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GXP Talk - Question #80 - Penicillin Considerations in Manufacturing

By **Sarah P. Banday Jun 7, 2019 10:13 am PDT**

"GXP Talk" provides a forum for addressing compliance issues identified by readers of the Journal of GXP Compliance. This feature is the longest running continuing series in the Journal of GXP Compliance addressing numerous questions. Previous discussions have addressed a wide range of compliance activities covering essentially all sections of the US GMPs. Responses to questions and associated opinions have been contributed by representatives from multiple pharmaceutical industries and regulatory agencies.

Readers are invited to participate ad contribute questions, answers, and discussion for this series – please share your successful practices with other readers. This column succeeds when we are able to address current GXP issues submitted by interested readers. Please contact column coordinators Jerry Lanese atjerry@lanesegroup.com or Rich Poska at richposka@gmail.com with comments or submissions for publication. We welcome your questions, opinions, or other input.

QUESTION #80. Must penicillin be manufactured in a separate CGMP manufacturing facility?

INTRODUCTION

Question #80 addresses a key topic in the manufacture of penicillin – the need for separation in manufacturing. This fundamental question leads to discussion on several associated topics. Considering drug molecule composition, for example:

- Penicillin. There are many "cillin" drugs - ampicillin, amoxicillin, oxacillin, and many others. Are they all considered to be penicillin? What causes the differences between these drugs?
- Bulk drugs and penicillin products. What about starting materials, intermediates, formulation ingredients, and other compounds related to penicillin manufacturing?
- Are there other drugs – not penicillins – that are similar to penicillin and must be considered as penicillin? What about cephalosporins and related drugs?

Industry professionals are very familiar with the drugs they manufacture, but often do not know about the clinical use of these products. For example:

- What are the uses of these many penicillins and related drugs? Why are these many drugs needed?
- How do patients know they are allergic to penicillin?
- What happens when a person with a penicillin allergy takes a penicillin-contaminated drug?
- Is there any way a penicillin-allergic patient can take a penicillin if a specific penicillin is needed to treat a serious infection?

Separation in manufacturing is a seemingly a straightforward topic. However, there are additional topics associated with separation that warrant further discussion. For example:

- What does "manufacturing separation" actually mean – separate buildings, separate rooms, separate equipment, separate people?
- What are FDA expectations regarding "separation?"
- Do manufacturing separation requirements apply to penicillin and associated non-penicillin drugs?
- What are some unspecified considerations that must be considered in separated facilities?

FDA INFORMATION

The FDA has addressed several topics related to the penicillin questions stated above in “Q&A on CGMPs (1). The section on Buildings and Facilities, Questions 1, 2, 3, and 4, provide discussion related to penicillin. Question 4 below provides 21 CFR GMP references directly related to penicillin manufacturing. Questions discussed by FDA are as follows:

1. What is penicillin?
Penicillin is defined as a group of natural or semisynthetic antibiotics derived from fungi strains of the genus Penicillium. Generally, all penicillins share a three-carbon, one-nitrogen, and four-member cyclic amide structure, known as the beta-lactam ring.

Reference:

- *Lewis, J, and K Bush, 2015, Antibacterial Agents, In: J Jorgensen, M Pfaller, K Carroll, G Funke, M Landry, S Richter, D Warnock, eds. Manual of Clinical Microbiology, 11th ed., Washington, DC: ASM Press, 1171-1211.*

2. *What are the penicillin drugs?*
The Manual of Clinical Microbiology, 11th edition, identifies penicillin drugs as follows:

- *Natural - Benzylpenicillin (penicillin G)* and phenoxymethyl penicillin (penicillin V)**
- *Semisynthetic - Penicillinase-resistant cloxacillin*, dicloxacillin*, nafcillin, oxacillin, and temocillin.***
- *Extended spectrum - Aminopenicillins (amoxicillin,* ampicillin,* and mecillinam,**) carboxypenicillin (ticarcillin,*) and ureidopenicillin (piperacillin.)*

