the CDC, 3%-10% of all adults in the United States have experienced an allergic response to penicillin (CDC, 2006). Reactions to these allergies can range from simple rashes to life-threatening anaphylaxis (Romano et al., 2002). Another possible reaction is blood pressure dropping to life-threatening levels, causing lightheadedness and loss of consciousness (Barza, 1985).

Due to the prevalence and potential severity of beta-lactam allergies, pharmaceutical manufacturers must take precautions to avoid cross-contamination. The gravity of beta-lactam cross-contamination is codified by the U.S. Federal government in Federal Regulation 21 CFR 211.176:

If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in *Procedures for Detecting and Measuring Penicillin Contamination in Drugs*.

The U.S. Food and Drug Administration requires detection of penicillin G and ampicillin residues in non-beta-lactam pharmaceuticals at the level of 0.03 ppm (U.S. FDA, 1999). To ensure the prevention of cross-contamination, beta-lactam manufacturing facilities are often dedicated to the production of beta-lactam products for the facility's life and then demolished upon the cessation of production.

A method for the inactivation of beta-lactams would allow for equipment and facilities used in the manufacture of beta-lactam products to be used in the future production of non-beta-lactam products (Kasai et al., 2002). This would allow companies to "recycle" beta-lactam production facilities instead of demolishing them upon the completion of production. With a novel method of beta-lactam inactivation available, production facilities could be more flexible in their functionality and be used to produce both beta-lactam and non-beta-lactam products. Increased flexibility for production facilities would lessen the required amount of capital equipment and the overall footprint necessary, providing substantial savings for the appropriate companies.

With these aims in mind, a study was put forth to test the efficacy of chlorine dioxide gas (CD) for the inactivation of beta-lactams. The study was issued by a pharmaceutical company that wished to reuse equipment from a decommissioned beta-lactam production facility in a different, non-beta-lactam production facility. While previous studies focused on the efficacy of liquid agents (Fukutsu et al., 2006; Takahashi et al., 2008), this study is the first to focus on a gaseous method. A gaseous method was considered superior as it would offer the best opportunity to contact all surfaces (interior and exterior) of the contaminated equipment. Chlorine dioxide gas was the agent selected for testing. CD has been gaining popularity as a sterilant and decontaminating agent since the mid-to-late 1980s (Rosenblatt et al., 1985; Rosenblatt et al., 1987). CD in both gaseous and aqueous phases is a strong oxidizing agent and has about 2.5 times the oxidation capacity of chlorine (Benarde et al., 1967). Additionally, CD has been ap-

proved for use as a sterilant/decontaminant by the United States Environmental Protection Agency (U.S. EPA, 2005). Both gaseous and aqueous phase CD have been shown to be effective sanitizing agents that have broad and high-biocidal effectiveness against bacteria (Benarde et al., 1965; Harakeh et al., 1985; Ridenour et al., 1949) including pathogens (Harakeh et al., 1985; Korich et al., 1990; Roberts & Raymond, 1994), viruses (Chen & Vaughn, 1990; Noss & Oliver, 1985), bacterial spores (Ridenour et al., 1949), algae (White, 1972), and various chemicals and compounds (Bakmutova-Albert et al., 2008; Rodriguez et al., 2007; Ryan et al., 2007).

CD has a chlorine-like odor which is detectable at its 8-hour safety threshold (OSHA, 2011). It has a yellow-green color, which enables it to be monitored by an ultraviolet (UV)-VIS spectrophotometer, allowing for tight process control. CD was selected to decontaminate the Brentwood postal sorting facility and the majority of the Hart Senate office building, both in Washington, DC, after the anthrax contaminations in 2001 and has also been used to decontaminate hospitals, surgical suites, laboratories, animal breeding facilities, processing tanks, isolators, and biological safety cabinets (BSCs) (National Sanitation Foundation, 2007).

Materials and Methods

Chemical Indicators

Testing was done using chemical indicators (CI) of various materials impregnated with eight types of beta-lactams, supplied by LCMS Limited (Raleigh, NC). Three carrier materials were selected for testing based on their prevalence in the manufacturing and laboratory workplace. Carrier materials evaluated in this study were polycarbonate plastic (lexan), stainless steel (304 L, passivated), and aluminum (non-anodized). The carriers were approximately 15-mm long by 5-mm wide by 2-mm thick. A single square-profiled channel approximately 0.5-1.0-mm deep and wide was machined lengthwise along the center on one side of each coupon to simulate the presence of beta-lactam residues in cracks and crevices.

Each CI was spiked with a cocktail of eight beta-lactams. These eight beta-lactams were chosen to represent a sampling of those on the equipment driving this study as well as some other common beta-lactams. For example, amoxicillin was selected as it is reported to be the most commonly used beta-lactam in the United States and many other countries (Cars et al., 2001; McCaig & Hughes, 1995). The cocktail consisted of beta-lactams from the penicillin, cephalosporin, and carbapenem groups. Penicillin G, penicillin V, ampicillin, and amoxicillin were included from the penicillin group. From the cephalosporin group, cefadroxil, cefazolin, and cephalexin were incorporated. Imipenem, from the car-

bapenem group, was the final component inside the cocktail. Each CI contained 5 µg/mL (≈ 5 ppm) inoculated on the surface of the CI. The inoculums were dried on the carriers prior to treatment with chlorine dioxide gas.

