Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmaceutical Quality/Manufacturing Standards (CGMP)
Revision 1

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TABLE OF CONTENTS

Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes methods, facility design elements, and controls that are important in preventing drugs[2] from being cross-contaminated with compounds containing a beta-lactam ring.[3] This guidance also provides information regarding the relative health risk of, and the potential for, cross-reactivity in the classes of non-penicillin beta-lactam antibacterial drugs and non-antibacterial beta-lactam compounds.[4]

This guidance recommends complete and comprehensive separation[5] of the manufacturing operations of non-penicillin beta-lactam antibacterial drugs from the manufacturing operations of other drugs. For manufacturers of non-antibacterial beta-lactam compounds, this guidance provides recommendations on cross-contamination prevention strategies, including examples of relevant design features and control approaches for those seeking to justify a cross-contamination prevention strategy other than complete and comprehensive separation when appropriate.

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purpose of this guidance, the term *drugs* includes biological products.

[3] See Appendix A, Chemical Structures of Representative Beta-Lactam Compounds.

[4] For the purposes of this guidance, the term *non-penicillin beta-lactam antibacterial drug(s)* refers to any drug that is not a penicillin, has a chemical structure that includes one or more beta-lactam rings, and has an antibacterial mechanism of action. The term *non-antibacterial beta-lactam compound(s)* refers to any compound, including an intermediate or derivative, that is not a penicillin, has a chemical structure that includes one or more beta-lactam rings, and has a mechanism of action other than an antibacterial mechanism of action.

[5] See the definition of *complete and comprehensive separation* in the Glossary.

Penicillin can be a sensitizing agent that triggers hypersensitivity or an allergic reaction in some people.[6] Drug cross-contamination is the contamination of one drug with one or more different drugs or compounds. Accordingly, facilities and controls must be designed to prevent cross-contamination of other drugs with penicillin in accordance with the current good manufacturing practice (CGMP) regulations (i.e., 21 CFR 211.42(d), 21 CFR 211.46(d), and 21 CFR 211.176). Because non-penicillin beta-lactam antibacterial drugs and non-antibacterial beta-lactam compounds can also be sensitizing agents, drug cross-contamination with such compounds could initiate the same types of drug-induced life-threatening allergic reactions that penicillins can trigger. Therefore, manufacturers handling any non-penicillin beta-lactam antibacterial drugs or non-antibacterial beta-lactam compounds should treat such drugs or compounds similarly to penicillin to prevent cross-contamination, thereby reducing the potential for drug-induced, life-threatening allergic reactions.

The information in this guidance is intended for human drug manufacturers (including finished pharmaceutical manufacturers, active pharmaceutical ingredient (API) manufacturers, re-packagers, and outsourcing facilities[7]) with operations that include one or more beta-lactam compounds.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

This guidance revises the guidance for industry of the same title issued in April 2013. When finalized, this guidance will replace the April 2013 guidance. Significant changes from the 2013 guidance include:

[6] The term *sensitizing* (allergenic) is commonly used in guidances for industry in discussions related to immunology.

[7] Section 503B of the Federal Food, Drug, and Cosmetic Act describes the conditions that must be satisfied for drug products compounded by a registered outsourcing facility to be exempt from certain statutory requirements. For the purposes of this guidance and for outsourcing facilities only, *processing of* beta-lactam compounds does not refer to mixing, reconstituting, or other such acts performed in accordance with directions contained in the manufacturer's approved labeling and other manufacturer directions consistent with that labeling at the immediate point of dispensing for administration to the intended patient if these limited activities are performed via closed fluid-pathway, single-use sterile transfer devices under appropriate local containment controls to prevent facility exposure to beta-lactam compounds. Although use of these sterile transfer devices (accomplishing transfers through the use of needles and needleless connectors) greatly mitigates risk of lost containment while preparing a drug in accordance with labeled directions, it is possible that breakage or spillage of the content of a pharmacy bulk package occurs. To prevent the risk of facility (e.g., surfaces, air) and product contamination with beta-lactam compounds, the outsourcing facility should have in place additional containment strategies, including restricting all preparation activities to only dedicated isolators, barrier units, or containment hoods to strictly localize any potential exposure. Use of appropriate procedures is also essential, including employing detailed steps for managing any localized aerosolization from a breakage/spillage incident by immediate and thorough decontamination with beta-lactam inactivating cleaning agent(s). The containment and decontamination procedures should be validated for their intended purposes of strictly preventing cross-contamination with beta-lactam compounds.

