
Guidance for Industry

Non-Penicillin Beta-Lactam

Drugs:

A CGMP Framework for
Preventing Cross-
Contamination

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

April 2013
Current Good Manufacturing Practices (CGMPs)

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Guidance for Industry¹

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I. INTRODUCTION

This guidance describes the importance of implementing manufacturing controls to prevent cross-contamination of finished pharmaceuticals and active pharmaceutical ingredients (APIs) with non-penicillin beta-lactam drugs. This guidance also provides information regarding the relative health risk of, and the potential for, cross-reactivity in the classes of sensitizing beta-lactams (including both penicillins and non-penicillin beta-lactams). Finally, this guidance clarifies that manufacturers generally should utilize separate facilities for the manufacture of non-penicillin beta-lactams because those compounds pose health risks associated with cross-reactivity.

Drug cross-contamination is the contamination of one drug with one or more different drugs. Penicillin can be a sensitizing agent that triggers a hypersensitive exaggerated allergic immune response in some people. Accordingly, implementing methods for preventing cross-contamination of other drugs with penicillin is a key element of manufacturing penicillin and current good manufacturing practice (CGMP) regulations require the use of such methods. See, e.g., 21 CFR §§ 211.42(d), 211.46(d), and 211.176. Non-penicillin beta-lactam drugs also may be sensitizing agents and cross-contamination with non-penicillin beta-lactam drugs can initiate the same types of drug-induced hypersensitivity reactions that penicillins can trigger, including life-threatening allergic reactions. Therefore, manufacturers of non-penicillin beta-lactam drugs should employ similar control strategies to prevent cross-contamination, thereby reducing the potential for drug-induced, life-threatening allergic reactions.

The information in this guidance is intended for manufacturers of finished pharmaceuticals and APIs, including repackagers. Other establishments that handle drugs, such as pharmacy compounders, may find this information useful.

¹ This guidance was developed by the Office of Compliance, Office of Manufacturing and Product Quality, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidance means that something is suggested or recommended, but not required.

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, with few exceptions, all drugs be manufactured in compliance with current good manufacturing practices (CGMPs). Drugs that are not in compliance with CGMPs are considered to be adulterated. Furthermore, finished pharmaceuticals are required to comply with the CGMP regulations at 21 CFR parts 210 and 211.

Several CGMP regulations directly address facility and equipment controls and cleaning. For example, § 211.42(c) requires building and facility controls in general to prevent cross-contamination of drug products. Specifically, the regulation states, “[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 mix-ups” during manufacturing, processing, packaging, storage, and holding.

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.” However, FDA has clarified that separate buildings may not be necessary, provided that the section of the manufacturing facility dedicated to manufacturing penicillin is isolated (i.e., completely and comprehensively separated) from the areas of the facility in which non-penicillin products are manufactured.² Under § 211.46(d), manufacturers must completely separate air handling systems for penicillin from those used for other drugs for human use. Additionally, § 211.176 requires manufacturers to test non-penicillin drug products for penicillin where the possibility of exposure to cross-contamination exists, and prohibits manufacturers from marketing such products if detectable levels of penicillin are found.³

Although FDA has not issued CGMP regulations specific to APIs, the Agency has provided guidance to API manufacturers in the guidance for industry, ICH⁴ Q7, *Good Manufacturing*

² Preamble to the final rule, “Current Good Manufacturing Practice, Processing, Packing, or Holding.” 43 FR 45014 at 45038 (September 29, 1978).

³ 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)), available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM095812.pdf>. NB: This link works as of 5/18/2012.

⁴ International Conference on Harmonization.

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Practice Guidance for Active Pharmaceutical Ingredients (ICH Q7 guidance).⁵ Because some APIs are sensitizing compounds that may cause anaphylactic shock, preventing cross-contamination in APIs is as important as preventing cross-contamination in finished products. The ICH Q7 guidance 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 cephalosporins.⁶

B. Beta-Lactam Antibiotics

Beta-lactam antibiotics, including penicillins and the non-penicillin classes, share a basic chemical structure that includes a three-carbon, one-nitrogen cyclic amine structure known as the beta-lactam ring. The side chain associated with the beta-lactam ring is a variable group attached to the core structure by a peptide bond; the side chain variability contributes to antibacterial activity. As of the date of this publication, FDA has approved over 34 beta-lactam compounds as active ingredients in drugs for human use.⁷ Beta-lactam antibiotics include the following five classes⁸:

- penicillins (e.g., ampicillin, oxacillin)
- cephalosporins (e.g., cephalexin, cefaclor)
- penems (e.g., imipenem, meropenem)
- carbacephems (e.g., loracarbef)
- monobactams (e.g., aztreonam)

Allergic reactions associated with penicillins and non-penicillin beta-lactams range from rashes to life-threatening anaphylaxis. Immunoglobulin E (IgE) antibodies mediate the immediate hypersensitivity reactions that are responsible for the symptoms of hay fever, asthma, hives, and anaphylactic shock. IgE-mediated hypersensitivity reactions are of primary concern because they may be associated with significant morbidity and mortality. There is evidence that patients with a history of hypersensitivity to penicillin may also experience IgE-mediated reactions to other beta-lactams, such as cephalosporins and penems.⁹

⁵ We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the Guidance Page at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁶ See section IV.D Containment (4.4) of the ICH Q7 guidance.

