Appendix A: Chemical Structures of Representative β-Lactam Compounds

β-Lactam Compounds

β-lactam antibacterial drugs, including penicillin and the non-penicillin classes, share a basic chemical structure that includes a three-carbon, one-nitrogen cyclic amide structure known as the β-lactam ring. The side chain associated with the β-lactam ring is a variable group that contributes to antibacterial activity. (Appendix A shows the chemical structures of some beta-lactam compounds.)

β-Lactam Antibacterial Drugs

Currently, β-lactam antibacterial drugs include:

- Penicillins (e.g., ampicillin, oxacillin)
- Cephalosporins (e.g., cephalexin, cefaclor)
- Penems (e.g., imipenem, meropenem)
- Monobactams (e.g., aztreonam)

Further similarities between **non-penicillin β-lactam antibacterial** drugs and penicillins are as follows:

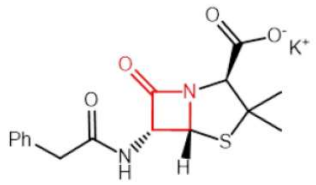
- It is difficult to define the minimal dose below which allergic responses are unlikely to occur in humans (Dayan 1993; Blanca et al. 1996)
- There is a lack of suitable animal or receptor testing models that are predictive of human sensitivity (Olson et al. 2000)
- The threshold dose at which allergenic response could occur is extremely low and difficult to detect with commonly used analytical methods (Perez Pimiento et al. 1998; Shepard 1991)
- The manufacturing operations of any class of non-penicillin β-lactam antibacterial drugs should be completely and comprehensively separated from areas in which any other drugs for human use are manufactured, including any other class of β-lactam antibiotics. This separation includes independent air handling systems. Manufacturing operations that are restricted solely to products within a specific class of non-penicillin β-lactam antibacterial drugs (e.g., cephalosporins) generally would not mandate separate facilities and air handling systems for each of those products; production campaigning in the same facility and appropriate cleaning (including qualification to demonstrate removal of β-lactams) after each campaign may be sufficient to prevent cross-contamination.

Non-Antibacterial β-Lactam Compounds

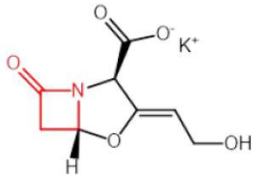
- β-lactamase inhibitors
- β-lactam intermediates and derivatives
- Other products containing a β-lactam structure

The β-lactam ring (shown in red on the figures below) can result in widely varying molecular structures having a sensitizing potential. Cross-contamination occurring during the manufacture of any of these compounds could pose a potentially life-threatening health risk to patients.

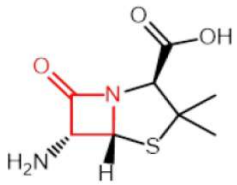
Penicillin G Potassium (beta-lactam antibacterial drug)
Monopotassium (2S,5R,6R)-3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate



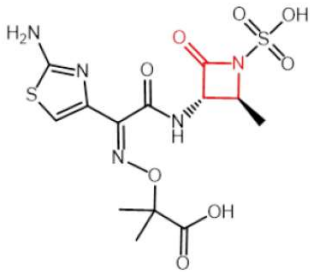
Clavulanate Potassium (beta-lactamase inhibitor)
Potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate



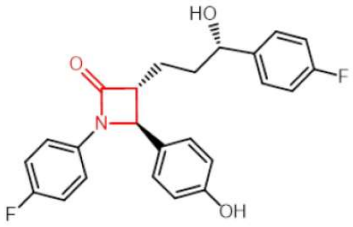
6-aminopenicillanic acid (intermediate)
(2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid



Aztreonam (non-penicillin beta-lactam antibacterial drug)
(Z)-2-{[[[2-Amino-4-thiazolyl]{[(2S,3S)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]carbamoyl]methylene]amino}oxy)-2-methylpropionic acid



