Are You Controlling Your Boundary?

by Stephanie Wilkins, PE

This article clarifies what constitutes a segregated and dedicated facility and discusses the risk of cross contamination if the boundary is not managed properly.

In April, the FDA published the Guidance for Industry **Non-Penicillin Beta-Lactam Drugs:** *A CGMP Framework for Preventing Cross-Contamination*. The document expanded upon the long-standing requirements associated with penicillin manufacturing by including similar expectations that all non-penicillin beta lactams (in addition to penicillin products) be manufactured in segregated and dedicated facilities. The guidance also states that each of the five classes of beta-lactams (penicillins, cephalosporins, penems, carbacephems, and monobactams) should be manufactured in separate segregated and dedicated facilities from each other.

The expectations may seem fairly straightforward indicating that risk-based approaches are not useful with these compounds. Nothing could be further from the truth.

First let's start with the actual regulatory requirements. Verbiage contained in both the FDA's Code of Federal Regulations and EMA's Manufacturing Annex requires that segregated and dedicated facilities be utilized for the manufacture of penicillin. From a compliance perspective, the FDA and EMA have maintained that this requirement does not necessarily mean a separate building. Over the last several decades, ambiguity and misinterpretation of the requirements have resulted in many manufacturers taking the highly conservative route of dedicating buildings – and even a more conservative approach by dedicating sites to the manufacture of beta lactams. In some instances, these may have been justified, but in many cases, that is not true. In fact, many installations of these dedicated buildings on multi-product sites are actually not managing the risk of cross contamination – but are adding to the inherent risks that exist.

While the regulators have communicated that they are not in support of a threshold value/Acceptable Daily Exposure (ADE) for these compounds, other aspects of ISPE's Risk-MaPP Baseline® Guide are relevant for managing the risk of cross-contamination from beta lactam products.

Fundamentally, the concept is to create a boundary which controls the entry and exit of product. The area outside the product boundary is considered "safe" and should not contain open product that could potentially cross-contaminate another product. Note this is the same concept for all products, not just beta lactams. When dealing with beta lactams, this compound boundary is the boundary of the segregated and dedicated space that can be a suite or suites within a building, a separate building or separate site.

In Figure 1, a typical site arrangement is shown where there is an administration building (Building A), warehouse and three manufacturing buildings. Let's assume one of the manufacturing buildings is dedicated to penicillin products (Building B), one is dedicated to cephalosporin products (Building C), and the other manufactures general products not in the beta lactam family (Building D). Note for Buildings B and C, the product boundary is the building boundary as only the same family of beta lactams is permitted in either facility. Building D is a multi-product facility which requires a more detailed assessment not only at the building boundary, but also within the facility at each of the product/compound boundaries.

The risk assessment effort in this scenario is to analyze the risk that product or product residues from Buildings B and C do not penetrate the building envelopes (the product boundary) for possible cross-contamination with each other or with Building D.

Figure 2 shows a dedicated and segregated suite within a multi-purpose facility. For the space to be segregated, the walls between the suite and the other rooms must extend from structure to structure with all penetrations sealed to be leak tight, have independent HVAC, and backflow prevention on any utilities that serve the dedicated and segregated suite from the multi-purpose facility. If the controls are established as deliverables from a meaningful risk assessment process and accompanied by the appropriate procedures for employee and material movement, there should be no reason why beta lactams cannot be processed in the facility.

As such, the key is to assess the controls at the product boundary. ISPE's Risk-MaPP Baseline Guide is an important tool as it provides an approach to completing and documenting these assessments.

ISPE's Risk-MaPP Baseline® Guide states there are four modes by which cross contamination can occur; mix-up, retention, mechanical transfer, and airborne transfer. To ensure that the risk of cross contamination is controlled, an assessment of the four potential modes should be completed.

Starting with the potential for mix-up, reviewing all procedures in place to ensure the right materials, people and equipment are in the areas they should be. It is especially important for sites that manufacture beta lactams to establish and routinely update a Site Master File, which provides clarity on how materials, people and equipment transit the site. It is essential that the procedures and methods be clearly defined so that any deviations from the requirements are identified and addressed. Some items to consider may be the use of color-coded gowning/uniforms and labels so that it is easier to identify if something is in the wrong place. Use of electronic access control can help further ensure that people – and even equipment and materials are only allowed to enter the facilities that they are allowed to enter.