⁷ Approved beta-lactam antibiotics are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, generally known as the *Orange Book* (available on the Internet at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>). The *Orange Book* is searchable by active ingredient and updated as newer drug products are added.

⁸ Yao, JDC, and RC Moellering, Jr., Antibacterial agents, in *Manual of Clinical Microbiology*, 9th edition, edited by PR Murray et al., Washington D.C., ASM Press, 2007.

⁹ Saxon, A, DC Adelman, A Patel, R Hajdu, and GB Calandra, 1988, Imipenem cross-reactivity with penicillin in humans, *J Allergy Clin Immunol*, 82:213-217; Saxon, A, GN Beall, AS Rohr, and DC Adelman, 1987, Immediate hypersensitivity reactions to beta-lactam antibiotics, *Ann Intern Med*, 107(2):204-215; Prescott, Jr., WA, DD

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All non-penicillin beta-lactams also have the potential to sensitize individuals, and subsequent exposure to penicillin may result in severe allergic reactions in some patients. Although the frequency of hypersensitivity reactions due to cross-reactivity between beta-lactam classes can be lower than the risk within a class,¹⁰ the hazard posed is present¹¹ and potentially life-threatening. The potential health hazard of non-penicillin beta-lactams therefore is similar to that of penicillins. Further similarities between non-penicillin beta-lactams and penicillins are as follows:

- It is difficult to define the minimal dose below which allergic responses are unlikely to occur in humans.¹²
- There is a lack of suitable animal or receptor testing models that are predictive of human sensitivity.¹³
- The threshold dose at which allergenic response could occur is extremely low and difficult to detect with current analytical methods.¹⁴

While beta-lactam antibiotics are similar to one another in many ways, they may differ in pharmacokinetics, antibacterial activity, and potential to cause serious allergic reactions. Because allergy testing methods have not been well-validated,¹⁵ it is clinically difficult to determine the occurrence and rate of cross-reactivity between beta-lactam antibiotics in humans. Therefore, undiagnosed or underreported cases of cross-reactivity likely exist. Some beta-lactam antibiotics have negligible potential for cross-reactivity with beta-lactams of other classes, whereas other beta-lactam compounds may exhibit sensitizing activity as derivatives before the incorporation of side chains that confer antibacterial activity.

Regardless of the rate of cross-reactivity between beta-lactam drugs or the mechanism of action by which such cross-reactivity may occur, the potential health risk to patients indicates that drug

DePestel, JJ Ellis, and RE Regal, 2004, Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy, *Clin Infect Dis*, 38:1102-1107.

¹⁰ Salkind, AR, PG Cuddy, and JW Foxworth, 2001, Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy, *JAMA*, 285:2498-2505.

¹¹ Khan, D. and R Solensky, 2010, Drug Allergy, *J Allergy Clin Immunol*. 125(2): S131.

¹² Dayan, AD, 1993, Allergy to antimicrobial residues in food: assessment of the risk to man, *Vet Microbiol*, 35:213-226; Blanca, M, J Garcia, JM Vega, A Miranda, MJ Carmona et al., 1996, Anaphylaxis to penicillins after non-therapeutic exposure: an immunological investigation, *Clin Exp Allergy*, 26:335-340.

¹³ Olson, H, G Betton, D Robinson, K Thomas, A Monro et al., 2000, Concordance of the toxicity of pharmaceuticals in humans and in animals, *Regul Toxicol Pharmacol*, 32:56-67.

¹⁴ Perez Pimiento, A, M Gomez Martinez, A Minguez Mena, A Trampal Gonzalez, S de Paz Arranz, and M Rodriguez Mosquera, 1998, Aztreonam and ceftazidime: evidence of in vivo cross-allergenicity, *Allergy*, 53:624-625; Shepard, GM, 1991, Allergy to B-lactam antibiotics, *Immunol Allergy Clin North Am*, 11(3):611-633.

¹⁵ Bernstein, IL, JT Li, DI Bernstein, et al., 2008, Allergy diagnostic testing: an updated practice parameter, *Ann Allergy Asthma Immunol*, 100:S1-S148.