- Clarifying that the scope of the guidance also includes all compounds, including intermediates or derivatives, that are not a penicillin, have a chemical structure that includes one or more beta-lactam rings, and have a mechanism of action other than an antibacterial mechanism of action

- Providing FDA's interpretation of terms, such as *allergic reaction*, *cross-reactivity*, and *complete and comprehensive separation*, used in this guidance

- Clarifying the distinction between non-penicillin beta-lactam antibacterial drug(s) and non-antibacterial beta-lactam compound(s) — in terms of the cross-contamination and patient exposure risks and the strategies appropriate for manufacturing operations involving each category

- Providing recommendations for drug manufacturers that seek to justify alternative cross-contamination prevention strategies for non-antibacterial beta-lactam compounds

II. BACKGROUND

A. Regulatory Framework

Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) requires that drugs (including APIs) be manufactured in compliance with CGMP. Drugs that are not manufactured in compliance with CGMP are considered adulterated. Furthermore, manufacturers of finished pharmaceuticals are required to comply with the CGMP regulations at 21 CFR parts 210 and 211.

Several CGMP requirements for finished pharmaceuticals address facility and equipment design, controls, and cleaning. For example, regarding design and construction features, § 211.42(c) requires building and facility provisions in general to prevent cross-contamination of drug products. Specifically, the regulation states that "[t]here shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups . . . ."

With respect to penicillin, § 211.42(d) requires that "[o]perations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use." [8]

Similarly, § 211.46(d) requires air-handling systems for the manufacture, processing, and packing of penicillin to be completely separated from those for other drugs for human use. Additionally, § 211.176 requires manufacturers to test non-penicillin drug products for penicillin

[8] See the definition of *complete and comprehensive separation* in the Glossary.

where the possibility of cross-contamination exists and prohibits manufacturers from marketing such drugs if detectable levels of penicillin are found.[9]

Although FDA has not issued CGMP regulations specific to APIs, section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act requires all drugs (including APIs) to be manufactured in compliance with CGMP. FDA recommends that drug manufacturers follow the International Council for Harmonisation (ICH) guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016).[10] Because some APIs are sensitizing compounds that may cause anaphylactic reactions, preventing cross-contamination in APIs is as important as preventing cross-contamination in finished drug products. Accordingly, ICH Q7 recommends using dedicated production areas, which can include facilities, air handling equipment, and processing equipment, in the production of highly sensitizing materials, such as penicillins and non-penicillin beta-lactam antibacterial drugs like cephalosporins.[11]

B. Beta-Lactam Compounds

Beta-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 beta-lactam ring. The side chain associated with the beta-lactam ring is a variable group that contributes to antibacterial activity. (Appendix A shows the chemical structures of some beta-lactam compounds.)

The beta-lactam ring and side chains are also responsible for the allergenic properties of beta-lactam antibacterial drugs. These structures can induce the formation of antigenic determinants that lead to the production of specific immunoglobulin E (IgE) antibodies that can induce Type 1 hypersensitivity (allergic) reactions in susceptible individuals.

There are compounds other than beta-lactam antibacterial drugs that contain the beta-lactam ring. Some of these compounds are derivatives and intermediates used or produced in the manufacture of beta-lactam drugs. Some beta-lactamase inhibitors contain a beta-lactam ring, as do some drugs that have no antibacterial activity, such as certain lipid-lowering and antiviral drugs.