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The risk of cross contamination from retention of residues after cleaning of shared equipment which is then available for carryover to the next product should be non existent as the regulations are clear that equipment should not be shared between beta lactam products and other products. Equipment between the different classes of beta lactams is also not to be shared. If existing equipment is to be re-used for either beta lactam products when previously used for other products or vice versa, a decontamination protocol should be developed and executed which contains quantifiable acceptance criteria intended to ensure that the risk of cross-contamination risk is compliantly managed. Accordingly, when reusing equipment that has previously processed beta lactams, an acceptance criteria should be established at a "no detect" level. It is also essential that the analytical methods be sufficiently sensitive. It should be noted that others have decontaminated equipment and even facilities with an analytical method sensitivity as low as 0.6 nanograms per cm^2.

Mechanical transfer is where residues on non-product contact surfaces are transferred to another product/process via equipment, materials, wastes and people transiting the facility. For example, residue on an employee's gowning could fall off the gowning into the next product's process if the gown is not changed. Clearly the best way to minimize mechanical transfer is to contain the compound/powders within the process. If the powder does not get out of the process, it is not available to get into another product/process. This is an area where many current facilities, which manufacture beta lactams, could use improve-

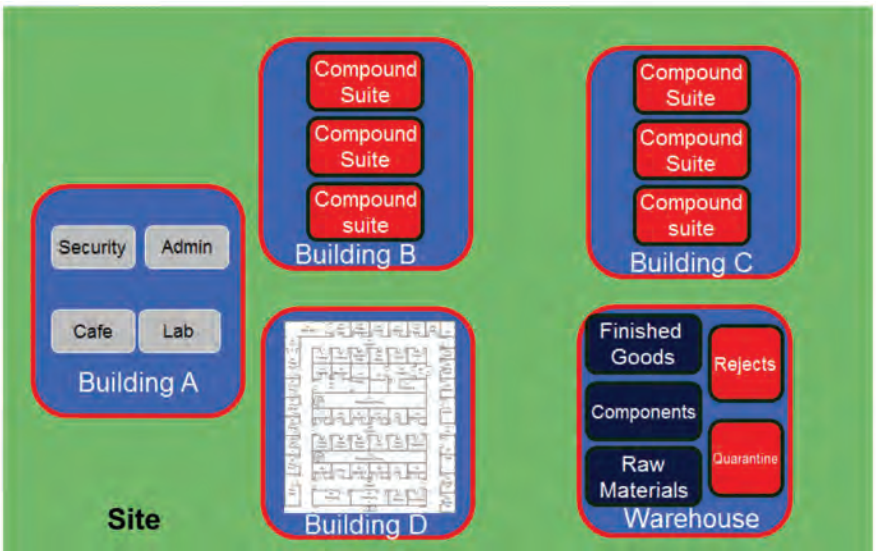

Figure 1. Typical site layout.

ment. Many facilities dedicated to producing beta lactams do not consider the impact of open processing and powder leakage/residues within the facility as a potential source of cross-contamination outside the facility via mechanical transfer. If a site is dedicated to manufacturing one of the classes of beta lactams, there may not be a cross-contamination concern; however, there may be an employee safety and environmental issue as employees may inadvertently transfer residues outside the site and even into their homes. An area to assess is the gowning. Is the gowning disposable? If so, is it disposed of in a manner, which limits mechanical transfer? Is the gowning reused and laundered? Is it laundered on site or off site? If it is laundered off site, how do you ensure that the laundry service is not mechanically transferring residues? Is it laundered separately? If you launder on site, do you have dedicated washers and dryers? If not, how does one ensure that there is no mechanical transfer from the laundering process? How do you control that it is laundered according to SOPs each time? Another area to assess is materials and wastes that are entering/exiting the processing facility. Are there residues on these items that could be mechanically transferred to other products or materials?