Decontamination

CI were placed inside a 17 ft³ two-glove isolator (Biospherix, Ltd., Lancona, NY) complete with CD injection, sampling, and aeration ports prior to the inactivation cycle. The CD inactivation cycle performed was a five-step process. The process begins with a preconditioning step. In this step, humidity is raised from ambient conditions to between 60%-75% relative humidity (RH) because CD has been shown effective as a decontaminating agent within this humidity range (Czarneski, 2009; Eylath et al., 2003). For these tests, a level of 75% RH was used. This was followed by the conditioning step, where the environment was held at the prescribed RH level for a set amount of time. The condition time for these studies was 30 minutes. Upon completion of the conditioning step, CD was introduced into the isolator in the charge step. Once the isolator was charged with the specified concentration of CD, the gas was held at that level for a prescribed amount of time in the exposure step. Both the concentration and exposure time were to be altered during the study to determine the optimal inactivation cycle. After the exposure step, the isolator was aerated of CD during the aeration step. Upon completion of the exposure of the CIs to CD, the CIs were sent to a laboratory for evaluation. Control CIs not exposed to CD were also sent to provide baseline recovery data to analyze the effect of CD exposure.

A Minidox-M Chlorine Dioxide Gas Generator (ClorDiSys Solutions, Inc., Lebanon, NJ) was used to control the decontamination cycle. It automated the process by controlling the humidity and chlorine dioxide gas concentration throughout the entire cycle. During the charge and exposure steps, gas concentrations were continuously monitored using a validated UV-VIS spectrophotometer within the Minidox-M to ensure that the correct concentration was reached and maintained (Shah et al., 2005). This process control allows for repeatability among the various inactivation cycles. With the ability to accurately reproduce the correct cycle parameters, the pharmaceutical manufacturer agreed to expose three CIs of each carrier material to one inactivation cycle for validation rather than expose CIs to three separate inactivation cycles for validation.

Various decontamination cycles of differing concentrations and exposure times were tested for efficacy towards inactivation of beta-lactams. Table 1 shows the various parameters that were associated with each inactivation cycle. Concentrations are measured in milligrams of chlorine dioxide gas per liter of volume (mg/L) in the chamber.

Chemical Indicator Testing

Upon completion of the inactivation cycles, exposed CIs as well as a set of positive control CIs were shipped to LCMS Limited for extraction and evaluation. In addition, a negative control was processed as well. Liquid chromatography (LC) and mass spectrometry (MS) were used during recovery to test for the presence of the beta-lactams (Straub & Voyksner, 1993; Voyksner et al., 1991) on the CIs. Post-exposure beta-lactam recovery was calculated as a percentage of the recovered amount on exposed CI divided by the recovered amount on the control (unexposed) CI of the same type (Table 2).

Results and Discussion

The pharmaceutical manufacturer's requirement of achieving 3-log (99.9%) reduction (maximum post-exposure recovery of 0.1%) was the baseline for acceptance. By calculating post-exposure recovery as a percentage of exposed/control CIs, loss due to shipping and handling becomes irrelevant as acceptance criteria

is 0.1% recovery in relation to control CIs. With approximately 5 ppm of each beta-lactam inoculated on each CI, acceptance criteria of 0.1% recovery would equal 0.005 ppm or less for each beta-lactam, assuming no loss on the control CIs. If controls returned with only 4 ppm recovered, cycle success would be measured at recovery values ≤ 0.004 ppm.

Results from the recovery testing are presented in Figures 1-9. Plotted in each figure are the percentages of each beta-lactam recovered after the inactivation cycles. The 3-log reduction line (0.1% recovered) is shown for reference as a dotted line. A successful inactivation cycle would have all recovery values below this line.

The three chemical indicators on aluminum carriers are represented by A-1, A-2, and A-3. Chemical indicators on lexan carriers are represented by L-1, L-2, L-3. Chemical indicators on stainless steel carriers are represented by S-1, S-2, S-3.

To further analyze the data, calculating the total exposure value by means of the cumulative parts per million-hours for each cycle gives an added depth to

Table 1

Parameters for each Inactivation Cycle.

Inactivation Cycle	Relative Humidity (%)	Condition Time (minutes)	CD Concentration (mg/L)	Exposure Time (hours)
1	75	30	1	6
2	75	30	3	6
3	75	30	5	4
4	75	30	5	6
5	75	30	7	2
6	75	30	7	4
7	75	30	7.5	4
8	75	30	9	2
9	75	30	30	4

Table 2

Limits of Quantitation (LOQs) and Limits of Detection (LODs) for the 8 target beta-lactam analytes.

Beta Lactam	Limit of Quantitation	Limit of Detection
Amoxicillin	10 ng/swab	3.5 ng/swab
Ampicillin	3.5 ng/swab	0.5 ng/swab
Cefadroxil	10 ng/swab	3.5 ng/swab
Cephalexin	3.5 ng/swab	1.5 ng/swab
Cefazolin	3.5 ng/swab	1.5 ng/swab
Imipenem	30 ng/swab	15 ng/swab
Penicillin V	3.5 ng/swab	1.5 ng/swab
Penicillin G	3.5 ng/swab	1.5 ng/swab

Provided by R. Voyksner, LCMS Limited

Figure 1

Results from Inactivation Cycle 1 (1 mg/L at a 6-hour exposure).