Like beta-lactam antibacterial drugs, non-antibacterial compounds containing a beta-lactam ring could have similar sensitizing and allergenic properties and may pose a significant health risk to patients. For many beta-lactam compounds the immunopathological mechanisms leading to cross-reactivity and hypersensitivity reactions have not been studied extensively or are not well understood. This, and the combined effect of multiple variables (e.g., dosage forms, patient

[9] See "A Review of Procedures for the Detection of Residual Penicillins in Drugs" (Appendix I, *Procedures for Detecting and Measuring Penicillin Contamination in Drugs*, FDA By-Lines No. 8 (November 1977)). Alternative validated test methods to detect penicillin residues may be used if demonstrated to be equivalent to or better than the referenced method. For example, the LC-MS/MS method has been validated for detecting several beta-lactam compounds, and could be validated for detecting others as well (Qiu et al. 2018).

[10] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[11] See section IV.D Containment (4.4) of ICH Q7.

history of sensitization, differences in pharmacokinetics), make it difficult to determine the sensitizing potential of many beta-lactam compounds. Nevertheless, the potential life-threatening hazard associated with beta-lactam compounds indicates that manufacturers should establish beta-lactam manufacturing operations that are completely and comprehensively separate from those of other drugs, to prevent cross-contamination.

1. Beta-Lactam Antibacterial Drugs

Currently, beta-lactam antibacterial drugs include:

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

Beta-lactam antibacterial drugs display properties of cross-reactivity, in which the secondary exposure need not be to the same compound. For example, patients with a history of hypersensitivity to a drug in one of the above classes, for example penicillin, may also experience an IgE-mediated reaction to a drug in another class, such as cephalosporins and penems (Saxon et al. 1988; Saxon et al. 1987; Prescott et al. 2004).

Although the frequency of allergic reactions due to cross-reactivity between beta-lactam classes can be lower than the risk within a class (Salkind et al. 2001), the hazard posed still may be life-threatening (Khan and Solensky 2010). Further similarities between non-penicillin beta-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)

Although beta-lactam antibacterial drugs may be chemically similar, they can differ in pharmacokinetics, antibacterial activity, and the potential to cause serious allergic reactions (Bernstein et al. 2008). It is clinically difficult to determine the occurrence and rate of allergic cross-reactivity among beta-lactam antibacterial drugs in humans. Therefore, undiagnosed or underreported cases of cross-reactivity may exist. Some beta-lactam antibacterial drugs may have negligible potential for cross-reactivity with beta-lactam antibacterial drugs of other classes, whereas beta-lactam derivatives may potentially exhibit sensitizing activity before the incorporation of side chains that confer antibacterial activity. Regardless of the rate of cross-reactivity among beta-lactam antibacterial drugs or the mechanism of action by which such cross-reactivity may occur, a potential health risk to patients — life-threatening anaphylaxis —

can result from cross-contamination among all classes of drugs and compounds containing a beta-lactam ring.[12]

2. Non-Antibacterial Beta-Lactam Compounds

a. Beta-lactamase inhibitors

Beta-lactam compounds such as clavulanic acid, tazobactam, and sulbactam are irreversible inhibitors of many beta-lactamases. These compounds, which are potential sensitizing agents, are typically used in combination with specific beta-lactam compounds to reduce degradation and preserve antibacterial activity (e.g., amoxicillin-clavulanate, piperacillin-tazobactam). Because beta-lactamase inhibitors typically are used in combination with specific beta-lactam antibacterial drugs, clinical observations of hypersensitivity reactions may be attributed to the beta-lactam antibacterial component rather than to the beta-lactamase inhibitor. Yet hypersensitivity reactions to clavulanic acid are reported in the literature, sometimes in the absence of a hypersensitivity reaction to the co-administered beta-lactam antibacterial drug, amoxicillin (Salas et al. 2017).

