Case Study Title:	**Pack-Out Remedies to Minimize Contamination and Exposure**	**Case No.**	**RMWG-06**
GMP System Impacted:	**Facilities and Engineering**		
Introduction / Background	Isolation, drying, milling (including micronizing), and packaging operations for non-sterile Active Pharmaceutical Ingredients (APIs) should be performed using a combination of suitably designed rooms and/or containment technology. The primary goals are to protect operators from exposure via the containment of the API, to minimize the risk of contamination of the API and packaging materials from other compounds and foreign material, and to minimize the risk of contamination of other compounds from the API. When evaluating isolation/packout environments for the API it is important to take into account the risk factors for contamination and operator exposure. The possible alternatives to address the risks will vary based on processing step, equipment design, building finishes and design, and whether the facility is multipurpose or dedicated. The use of cleanable/controlled rooms presents the least risk but the utilization of engineering and processing controls can facilitate the use of other types of environments for isolating and packaging API. In the current case study, the manufacturer identifies contamination and occupational exposure risk factors for final isolation and packout of non-sterile APIs and uses quality risk management to evaluate the proposed alternatives to minimize these risks.		
Defining the Risk Question	The risk question developed for the subject case study is: ***Are there effective room designs and/or containment technologies that may be utilized during pack-out operations at existing facilities without significant capital investment to minimize the potential for cross contamination and operator exposure?***		
Selecting a Risk Assessment Method	In this case study, the risk factors are more qualitative than quantitative. The risk methodology selected for the subject case study is: **Decision Table (modified HAZOP)**		

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Risk Assessment (Risk Identification, Analysis and Evaluation)	*Risk Identification, Analysis and Evaluation* - A multidisciplinary team made up of Quality, Safety, Engineering and Manufacturing reviewed possible room designs, containment techniques, and operator protection strategies. Some of the options reviewed were cleanable/controlled rooms, general purpose processing rooms, pressure differentials between zones, airlocks, packout booths, continuous liners and dust tight direct connect technology with bulk container. As part of the exercise various risks were identified for the packout process. Identification, definition, and documentation of the risks are very critical to the process. Examples of the potential risks are: • Cross-contamination • Foreign Material contamination • Contamination of packaging material with other chemicals and foreign materials • Operator exposure In determining ways to cost effectively manage the above risks two key approaches are: 1) To minimize the environment around the package to facilitate control and 2) To utilize pressure differentials to help prevent the airborne migration of powder and foreign material. Four possible pressure differential zones around the package are packout booths, rooms, airlocks, and the general processing floor. Each zone can either be positive, negative, or equal to adjacent zones depending upon the hygiene/control strategy. The assessment process first involves using the risk factors to determine if a respective packaging room or pack-out strategy is appropriate. A risk level of high, medium or low is assigned to each risk factor. If the risk level is determined to be medium or high, then actions to mitigate the identified risk are considered and ultimately reviewed to determine their impact to reduce the identified risk level. The scenario below involves the use of a general purpose processing room for API packaging. This type of room is typical for many API plants. It is designed to segregate critical processing activities from the general manufacturing floor. Considerations when evaluating this type of room include:

- The presence of rough surfaces or ledges make the room difficult to clean.
- The room is typically not designed for easy maintenance.
- The air in this type of room may not be HEPA filtered but the air is normally filtered to some degree to remove dust.

Contamination/Operator Exposure Risks	**Open drum packaging of an API through a sealed chute from a dryer on the second floor into a general purpose processing room with no airlock and no differential pressure relative to the general manufacturing floor**		
	Initial Assessment	Adjusted Control Strategy	Follow-up Assessment
Contamination of API by other Compounds	Medium risk	1) Strict cleaning and maintenance program for the general purpose processing room 2) Positive differential pressure relative to general manufacturing floor	None to low risk
Contamination of API by Foreign Material	Medium risk		None to low risk
Contamination of packaging material by other Compounds	Medium risk		None to low risk
Contamination of packaging material by Foreign Material	Medium risk		None to low risk
Contamination of other Compounds outside the room by API	Medium risk	1. Continuous Liner system. or 2. Negative pressure packout booth or 3. Dust tight direct connect technology with bulk container.	None to low risk
Exposure to the operator in the room	High risk		None to low risk
Exposure to operators outside the room	Medium risk		None to low risk

In the example above, an initial assessment is performed on the general purpose processing room regarding the risk factors. The risk levels are determined to be medium for all factors except "Exposure to the operator in the room" which is assigned high. This assessment requires mitigation for all factors. Instituting a strict cleaning and maintenance program along with a positive pressure differential protects the API being packaged and the packaging materials being used for packaging. There are three options regarding mitigation for the remaining three factors that could protect other compounds outside the room and operators inside or outside the room. After the mitigation, a follow-up assessment is performed and the new risk level is "None to low" for all factors

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Risk Control	After reviewing the adjusted control strategy against the risk factors, if the risks are not sufficiently reduced then additional solutions should be considered until the risk is at least reduced to a low level.
Risk Documentation and Communication	The packaging control strategy for each packaging room and product should be documented using the risk assessment table and approved by both Quality and Safety. A copy of the approved control strategy is then sent to Quality, Safety, Engineering, and Manufacturing for implementation.
Risk Review	The packaging room and the packaging strategy should be reviewed annually to assess potential changes to facilities, equipment and systems to assess cumulative impact of changes upon cross contamination, foreign material, and hygiene control.