**Approved for veterinary use; **Not approved in the United States*

Reference:

- *Lewis, J, and K Bush, 2015, Antibacterial Agents, In: J Jorgensen, M Pfaller, K Carroll, G Funke, M Landry, S Richter, D Warnock, eds. Manual of Clinical Microbiology, 11th ed., Washington, DC: ASM Press, 1171-1211.*
- *FDA Orange Book*
- *Drugs@FDA*

3. Is cross-contamination a concern with penicillin drugs?
Yes, penicillin can be a sensitizing agent that triggers a hypersensitive exaggerated allergic immune response in some people. Differences in the 6-aminopenicillanic acid side chain can generate allergic reactions ranging from skin rashes to life-threatening anaphylaxis.

Reference:

- *Lewis, J, and K Bush, 2015, Antibacterial Agents, In: J Jorgensen, M Pfaller, K Carroll, G Funke, M Landry, S Richter, D Warnock, eds. Manual of Clinical Microbiology, 11th ed., Washington, DC: ASM Press, 1171-1211.*

4. Are there special manufacturing requirements for penicillin drugs?
Yes, all penicillin finished pharmaceutical manufacturers, including repackers, are required by the CGMP regulations to establish a comprehensive control strategy designed to prevent cross-contamination of other drugs with penicillin. These requirements include:

- *21 CFR 211.42(d): Separation of facility and equipment*
- *21 CFR 211.46(d): Separate air handling systems (HVAC)*
- *21 CFR 211.176: Test for traces of penicillin where possible exposure exists.*

Penicillin active pharmaceutical ingredients (APIs) are also required to be manufactured under CGMPs in accordance with section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. FDA has published internationally harmonized guidance on the manufacture of APIs; see ICH guidance for industry,Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. Chapter 4, section 4.4 of this guidance describes actions API manufacturers, including those that manufacture or package APIs or penicillin intermediates, are to follow to ensure such material is contained and does not contaminate other drugs.

Reference:

- *FDA CGMP regulations (21 CFR parts 210–211)*
- *Federal Food, Drug, and Cosmetic Act, section 501(a)(2)(B)*
- *FDA Guidance for Industry, 2001, ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*

Non-Penicillin Beta-Lactam Guidance

FDA has also published *Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination* (2) in 2013. This document addresses considerations for drugs containing the beta-lactam structure with hypersensitivity potential. More importantly, it also provides useful information applicable to all beta-lactam drugs – penicillins and non-penicillins – including recommendations for manufacturing. Cephalosporins are the major category of non-penicillin beta-lactam drugs. Compliance professionals must be mindful of all drugs and related compounds of this type processed in their facilities.

DISCUSSION TOPICS

The following addresses topics associated with penicillin and related drugs. Specific areas discussed are as follows:

- Drugs overview. Types of penicillins, non-penicillin beta-lactams, chemical structures, and differences between drugs.
- Drug clinical use and allergic reactions. Use of penicillin drugs, types of allergic reactions, symptoms, mechanisms, and methods to overcome allergic reactions.
- Manufacturing penicillin and non-penicillin beta-lactam drugs. Separation from other drugs, FDA expectations, causes for cross-contamination, and other risk considerations.

DRUGS OVERVIEW

Penicillin is defined as a group of natural or semisynthetic lactam antibiotics derived from fungi strains of the genus *Penicillium* (3.) The “lactam” terminology refers to the chemical structure of the drug molecule. A lactam is a cyclic amide. The four-membered cyclic amide ring in the molecule is usually linked to the beta carbon of an attached carbonyl group; hence the term “beta-lactam” (or “?-lactam”) antibiotic.

Penicillins are antibiotics. They are active against bacterial infections. They are not active against viruses causing flu symptoms or influenza. Penicillin drugs are categorized by microbiological susceptibility -- the types of bacteria against which they are effective.