b. Beta-lactam intermediates and derivatives

Some beta-lactam intermediate compounds and derivatives possess similar sensitization and cross-reactivity properties to those of beta-lactam compounds. Beta-lactam intermediate compounds usually are precursor materials that undergo molecular change or purification before they are used in the manufacture of beta-lactam APIs. As a result of these molecular changes, intermediate compounds containing a beta-lactam ring in their structures may be recognized by the immune system as an antigen that triggers an allergic response. For example, 6-aminopenicillanic acid (6-APA) serves as the intermediate for the formation of all synthetic penicillins that are formed by attaching various side chains. The structure of 6-APA includes beta-lactam and thiazolidine rings. The beta-lactam ring is relatively unstable and can open. In the case of 6-APA, the opening of the beta-lactam ring leads to the formation of a penicilloyl moiety, which is the major antigenic determinant of penicillin. This moiety is thought to be a common cause of penicillin urticarial reaction (Çelik et al. 2008).

Beta-lactam derivatives are by-products that may arise during manufacturing (i.e., an impurity or degradant) that include a beta-lactam ring structure. Like intermediates, beta-lactam derivatives could have sensitizing properties and may develop antigenic properties that can produce allergic reactions. Beta-lactam manufacturing processes (e.g., fermentation and synthesis) may create beta-lactam intermediates or derivatives with unknown health consequences.

[12] After reviewing relevant scientific and medical literature, FDA determined that the relative risk of cross-reactivity associated with aztreonam, when compared to other beta-lactams, is a matter of scientific uncertainty. Recently there is an increased body of evidence in published scientific literature describing that patients with ceftazadine hypersensitivity can experience cross-reactivity to aztreonam. Accordingly, this guidance does not recommend manufacturing controls that treat aztreonam differently from other beta-lactam drugs. As with any nonbinding recommendations offered in guidance to industry, manufacturers can use an alternative approach if the alternative approach satisfies the requirements of the applicable statutes and regulations. Manufacturers should discuss with FDA as early as possible about alternative separation designs and control strategies for a non-penicillin beta-lactam monobactam, such as aztreonam.

c. Other products containing a beta-lactam structure

As discussed above, compounds containing a beta-lactam ring have a sensitizing potential, and subsequent exposure to those compounds or related compounds due to cross-contamination may result in severe allergic reactions in some patients. Therefore, manufacturers should manage the risk of cross-contamination throughout the products' life cycles, not only non-penicillin beta-lactam antibacterial drugs, but also products with no antibacterial activity that may be potential sources of a beta-lactam ring (e.g., degradants that contain a beta-lactam ring even though the parent compound may not).

III. RECOMMENDATIONS

Because of the potential health risks of cross-reactivity and hypersensitivity reactions associated with beta-lactam compounds, manufacturers' risk management strategies should include stringent controls to prevent cross-contamination.

The risks associated with the cross-reactivity of beta-lactam antibacterial drugs have been described (Terico and Gallagher 2014; Joint Task Force on Practice Parameters 2010; Çelik et al. 2008); however, the risks associated with the cross-reactivity of non-antibacterial beta-lactam compounds are less well understood. Accordingly, FDA addresses beta-lactam antibacterial drugs and non-penicillin beta-lactam compounds separately in this guidance. Specific recommendations for beta-lactam antibacterial drugs and non-antibacterial beta-lactam compounds are further detailed below.

A. Non-Penicillin Beta-Lactam Antibacterial Drugs

The manufacturing operations of any class of non-penicillin beta-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 beta-lactam antibiotics. This separation includes independent air handling systems. Manufacturing operations that are restricted solely to products within a specific class of non-penicillin beta-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 beta-lactams) after each campaign may be sufficient to prevent cross-contamination.