Ezetimibe (non-antibacterial beta-lactam compound)
(3R,4S)-1-(4-Fluorophenyl)-3-[(S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-azetidin-2-one



APPENDIX B: Design Features and Controls to Prevent Cross-Contamination[1]

When considering alternative strategies to prevent cross-contamination with non-antibacterial β-lactam compounds, the appropriate combination of controls depends on various factors such as the state of material (e.g., liquid, powder), stage of manufacturing (e.g., incoming sampling, blending, filling and sealing), and the dosage form.[2] Design features and control approaches that manufacturers should consider implementing to prevent cross-contamination include, but are not limited, to:

- Integration of a series of design provisions and controls to form a robust holistic contamination prevention system, rather than implementing controls in a piecemeal fashion, or relying on one single design or control element.
- Use of closed systems, such as an isolator with its own air handling system, and the use of adequate dust control removal systems from exhaust air from rooms and use of air purification systems such as the use of high-efficiency particulate air filters (or better) on exhaust ducts.
- Separation and containment of different manufacturing processes or process steps; use of barrier technology, including glove boxes.
- Maintaining adequate pressure differentials, in tandem with use of airlocks, between areas manufacturing non-antibacterial β-lactam compounds and those manufacturing non-β-lactam drugs.
- Segregated suite of rooms and other facility design features to create redundancy of separation.
- Use of dedicated equipment and air systems.
- Establishing rigorous and validated monitoring, cleaning, and decontamination procedures including routine verification surface testing using appropriate acceptance criteria for residual levels of the specific non-antibacterial β-lactam compound. Modern methods with appropriate levels of sensitivity should be used.[3]
- Use of measures to deactivate the β-lactam ring structure (i.e., breaking the ring) to further reduce the risk of cross-contamination from residual β-lactam levels that could be present below the limit of detection of analytical methods.
- Dedicated personnel and control of material and personnel movement (e.g., staff entries and exits).
- Procedures for maintenance personnel and contractors regarding garment and decontamination controls if they are working in, and moving between, multiple areas where β-lactams may be present.
- Strict controls over cross-over points for personnel, products, waste, materials, and equipment.
- Examination and testing of environment for potential cross-contamination routes.
- Quality control testing of non-β-lactam drugs for potential β-lactam contamination at adequate detection levels at stages of manufacturing determined by a risk assessment to be susceptible to

cross-contamination; however, testing for the presence of β-lactams in drugs or the manufacturing environment is not a substitute for adequate control systems.

- Procedural controls to prevent mix-ups of materials and products.
- Risk assessment of changes in manufacturing products/processes, introduction of new products, and procedures in the event of a breach of controls.

[1] This appendix is intended as a resource for developing alternative facility design and control strategies for preventing cross-contamination involving non-antibacterial β-lactam manufacturing operations. Some of the measures discussed could also be part of a strategy involving complete and comprehensive separation that should be used to prevent cross-contamination involving non-penicillin β-lactam antibacterial manufacturing operations.

[2] As an example, see ISPE (International Society for Pharmaceutical Engineering) Baseline Guide Volume 7, Risk-Based Manufacture of Pharmaceutical Products (2010) for additional discussions about sources of cross-contamination, procedures for assessing risks associated with cross-contamination, and strategies-including analyses of options for manufacturing controls-for mitigating this risk.

[3] C Qiu, H Zhu, C Ruzicka, D Keire, and H Ye, 2018, A General LC-MS/MS Method for Monitoring Potential β-Lactam Contamination in Drugs and Drug-Manufacturing Surfaces, AAPS J, 20(4):70, published May 15, 2018, doi:10.1208/s12248-018-0224-7.

If a reasonable possibility exists that a non-β-lactam drug has been cross-contaminated with a non-antibacterial β-lactam compound, the non-β-lactam drug(s) should be tested for the presence of β-lactam and should not be marketed if detectable levels are found.

Reference:

ISPE Non-Penicillin β-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination, Jun2022 (Ver01)