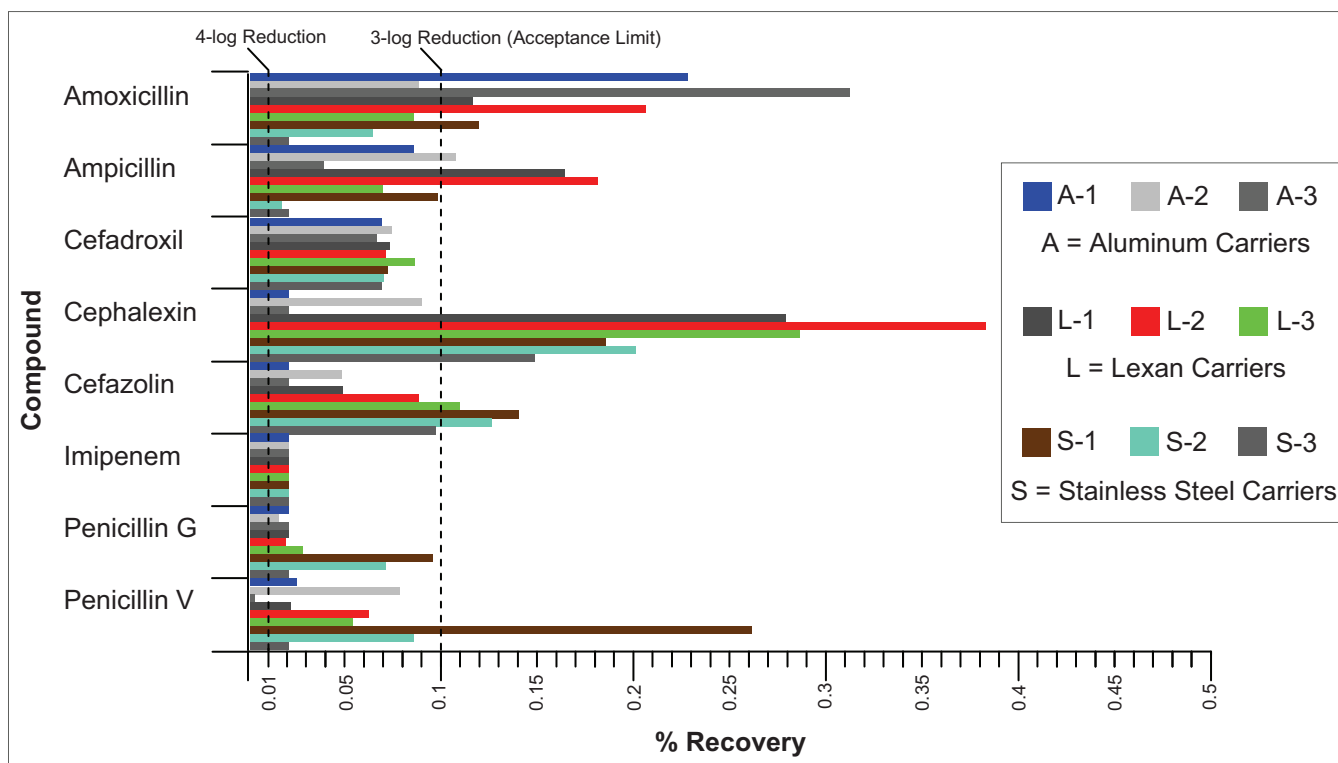


Figure 2

Results from Inactivation Cycle 2 (3 mg/L at a 6-hour exposure).

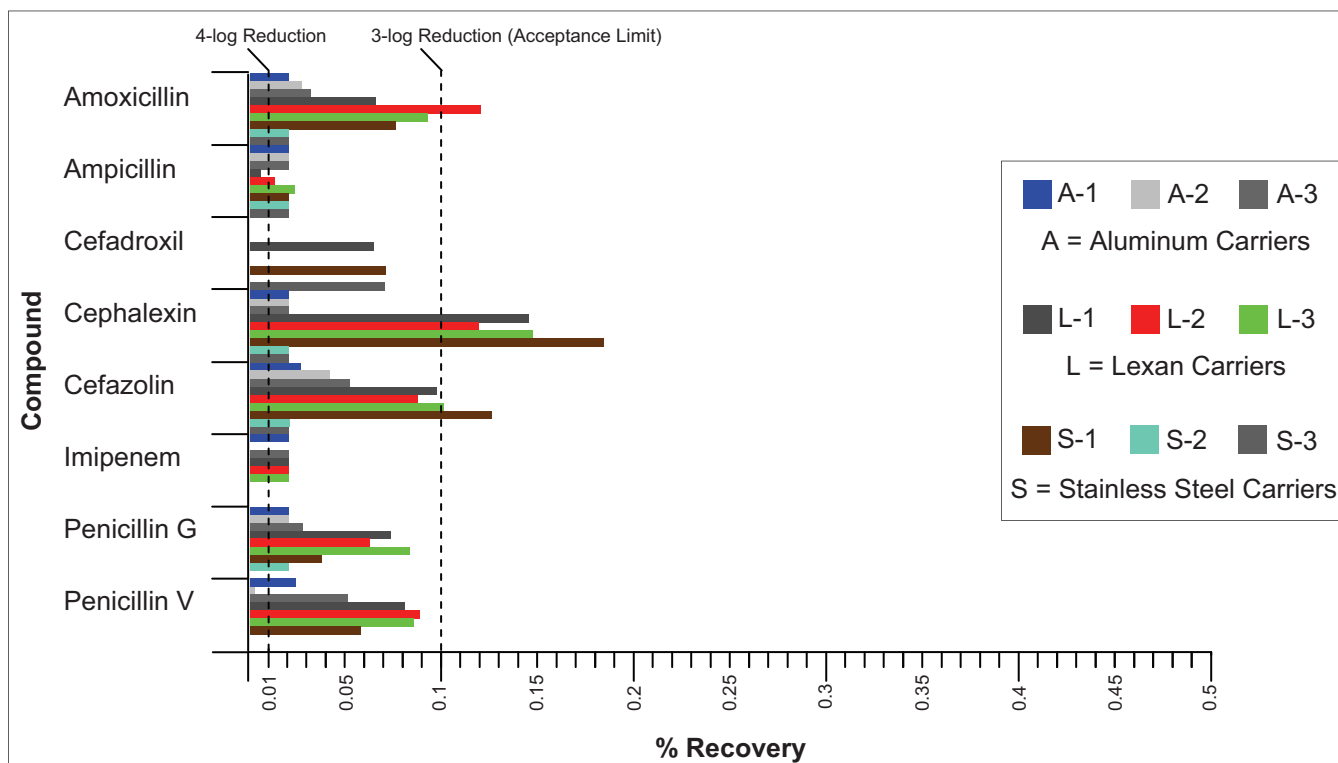


Figure 3

Results from Inactivation Cycle 3 (5 mg/L at a 4-hour exposure).