Natural Penicillins. Natural penicillins include Penicillin G and Penicillin V. Natural penicillins are highly active against gram-positive cocci (4.) However, natural penicillins are ineffective against most strains of *S. aureus* due to readily being hydrolyzed by penicillinase. Penicillinase is an enzyme produced by bacteria that counteracts penicillin. Some bacteria are able to destroy penicillin through an enzymatic reaction with penicillinase (also known as beta-lactamase.) Some penicillin molecules have been modified by chemical synthesis to protect from reaction with penicillinase.

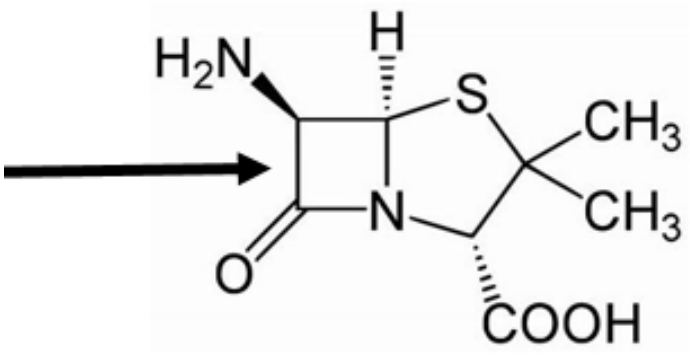
Semisynthetic penicillins. Semisynthetic penicillins include penicillinase-resistant drugs that are not destroyed by penicillinase and extended spectrum penicillins that kill a greater range of microorganisms.

Penicillinase resistant drugs. This includes cloxacillin, dicloxacillin, nafcillin, oxacillin, and temocillin. These agents have less-potent antimicrobial activity against microorganisms that are sensitive to natural penicillin drugs, but they are preferred agents for treatment of non-methicillin resistant penicillinase-producing *S. aureus* and *S. epidermidis*.

Extended spectrum drugs. Inclusive of aminopenicillins, (amoxicillin, ampicillin, mecillinam,) carboxypenicillin (ticarcillin,) and ureidopenicillin (piperacillin.) Extended spectrum penicillins have a broader spectrum of antimicrobial activity including some Gram-negative microorganisms. These drugs are also available as coformulations with a ?-lactamase inhibitors such as clavulanate or sulbactam. Increase antibacterial coverage is due to inactivation by extended-spectrum ?-lactamases (ESBLs) and/or because they more readily penetrate the outer membranes of the Gram-negative organisms.

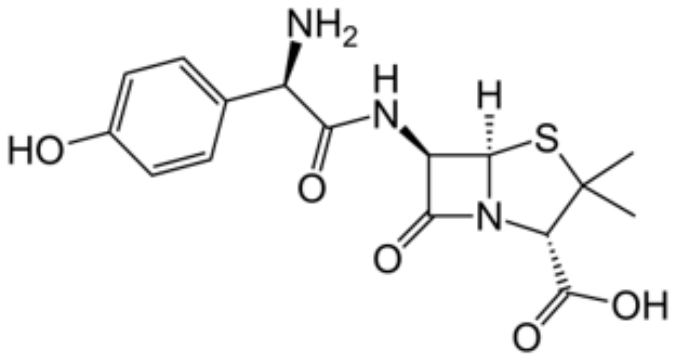
Penicillins Molecular Structures

Differences between penicillin drugs are due to different molecular substitutions on the core penicillin molecular structure. Penicillins are derivatives of 6-amino penicillanic acid, the core penicillin structure.



6-Aminopenicillanic Acid (6-APA)

Note the three-carbon, one-nitrogen, and four-member cyclic amide structure in the molecule (arrow) -- the beta-lactam ring. Side chain additions at the 6-amino group alter the antimicrobial properties of penicillin compounds (4) making them more effective against different types of bacteria. Amoxicillin illustrates the basic structure of penicillin drugs with substitutions at the 6-amino nitrogen.