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manufacturers should take steps to control for the risk of cross-contamination for all beta-lactam products.¹⁶

C. Beta-Lactamase Inhibitors

Beta-lactam compounds such as clavulanic acid, tazobactam, and sulbactam have weak antibacterial activity but are irreversible inhibitors of many beta-lactamases. These compounds, which are potential sensitizing agents, are typically used in combination with specific beta-lactam agents to preserve antibacterial activity (e.g., amoxicillin-clavulanate, piperacillin-tazobactam). Because these compounds are almost always used in combination with specific beta-lactam agents, any clinical observations of hypersensitivity reactions likely would be attributed to the beta-lactam antibiotic component rather than the inhibitor. Although there have been no case reports confirming anaphylactic reactions to a beta-lactamase inhibitor that is also a beta-lactam, these compounds are potentially sensitizing agents, and manufacturers should implement controls to reduce the risk of cross-contamination with beta-lactamase inhibitors as with all other beta-lactam products.

D. Beta-Lactam Intermediates and Derivatives

Some beta-lactam intermediate compounds and derivatives also possess similar sensitization and cross-reactivity properties. Beta-lactam intermediate compounds usually are API precursor materials that undergo molecular change or purification before use in the manufacture of beta-lactam antibiotic APIs. As a result of these changes, the intermediate compounds may develop antigenic characteristics that can produce allergic reactions. 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 unbroken beta-lactam and thiazolidine rings. The beta-lactam ring is relatively unstable, and it commonly breaks open. In the case of 6-APA, this breakage 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.¹⁷ Degradation of 6-APA can also result in the formation of minor antigenic determinants, including penicilloic acids, penaldic acid, and penicillamine. Anaphylactic reactions to penicillins usually are due to the presence of IgE antibodies to minor determinants in the body. Although 6-APA is not a true antibiotic, it still carries with it a potential to induce allergenicity.

¹⁶ Following publication of the draft version of this guidance (76 FR 14024), several commenters suggested that monobactams, specifically aztreonam, have a lower risk profile than other beta-lactam products and therefore should be exempted from the separation and control recommendations set forth in this guidance. We have reviewed relevant scientific and medical literature and determined that the relative risk of cross-reactivity associated with aztreonam, when compared to other beta-lactams, is a matter of scientific uncertainty. Accordingly, at this time, FDA does not recommend manufacturing controls that treat aztreonam differently from other beta-lactam products. As with any non-binding 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 who wish to discuss an alternative separation and control strategy for a non-penicillin beta-lactam such as aztreonam with FDA are invited to do so through the application submission and review process.

¹⁷ Middleton's Allergy: Principles and Practice, 7th ed. (electronic) (2009). Chapter 68: Drug Allergy.

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Derivatives are unintended by-products that occur during the manufacturing process (i.e., an impurity or degradant). Like intermediates, beta-lactam derivatives could have sensitizing properties and may develop antigenic properties that can produce allergic reactions. Beta-lactam chemical manufacturing processes including, but not limited to, fermentation and synthesis, may create beta-lactam intermediates or derivatives with unknown health consequences. Although the health risk of sensitization and cross-reaction is difficult to predetermine for beta-lactam intermediates and derivatives and is not always well-defined, manufacturing controls intended to reduce the risk of cross-contamination should be considered for operations that produce beta-lactam intermediates or derivatives.

III. RECOMMENDATIONS

Because of the potential health risks associated with cross-reactivity (cross-sensitivity) of beta-lactams, manufacturers should assess and establish stringent controls (including appropriate facility design provisions assuring separation) to prevent cross-contamination. Just as FDA considers the separation of production facilities for penicillins to be current good manufacturing practice, FDA expects manufacturers to treat sensitizing non-penicillin beta-lactam-based products similarly. Specifically, FDA recommends that manufacturers establish appropriate separation and control systems designed to prevent two types of contamination: (1) the contamination of a non-penicillin beta-lactam by any other non-penicillin beta-lactam, and (2) the contamination of any other type of product by a non-penicillin beta-lactam. Accordingly, FDA recommends that the area in which any class of sensitizing beta-lactam is manufactured be separated from areas in which any other products are manufactured, and have an independent air handling system.

As with penicillin, the section of a facility dedicated to manufacturing a sensitizing non-penicillin beta-lactam should be isolated (i.e., completely and comprehensively separated) from areas in the facility in which other products are manufactured. This control applies to each of the five classes of sensitizing beta-lactams; the area in which any class of sensitizing beta-lactam is manufactured should be separated from areas in which any other products are manufactured, including any other class of sensitizing beta-lactam. Manufacturing that is restricted to a specific class of beta-lactam compound (e.g., the cephalosporin family of products) generally would not mandate separate facilities and air handling systems, and could permit production campaigning and cleaning as sufficient control.

Finally, as discussed above, beta-lactam intermediates and derivatives may induce allergic reactions and therefore pose risks of cross-contamination. Accordingly, firms that manufacture beta-lactam intermediates or receive them for further processing, as well as firms whose manufacturing processes result in beta-lactam derivatives, should evaluate their manufacturing operations for the possibility of cross-contamination and implement appropriate controls to reduce or mitigate the potential for cross-contamination. As with penicillin and non-penicillin beta-lactam drugs, such controls could include, but are not limited to, isolation and separation of intermediate and derivative materials, facilities, equipment, and personnel.