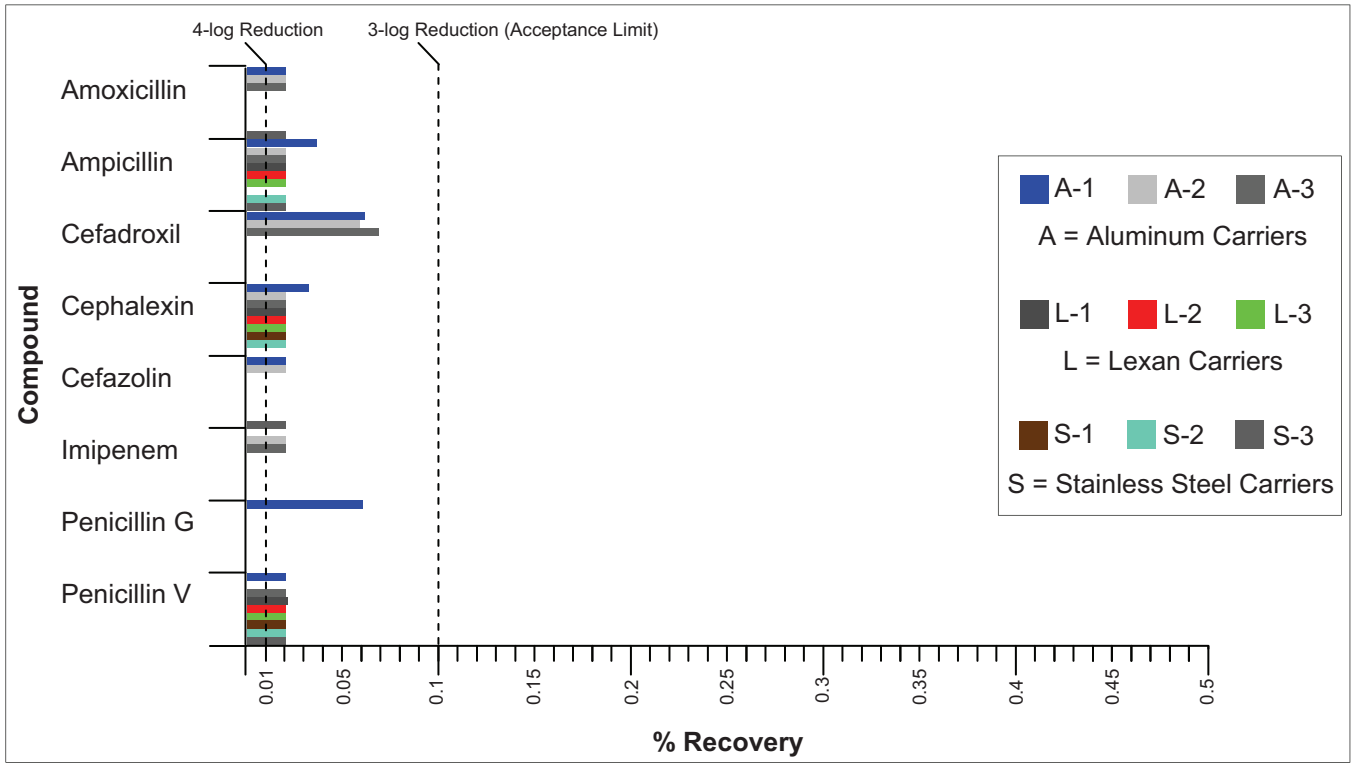


Figure 4

Results from Inactivation Cycle 4 (5 mg/L at a 6-hour exposure).