Amoxicillin

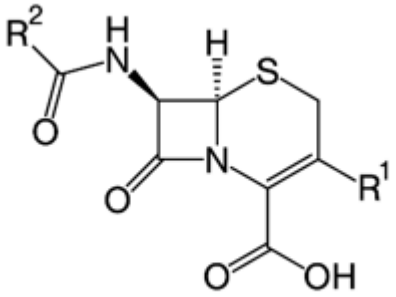
All drugs with this basic beta-lactam ring structure are considered to be equivalent to penicillins regarding potential for allergic reactions.

Non-Penicillin Beta-Lactam Drugs

The FDA Non-Penicillin Beta-Lactam Drug guidance (2) provides useful and comprehensive information applicable to both penicillin and non-penicillin drugs containing the beta-lactam structure. A key section of this guidance provides a listing of beta-lactam drug categories that may cause hypersensitivity reactions.

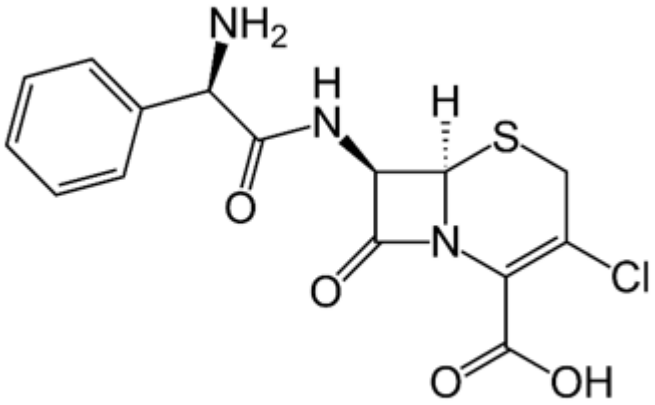
Cephalsporins

Cephalosporins are a major category of non-penicillin beta-lactam drugs. Wikipedia list five generations of cephalosporin drugs containing more than 50 individual commercialized drug products built on a core chemical structure (7-ACA) with a beta-lactam ring (5.) Each generation has differing chemical substitutions (R1 and R2) on the core structure and differing susceptibility to Gram-positive and Gram-negative bacteria.



7-aminocephalosporanic acid (7-ACA)

Cefaclor illustrates the basic structure of the cephalosporin drugs.



