THE NON-PENICILLIN BETA-LACTAM DRUG CROSS CONTAMINATION PREVENTION; USFDA PERSPECTIVE

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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. 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 re-packagers. Other establishments that handle drugs, such as pharmacy compounders, may find this information useful. 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.

I. 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.

Contamination

The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.

Cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or material during production.

Containment

A process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

In regard to Ventilation; Adequate ventilation shall be provided. The ventilation system shall provide adequate product protection, personnel protection and environmental protection. Air filtration and air change rates should ensure that the defined clean area classification is attained. The air change rates should be determined by the manufacturer and designer, taking the various critical parameters into account. Primarily the air change rate should be set to a level that will achieve the required clean area classification. Air change rates normally vary between 6 and 20 air changes per hour and are normally determined by the following considerations:

③ The quality and filtration of the supply air
- Particulates generated by the manufacturing process
- Particulates generated by the operators
- Configuration of the room and air supply and extract locations
- Sufficient air to achieve containment effect
- Sufficient air to cope with the room heat load
- Sufficient air to maintain the required room pressure

Manufacturing facilities should be maintained at a positive pressure relative to the outside, in order to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to ambient, in order to prevent the escape of harmful products to the outside (such as penicillin and hormones), then special precautions should be taken.

Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should

be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks. Depending of the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some medicinal products. Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:

- the risk cannot be adequately controlled by operational and/ or technical measures,
- scientific data from the toxicological evaluation does not support a controllable risk (E.g. allergenic potential from highly sensitizing materials such as beta lactams) or
- relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method

With respect to penicillin, § 211.42(d) requires that "operations 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. 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.

Although FDA has not issued CGMP regulations specific to APIs, the Agency has provided guidance to API manufacturers in the guidance for industry, ICH Q7, *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (ICH Q7 guidance). 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.

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. Beta-lactam antibiotics include the following five classes:

- 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.

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, the hazard posed is present 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.
- There is a lack of suitable animal or receptor testing models that are predictive of human sensitivity
- The threshold dose at which allergenic response could occur is extremely low and difficult to detect with current analytical methods.

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

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. 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. 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.

II. 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.

Think about it

Stringent measures are in place for beta - lactam manufacturers to protect the patient. Might there be need for appropriate precautions at the Community and Hospital dispensing levels to similarly protect the patient?

Questions

1. Which of the following statements is not true in regard to penicillin;

    a. Penicillin can be a sensitizing agent that triggers a hypersensitive exaggerated allergic immune response in some people
    b. Implementing methods for preventing cross- contamination of other drugs with penicillin is a key element of manufacturing penicillin
    c. Preventing cross contamination is current good manufacturing practice (CGMP) and regulations require the use of such methods
    d. Manufacturers of non-penicillin beta-lactam drugs should not employ control strategies to prevent cross-contamination.

2. Which of the following statements is not true

    a. Contamination is the undesired introduction of impurities, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.
    b. Chemical, microbes, or foreign matter are examples of contaminants
    c. *Containment is* a process or device to contain product, dust or contaminants in one zone
    d. Containment is not applicable during the production of penicillin

3. Which of the following statements is not true

    a. The ventilation system provides only product protection and personnel protection.
    b. Air filtration and air change rates should ensure that the defined clean area classification is attained.
    c. Primarily the air change rate should be set to a level that will achieve the required clean area classification
    d. Air change rates normally vary between 6 and 20 air changes per hour

4. In regard to pharmaceutical manufacturing facilities, which of the statements is true
    a. Cross-contamination should not be prevented for all products by appropriate design of manufacturing facilities
    b. Facilities for manufacture of penicillin and hormones should not be maintained at positive pressures relative to ambient
    c. The measures to prevent cross-contamination need not be commensurate with the risks.
    d. Depending on the level of risk, it may not be necessary to dedicate premises and equipment for manufacturing

5. The following statements are false in regard to air changes except

   a. air changes per hour are determined by considering the quality and filtration of the supply air

   b. Particulates generated by the manufacturing are not considered when determining air changes per hour

   c. Particulates generated by the operators are not considered when determining air changes per hour

   d. Configuration of the room and air supply and extract locations not considered when determining air changes per hour

6. The following statements are true except;

   a. Dedicated facilities are required for manufacturing when a medicinal product presents a risk because the risk cannot be adequately controlled by operational and/ or technical measures,

   b. Dedicated facilities are required when relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method

   c. 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)

   d. It is a requirement for manufacturers to test non-penicillin drug products for penicillin where the possibility of exposure to cross-contamination exists, and manufacturers may market such products if detectable levels of penicillin are found.

7. In regard to non-penicillin beta-lactams and penicillins; which of the statements below is not true

   a. It is difficult to define the minimal dose below which allergic responses are unlikely to occur in humans.

   b. There is a lack of suitable animal or receptor testing models that are predictive of human sensitivity

   c. The threshold dose at which allergenic response could occur is extremely low and difficult to detect with current analytical methods.

   d. The manufacturing of Cephalosporins and penicillins (e.g., ampicillin, oxacillin) may be carried out under the same air handling unit with appropriate air filtration

8. Which of this statements is not recommended by FDA

   a. Manufacturers should assess and establish stringent controls (including appropriate facility design provisions assuring separation) to prevent cross-contamination.
   b. Manufacturers should establish appropriate separation and control systems designed to prevent the contamination of a non-penicillin beta-lactam by any other non-penicillin beta-lactam.
   c. Manufacturers establish appropriate separation and control systems designed to prevent the contamination of any other type of product by a non-penicillin beta-lactam.
   d. The area in which some classes of sensitizing beta-lactam are to be manufactured be separate from areas in which other products are manufactured

9. Which of the statements is not True

   a. All non-penicillin beta-lactam have the potential to sensitize individuals.
   b. Prevention of cross-contamination in an API plant is not as important as preventing cross-contamination in finished pharmaceutical product manufacture?
   c. Non-penicillin product facilities should be separated / isolated from non-penicillin beta-lactam production area.
   d. Some beta-lactam intermediate compounds and derivatives also possess similar sensitization and cross–reactivity properties.

10. In regard to manufacture of beta-lactam intermediates, which statement is true?

    a. Firms whose manufacturing processes result in beta-lactam derivatives, are not required to evaluate their manufacturing operations for the possibility of cross-contamination
    b. Implementation of appropriate controls to reduce or mitigate the potential for cross-contamination.
    c. isolation and separation of intermediate and derivative materials, facilities, equipment, and personnel are not required
    d. All the above