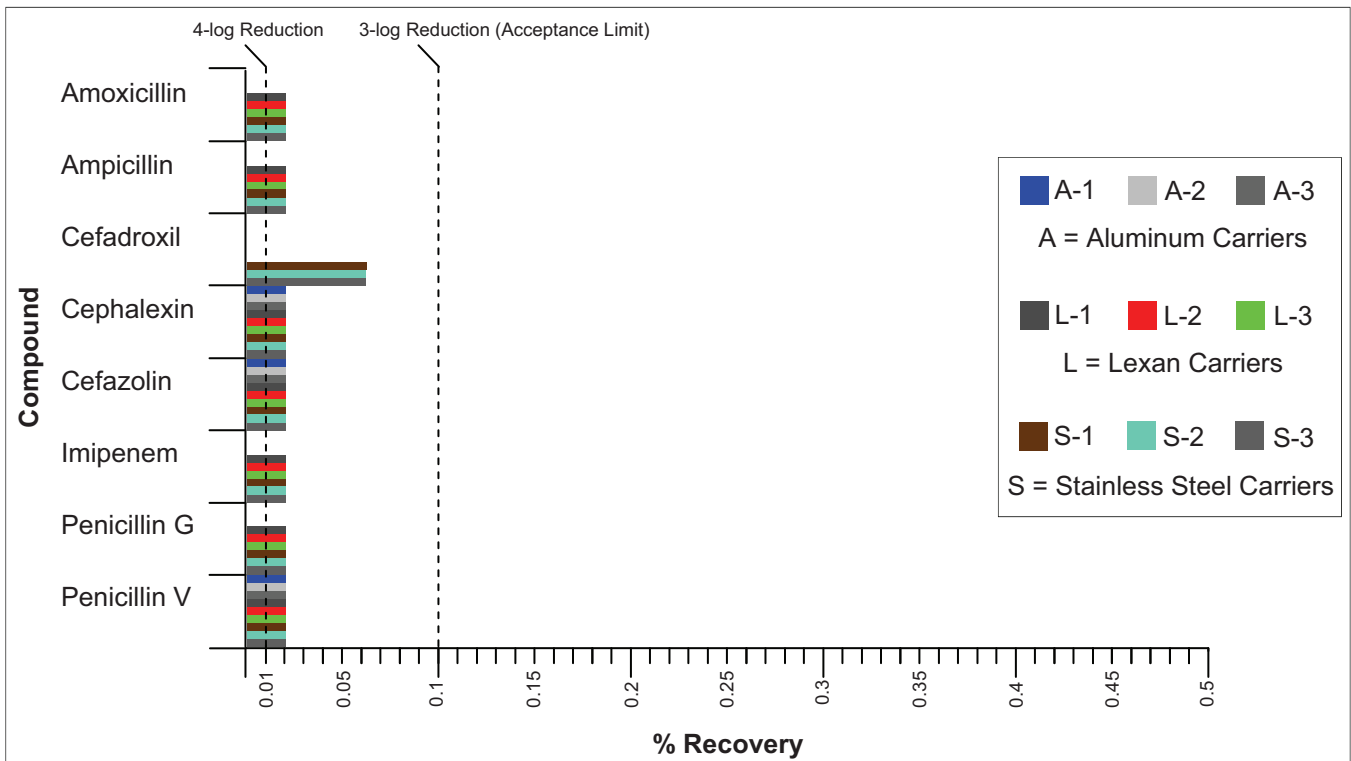


Figure 5

Results from Inactivation Cycle 5 (7 mg/L at a 2-hour exposure).

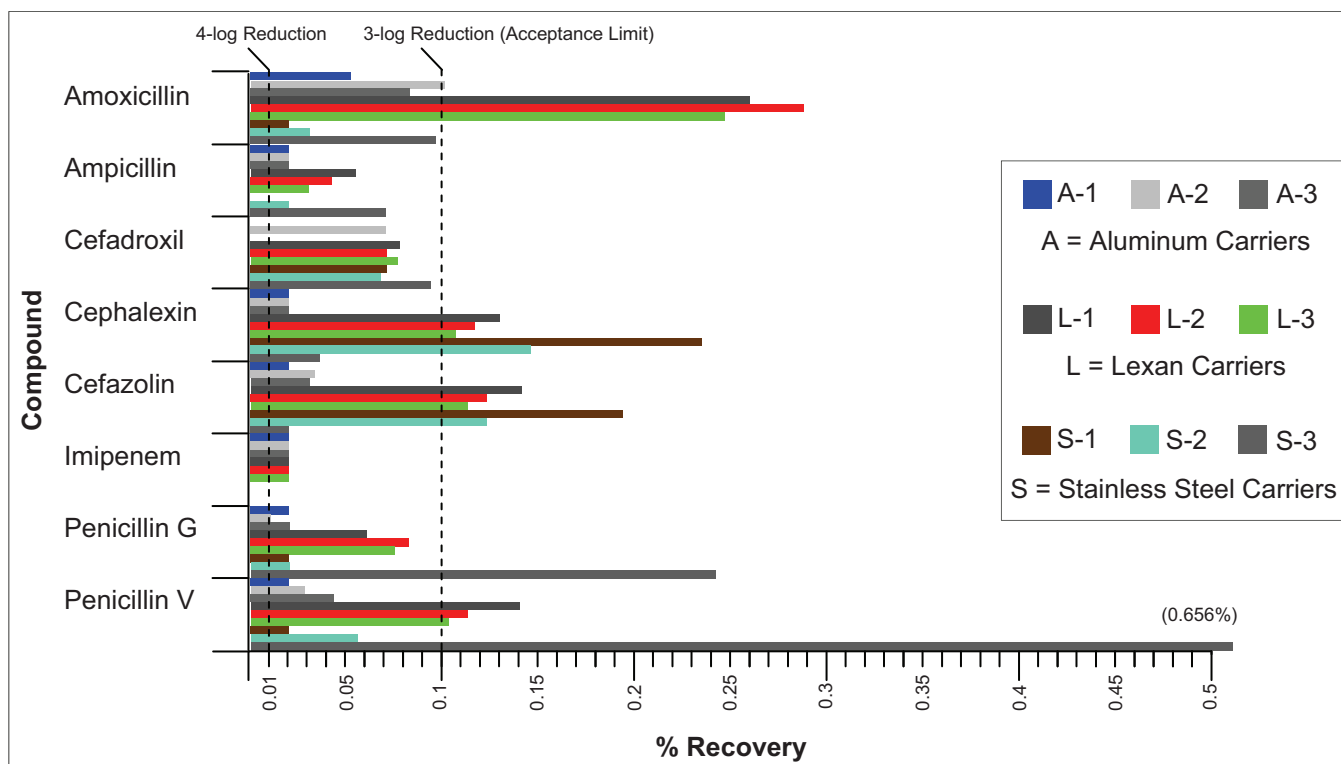


Figure 6

Results from Inactivation Cycle 6 (7 mg/L at a 4-hour exposure).

