Case Study Title:	**Facility Bio-containment and Inactivation**	**Case No.**	**RMWG-04**
GMP System Impacted:	**Facilities and Engineering**		
Introduction / Background	When a manufacturer produces two or more different drug substances in the same manufacturing facility the facility is considered to be multi-product. The facility designs, operations and controls related to the use for multiple products should provide for appropriate measures to prevent cross-contamination between products. This includes considerations around the containment procedures employed to prevent the release of hazardous agents within the facility. There are numerous facility design and operational attributes that may significantly affect the quality of products being manufactured. These include, but are not limited to, area classifications, open versus closed processing, utility system design, cleaning validation/CIP systems, rules around equipment sharing, and critical flows throughout the facility. Facility designs and operations should provide for appropriate segregation of products to prevent cross-contamination. For facilities with multiple products or processes the impact of potential process or product failures on the other operations in the same facility should be evaluated. In the current case study, two existing manufacturing suites were proposed to be remodeled to accommodate and contain manufacturing operations involving bacterial fermentation via viable cells of *S. pneumoniae,* a pathogenic BL2 organism. These suites were separate manufacturing areas located adjacent to mammalian cell culture manufacturing processing areas. Regulatory guidance requires BL2-LS waste and residues to be inactivated prior to exiting the manufacturing area. An inactivation autoclave was identified during the initial risk assessment as one of the primary means of inactivation of BL2 waste and process equipment prior to exiting the fermentation suite. The risk review step in the risk management process identified that there was only one inactivation autoclave in the fermentation suite and that alternative back-up inactivation procedures were desired to maintain continuity of manufacturing operations during autoclave preventative maintenance and corrective maintenance activities. This case study describes the evaluation of various back-up inactivation procedures for both operational feasibility as well as demonstration of an appropriate level of inactivation of the BL2 waste and equipment.		

Defining the Risk Question

The risk question developed for the subject case study is:

What are the appropriate back-up inactivation methods (procedures) that are operationally feasible and provide an appropriate level of decontamination capability that can be utilized in the fermentation suite to inactivate BL2 waste and equipment when the inactivation autoclave is unavailable?

Selecting a Risk Assessment Method

Selection of a back-up inactivation procedure is a precise exercise requiring an objective evaluation of the effectiveness of proposed procedures at inactivating the BL2 organism along with demonstration of consistent execution of these procedures each time they are performed.

HACCP is a risk assessment tool that can be proactively utilized to identify and implement process controls that consistently and effectively prevent hazards from occurring through evaluation of critical procedural limits and determination of how they will be routinely achieved. Since it is essential that the back-up inactivation procedures prevent the release of the BL2 organism outside of the fermentation suite HACCP was selected as the risk assessment tool to use to determine the appropriate preventative controls.

The risk methodology selected for the subject case study is:

HACCP

Risk Assessment (Risk Identification, Analysis and Evaluation)

Risk Identification -

For this evaluation there was only one hazard for consideration, the BL2 organism, thus the HACCP process was significantly streamlined. Due to operator safety considerations and the high level of regulatory requirements for control of pathogenic BL2 organisms. The hazard was always considered to be significant in this case study. (Table 1).

Categories of items	Actual & Potential Hazards introduced, controlled or enhanced at this step	Introduced, Controlled or Enhanced	Are any potential Safety hazards significant?	Justify response	What Preventative Measures were applied to prevent the significant hazard?	Is this a Critical Control Point? (Yes/No)	CCP rationale (for both Yes and No)
Mixed Trash	BL2 host organism – known infectious pathogen	Introduced	Yes	BL2 host organism	Place trash bag into another trash bag, seal for transport, and sanitize bag exterior. Place bags in a covered container for transport to an external autoclave.	Yes	This is the primary means of containment until inactivation
		Controlled	Yes	BL2 host organism	Inactivation within an external autoclave	Yes	This is the primary means of inactivation

Risk Analysis and Evaluation –
Each proposed inactivation mechanism or procedure was deemed critical (Table 1) since they were proposed as back-ups for the primary autoclave inactivation method (which was itself deemed critical). The evaluation of the effectiveness of the procedures as well as how they will be controlled such that the critical parameters will be consistently achieved is shown in Table 2.

Critical Control Point	Significant hazards	Critical Limits for each Preventive Measure	Monitoring				Verification	Documentation/ Supporting Studies, Records	Recommended Actions
			What	How	Frequency	Who			
Place trash bag into another trash bag, seal for transport, and sanitize bag exterior. Place bags in a covered container for transport to an external autoclave.	BL2 host organism	Bag closure via tie-knot	Closure	Visual	Once – upon closure	Trained technician	Bag not accepted if not sealed	None	SOP for this activity is required. Any bags containing sharps must be relabeled with appropriate external sharps indicator stickers to ensure those bags are routed for incineration rather than autoclave inactivation.
		70% vol/vol	Ethanol concentration for wipe-down	Certificate of Analysis	Once – upon release	Quality Control	Release of ethanol for GMP use	Validation Reports	
		1 minute	Ethanol contact time for wipe - down	Wall - clock	Once – upon wipe down	Trained technician	Placement of bags into airlock only after ethanol inactivation performed per SOP	Validation Reports	
		Complete coverage	Ethanol spray coverage of bag	Visual – ensure surfaces are wetted	Once – upon wipe down	Trained technician	Placement of bags into airlock only after ethanol inactivation performed per SOP	Validation Reports	
Inactivation within external autoclave	BL2 host organism	12 minutes	Sterilization hold time – set at 90 minutes	Controller timer	Throughout cycle	Automated unit controller	Cycle tape reviewed and retained for at least 3 years. Unit is alarmed if cycle acceptance parameters not achieved.	Autoclave loads are challenged monthly with *B. stearothermophilus*. Records of these verifications are retained for at least 3 years.	Flow for these materials will need to be proceduralized and training of all impacted functional areas will need to be determined. EH&S will need to ensure that autoclaved gowns are not disposed and are returned for laundering.
		121 C	Sterilization temperature	RTD	Throughout cycle	Automated unit controller	Cycle tape reviewed and retained for at least 3 years. Unit is alarmed if cycle acceptance parameters not achieved.		

Risk Control

In this case study, identifying effective back-up inactivation methods for times when the primary inactivation autoclave is unavailable for use reduces the risk of a breach of containment in the facility. Table 2 demonstrates that the back-up procedures that were identified are effective and can be consistently controlled. Table 2 also indicates that additional more detailed procedural controls and more clearly defined functional area responsibilities, beyond what is currently outlined in the back-up procedures, will be required to ensure that proper containment of the BL2 organism is maintained. These additional procedural controls are identified in the "recommended actions" column.

Risk Documentation and Control

For this case study, the outputs of the risk assessment process, including recommendations for additional procedural and functional area controls, were documented in a risk assessment report. This report becomes part of the operating history for the manufacturing facility and the associated product. Each functional area impacted by the results of the risk assessment reviewed and signed off on the results and recommendations. The project team assumed responsibility for implementation of the recommendations that arose from the QRM process.

Risk Review	In the case study presented, it may be appropriate to review the back-up procedures as additional detailed procedures are developed. This will ensure that the back-up procedures are fully effective and controlled such that the BL2 organism is appropriately contained.