B. Non-Antibacterial Beta-Lactam Compounds

As with non-penicillin beta-lactam antibacterial drugs, non-antibacterial beta-lactam compounds have the potential to induce allergic reactions. Similar difficulties exist in characterizing and quantifying the potential health risks posed by non-antibacterial beta-lactam compounds (i.e., defining the minimal dose below which allergic responses are unlikely to occur in humans, lack of suitable animal or receptor testing models predictive of human sensitivity, and the likelihood that the threshold dose for human allergenic response could be extremely low and difficult to

detect with current analytical methods). Nevertheless, consideration should be given to the potential health risks that may be life-threatening. Thus, when there is uncertainty regarding the risks associated with non-antibacterial beta-lactam compounds, or there is a known risk of adverse effect in patients, FDA recommends that drug manufacturers implement a complete and comprehensive separation cross-contamination prevention strategy, as is recommended for non-penicillin beta-lactam antibacterial drugs, to prevent beta-lactam cross-contamination.

However, there may be conditions under which manufacturers may justify the use of alternative cross-contamination prevention strategies for certain non-antibacterial beta-lactam compounds.[13] For example, non-antibacterial beta-lactam compounds can have widely varying molecular structures, and there may be cases where direct studies have shown no incidence of, or exceedingly low potential for, adverse events involving hypersensitivity or allergic reactions in patients. In such cases, if a manufacturer considers a prevention strategy other than complete and comprehensive separation to suffice, robust data to support no incidence or a clear threshold below which adverse reactions are exceedingly unlikely to occur should be available for FDA assessment. An extensive body of data to evaluate this potential approach can include in vitro data, animal studies, clinical studies,[14] experience with related products, and published scientific literature. Manufacturers should use appropriate risk management tools to assess the risks and to design and implement prevention strategies that prevent cross-contamination and mix-ups. This would include consideration of a combination of rigorous facility design, segregation, process, and procedural controls, and ongoing life cycle risk review.[15] Examples of such design and controls provisions are provided in Appendix B.

[13] See the definition of *control strategy* in the Glossary.

[14] If a clinical investigation is necessary to demonstrate the safety or effectiveness of a proposed drug product, generally this type of study goes beyond the scope of information that may be relied upon as necessary for approval of an abbreviated new drug application.

[15] Consideration of alternative cross-contamination prevention strategies will be subject to assessment by FDA, on a case-by-case basis, at the time of application review.

GLOSSARY

Allergic reaction: An immunologic reaction experienced by an individual to a drug or compound mediated by a number of mechanisms, including, for example, IgE-mediated activation of mast cells and basophils; direct activation of mast cells and basophils; sensitized T-cell-induced inflammation; complement activation; contact system activation; or coagulation system activation. In any given patient, exposure to a drug or compound may trigger an allergic reaction caused by more than one mechanism. Allergic reactions may be life-threatening events, such as anaphylaxis and other syndromes associated with cardiovascular collapse and death.

Complete and comprehensive separation: A cross-contamination prevention strategy that consists of: (1) the complete physical separation of beta-lactam production area(s) (including separate air handling system(s)) from production areas for other drugs; and (2) additional design and procedural controls for facilities, equipment, material, and personnel that are necessary to support and maintain the integrity of the physical separation (e.g., dedicated equipment; utilities management (waste flow, including the potential for beta-lactam production exhaust to contaminate an adjacent building air intake, vacuum systems); people/material/equipment flow; personnel gowning, decontamination; monitoring containment; testing; compliance with procedures; investigations). It is required by regulation for penicillin manufacturing, including § 211.42(d): separation of facility and equipment, and § 211.46(d): separate air handling systems, and it is recommended to prevent cross-contamination with other non-penicillin and non-antibacterial beta-lactam drugs and compounds. The essential element and foundation of this strategy is complete physical separation (i.e., "isolation and sealing off") as described in paragraph 142 of the preamble to the final rule, "Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding" (43 FR 45014 at 45038, September 29, 1978):

> Separation can be achieved . . . by effectively isolating and sealing off from one another these two types of operations. This does not necessarily mean separation by geographical distance or the placement of these operations in separate buildings. Effective means can almost certainly be developed to separate such activities from one another to prevent cross-contamination problems within a single building.