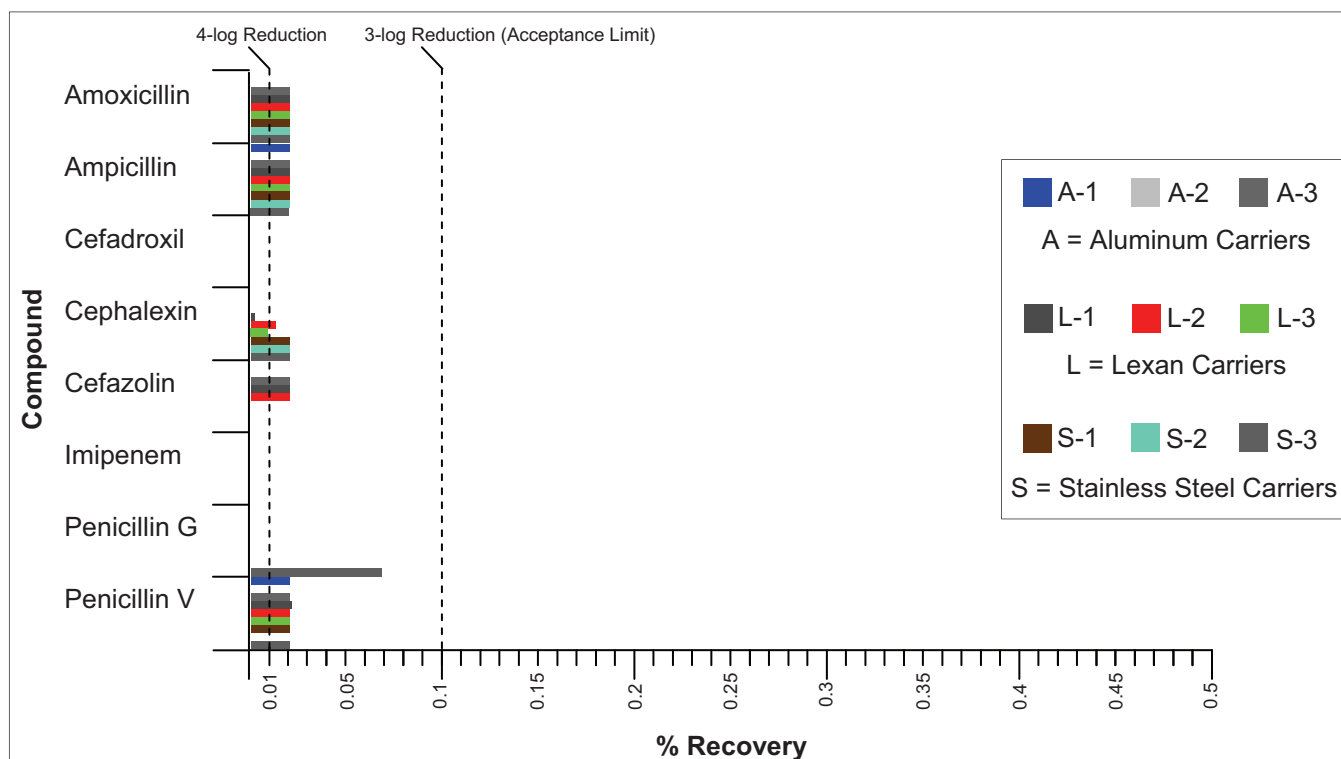


Figure 7

Results from Inactivation Cycle 7 (7.5 mg/L at a 4-hour exposure).