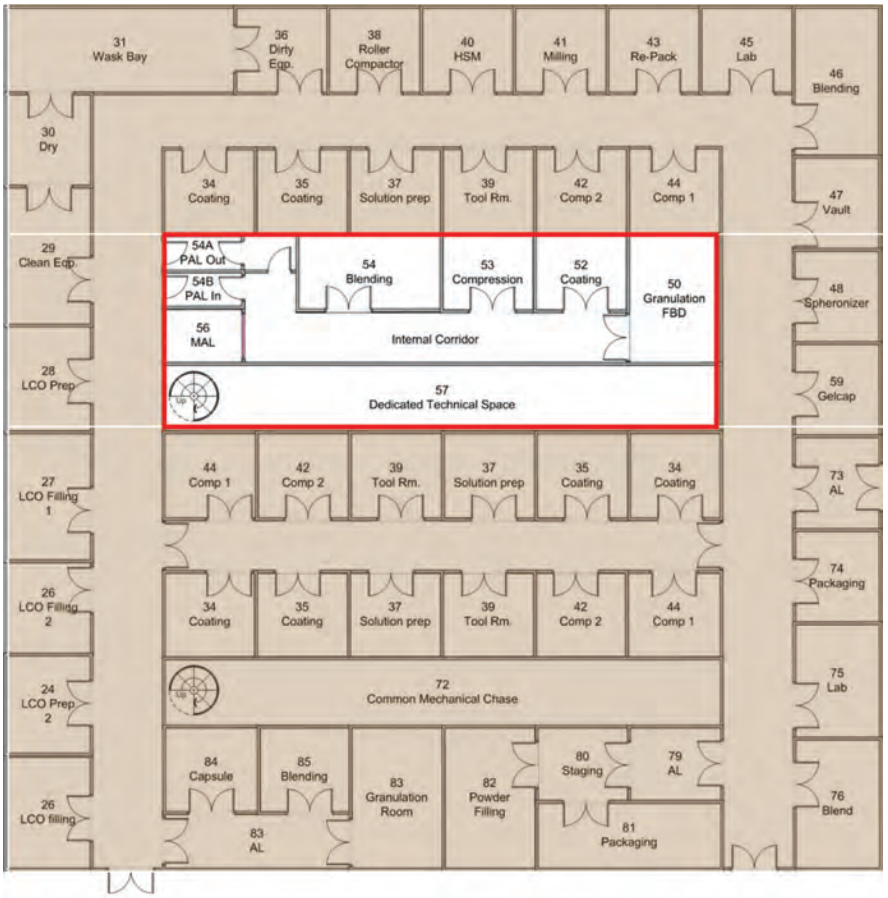

Figure 2. Dedicated and segregated suite within a multi-purpose facility.

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Airborne transfer is where airborne particulate is transferred to another product/process either directly in air or by re-aerosolization of sedimented particulate. Similar to mechanical transfer, the best way to minimize airborne transfer is to contain the compound/powders within the process. When dealing with either a separate building or a segregated area in a multi-product site or building as the compound boundary an assessment of the incoming and exhaust air as well as the pressure gradient is needed to ensure the risk of cross contamination by the airborne route is controlled. The incoming air requires filtration. The most common approach is to filter the incoming air as well as the exhaust air. As these filters are considered critical controls for cross contamination control, they should be dynamically monitored.

Having controls in place to manage the risk of cross-contamination by any of the four modes is just one piece of the process. Routine performance monitoring is also required to ensure that the risk of cross-contamination continues to be managed to acceptable levels. There are various schools of thought on exactly what routine performance monitoring for the risk of cross-contamination entails. One idea is to provide monitoring which

should include alarms for all the controls that manage the risk such as:

- Electronic access control for mix-up
- Cleaning verification for retention
- Containment of closed systems for mechanical and air-borne transfer
- Pressure gradient for mechanical and airborne transfer
- Filter performance for airborne transfer
- SOP adherence for gowning, wipe down of materials/equipment, mix-up, cleaning processes, filter change out, etc.

The other school is to routinely perform actual air sampling, swab sampling, and even surrogate/placebo testing to assess the operation of all the systems to manage the risk of cross-contamination. Whichever option is used, a justification is required as to why the chosen option is appropriate.

In conclusion, simply following the requirements of the recent FDA Guidance to Industry on Non-Penicillin Beta Lactam Drugs is not enough to manage the risk of cross-contamination when these products are produced on sites that manufacture multiple products including more than one class of the beta lactams. A risk assessment of all four modes of cross-contamination is necessary to show that the risk is being managed to acceptable levels. ISPE's Risk-MaPP Baseline® Guide is an essential tool for assessing the risk of cross-contamination.

About the Author

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