In other words, although separate buildings would ensure separation of beta-lactam operations from non-beta-lactam operations, it is feasible for one building to contain a dedicated area for beta-lactam manufacturing that is completely isolated and sealed off from the rest of the building. For example, separate entries and exits to the beta-lactam segment of the building would be necessary to ensure comprehensive separation. In the limited cases in which this design concept could be considered, a risk assessment should demonstrate that the design provides as much protection against cross-contamination as is achieved by manufacturing in a separate building.

Control strategy: As defined in the ICH guidances for industry *Q8(R2) Pharmaceutical Development* (November 2009), *Q10 Pharmaceutical Quality System* (April 2009), and *Q11 Development and Manufacture of Drug Substances* (November 2012), a control strategy is established through use of quality risk management and consists of a planned set of controls that ensure process performance and product quality. These controls can be related to facility and

equipment operating conditions, monitoring and testing of incoming materials, process performance and product quality, and personnel following procedures.

As stated above, *complete and comprehensive separation* is itself both a facility design strategy and a control strategy for preventing beta-lactam cross-contamination. In the sense that the strategy consists of complete segregation of manufacturing operations, it is unique among cross-contamination prevention strategies, distinguished from those *alternative strategies* that would be employed in shared or multiuse facilities. Alternative strategies rely primarily on design and procedural controls involving facilities, equipment, material, and personnel, and do not necessarily include the physical separation of manufacturing areas.

Cross-reactivity: The process by which a compound induces a hypersensitivity immune response, such as an allergic reaction, due to the sensitizing effects of a prior exposure to a different, but chemically related, antigen. Also referred to as *cross-sensitivity* or *cross-sensitization*.

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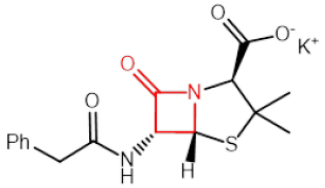
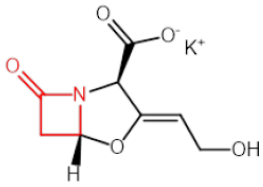
APPENDIX A: CHEMICAL STRUCTURES OF REPRESENTATIVE BETA-LACTAM COMPOUNDS

The beta-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.

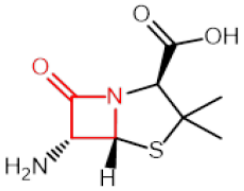
Penicillin G Potassium (beta-lactam antibacterial drug)
Monopotassium (2S,5R,6R)-3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate



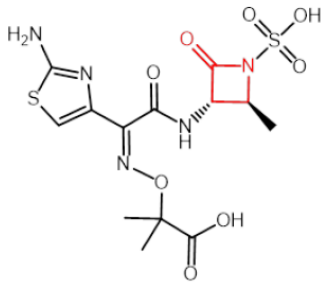
Clavulanate Potassium (beta-lactamase inhibitor)
Potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate



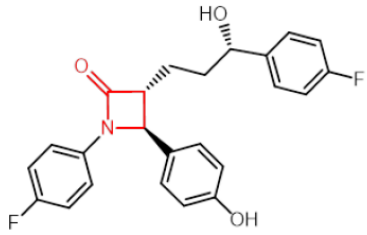
6-aminopenicillanic acid (intermediate)
(2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid



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 beta-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 beta-lactam compounds and those manufacturing non-beta-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

[1] This appendix is intended as a resource for developing alternative facility design and control strategies for preventing cross-contamination involving non-antibacterial beta-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 beta-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.

criteria for residual levels of the specific non-antibacterial beta-lactam compound. Modern methods with appropriate levels of sensitivity should be used.[3]

- Use of measures to deactivate the beta-lactam ring structure (i.e., breaking the ring) to further reduce the risk of cross-contamination from residual beta-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 beta-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-beta-lactam drugs for potential beta-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 beta-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.

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

[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.