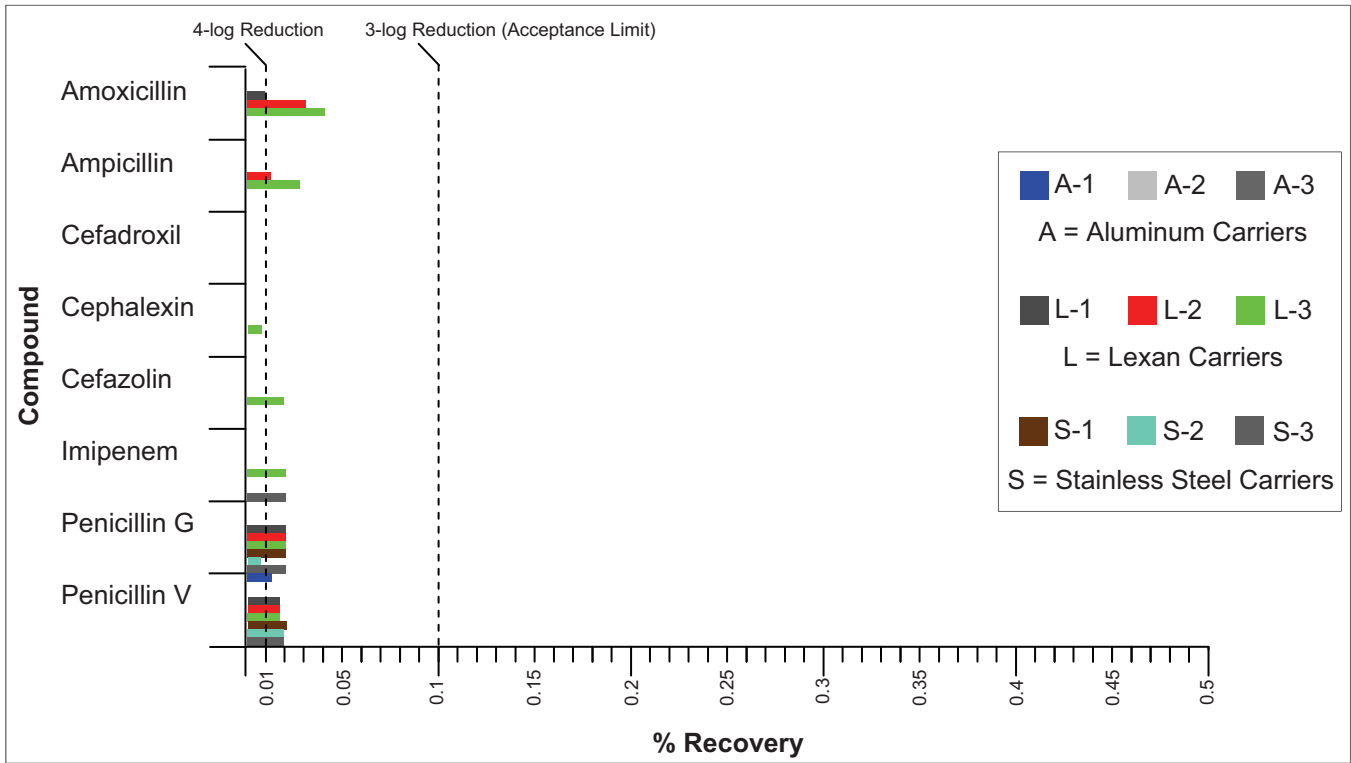
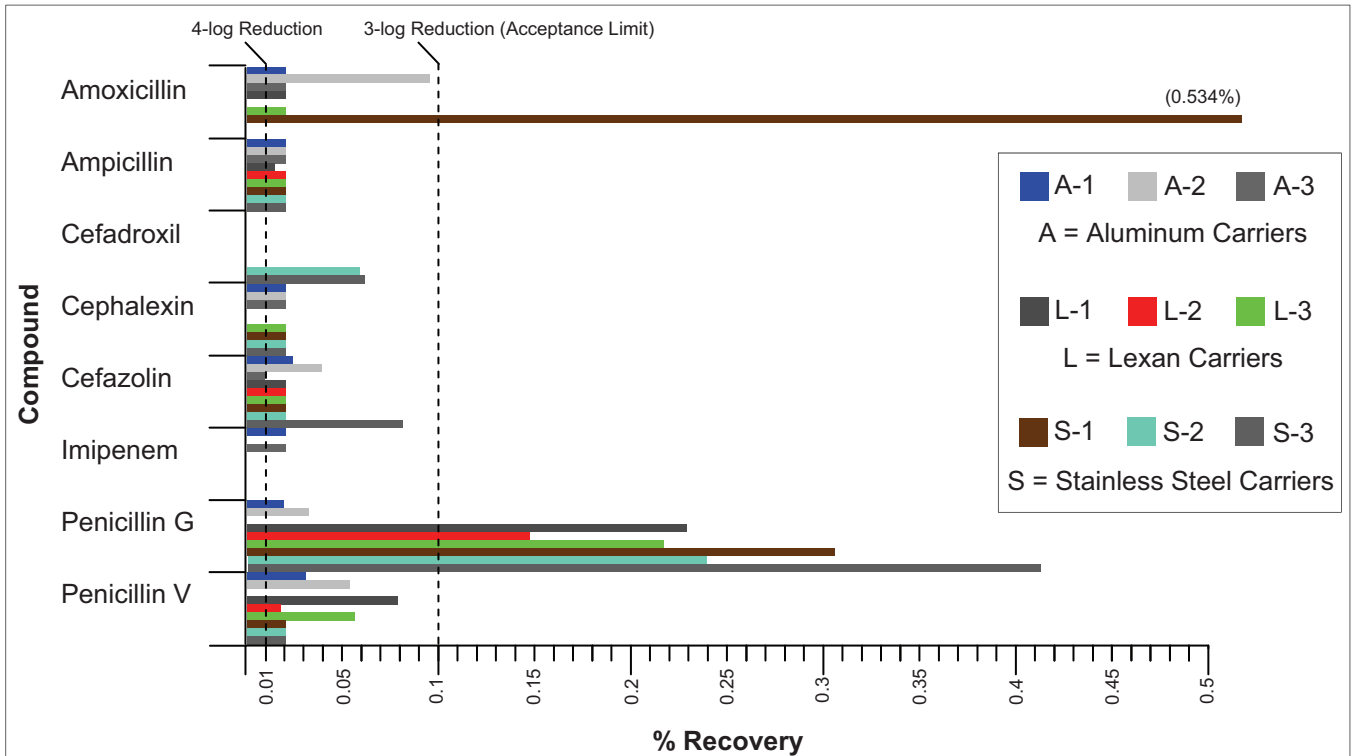


Figure 8

Results from Inactivation Cycle 8 (9 mg/L at a 2-hour exposure).



these 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 1 ppm-hour representing the exposure of 1 ppm of chlorine dioxide gas for the duration of 1 hour. Determining the cumulative exposure using ppm-hours for chlorine dioxide gas for each cycle consists of multiplying the gas concentration (in mg/L) by 362 (ppm per mg/L) and then multiplying that number by the exposure time (in hours). Table 3 shows the cumulative exposure in ppm-hours for each inactivation cycle. The successful inactivation cycles are shown in bold.

Conclusion

Test results demonstrated that chlorine dioxide gas was effective towards the inactivation of the eight beta-lactams involved at varying concentrations and exposure lengths. Nine inactivation cycles were tested, with five passing the acceptance criteria of achieving a 3-log reduction of the eight beta-lactams to beneath U.S. Food and Drug Administration (FDA)-required 0.03 ppm residue detection level. Inactivation cycles numbered 3, 4, 6, 7, and 9 each achieved the targeted 3-log reduction of beta-lactams on aluminum, lexan, and stainless steel Cls.

Figure 9
Results from Inactivation Cycle 9 (30 mg/L at a 4-hour exposure).

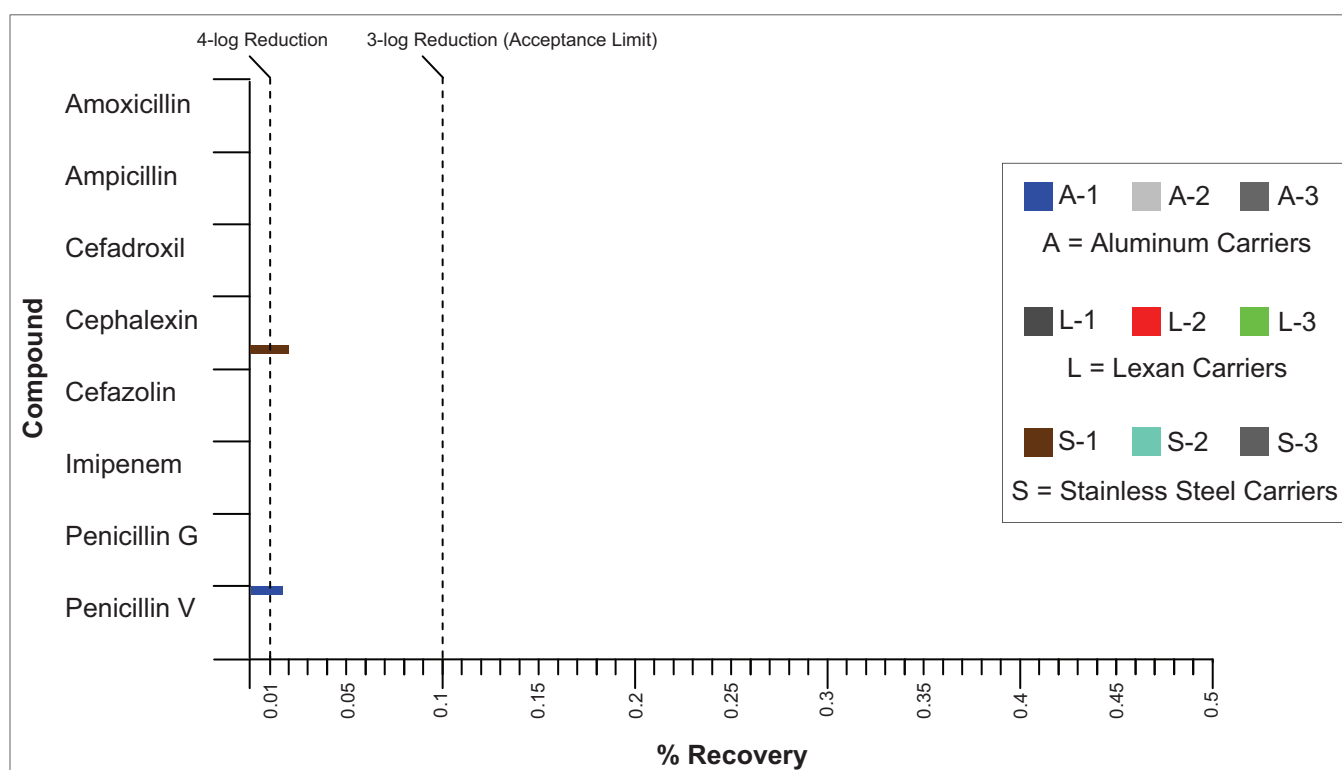


Table 3
Cumulative ppm-hours per inactivation cycle.

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

Successful inactivation cycles which achieved 3-log reduction of all eight beta-lactam compounds all had cumulative exposures of over 7,240 ppm-hours. Based on this, it can be concluded that in order to achieve a 3-log reduction of beta-lactams, an inactivation cycle consisting of a 30-minute conditioning phase at 75% relative humidity, followed by an exposure to CD of at least 7,240 ppm-hours, is required.

Results demonstrate that beta-lactam contaminated equipment and facilities can be treated with CD using a validated cycle and reused to manufacture non-penicillin products based on the manufacturer's risk assessment. This provides pharmaceutical manufacturers the option of reusing capital equipment previously used for beta-lactam production. It also provides a means to routinely treat equipment in an effort to minimize the risk of cross-contamination of beta-lactams.

Additional Remarks

Since the original test study, multiple beta-lactam facilities have been treated with CD inactivation cycle #3, consisting of 30 minutes of conditioning at 75% relative humidity followed by approximately 7,240 ppm-hours of CD exposure. In some cases, the beta-lactam manufacturing facilities were converted into non beta-lactam manufacturing facilities post-treatment. In others, the beta-lactam manufacturing facilities were repurposed as training facilities. These inactivation cycles have all included the facility's HVAC systems and all equipment located inside the facility, including BSCs and production and packaging equipment. To test the efficacy of the CD inactivation cycles, the facilities performed swab tests pre- and post-exposure. Swab locations included inside HVAC ductwork and inside and underneath equipment, among others. Swab tests utilizing liquid chromatography confirmed the effectiveness of the CD inactivation cycles in all facilities with zero positive swabs at post-exposure test locations. These decontaminations proved that the chlorine dioxide gas inactivation cycles could be successfully used outside of the controlled laboratory setting.

Acknowledgments

ClorDySis' research on this project was funded by the pharmaceutical industry. The author would like to thank Dr. Robert Voyksner of LCMS Limited for his help and support during the study and Dr. Henry Luftman of DRS Laboratories for his support in writing this article. Kevin Lorcheim is employed by ClorDiSys Solutions, Inc. Correspondence should be addressed to Kevin Lorcheim at kevinlorcheim@clordisys.com.

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Training Announcements

Principles & Practices of Biosafety (PPB)

The Principles & Practices of Biosafety is a comprehensive, interactive, 5-day course that introduces the essential elements of biosafety and provides extensive resource lists for use after the course. Interactive exercises are used throughout to provide hands-on experience and to encourage networking and problem-solving among participants and instructors.

ABSA/ERGRF Road to Leadership

The American Biological Safety Association and the Elizabeth R. Griffin Research Foundation are partnering to offer the ABSA/ERGRF Road to Leadership event. The Road to Leadership features 2 independent courses—the Leadership Institute and the Review Course.

The Leadership Institute is an experience designed for biosafety professionals and other leaders who may support the biosafety profession. Participants have the opportunity to challenge themselves and biosafety experts through interactive small group exercises and discussions. The Leadership Institute provides many professionals with the opportunity to explore solutions for common problems. Together, the small group exercises and discussions, fosters leadership skills and abilities which are increasingly needed for today's biosafety practitioner.

The Review Course is a 2-day instructor-led course that provides a comprehensive overview of the essential elements of biological safety as prescribed in the NRCM Specialist Microbiologist Task List for Biological Safety Microbiology.

Webinars

"Basic Disinfection" and "Effective Biosafety Training" webinars will occur before the end of the year. A "Call for Webinars" will be announced and posted on the ABSA web site in April 2011.