Cefaclor

Categories of Beta-Lactam Drugs

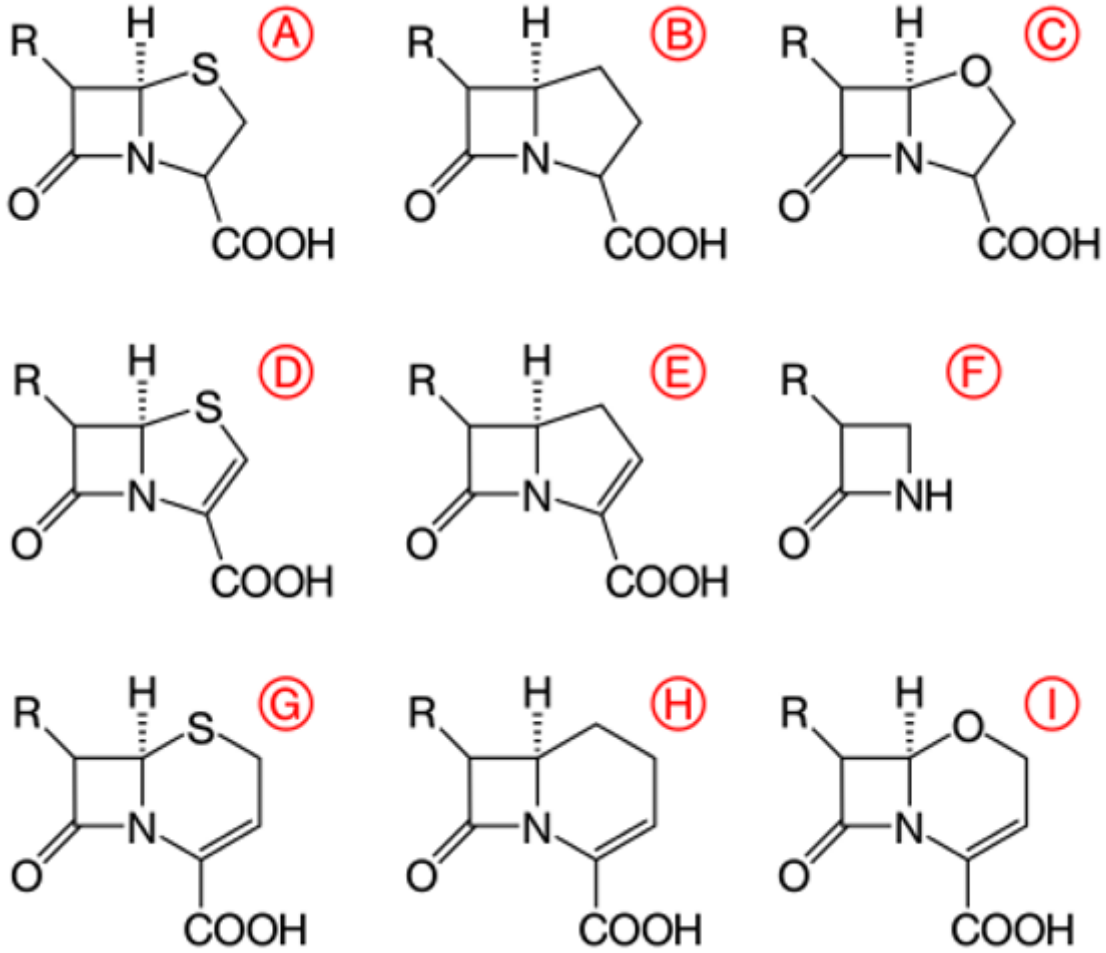
Drugs containing the beta-lactam molecular structure are considered analogous to penicillins regarding hypersensitivity. The 2013 FDA guidance identified five non-penicillin categories of beta-lactam drugs as follows:

- Penicillins
- Cephalosporins
- Penems
- Carbacephems
- Monobactams.

Wikipedia has listed additional lactam categories (6) based on chemical structure. All molecules have the lactam molecular structure with individual molecule differences. Differences between molecules depend on the molecule group to which the lactam structure is attached. The table below describes all categories of beta-lactams. The figure below illustrates their respective structures.

LACTAM CATEGORY	CORE STRUCTURE FIGURE	RING ATTACHMENT	SATURATED OR UNSATURATED RING	RING ATOM	EXAMPLES
Penam	A	5-member	Saturated	Sulfur	Penicillin Tazobactam Sulbactam

Carbapenam	B	5-member	Saturated	Carbon	Synthesis intermediate
Oxapenam or Clavan	C	5-member	Saturated	Oxygen	Clavulanic acid
Penem	D	5-member	Unsaturated	Sulfur	Faropenem
Carbapenem	E	5-member	Unsaturated	Carbon	Doripenem
Monobactam	F	No attachment	No attachment	No attachment	Aztreonam
Cephem	G	6-member	Unsaturated	Sulfur	Cephalosporins
Carbacephem	H	6-member	Unsaturated	Carbon	Loracarbef
Oxacephem	I	6-member	Unsaturated	Oxygen	Moxalactam



OTHER DRUG CONSIDERATIONS

The FDA guidance also discussed beta-lactamase inhibitors and beta-lactam compounds used in manufacturing. Beta-

lactamase inhibitors include drugs such as clavulanic acid, tazobactam, and sulbactam. These compounds are combined with beta-lactam antibiotics to yield products with enhanced antimicrobial activity. For example, amoxicillin is combined with clavulanate in a commercial antibiotic product. The beta-lactamase inhibitors are also potential sensitizing agents and must be considered for separation along with beta-lactam drugs.

Beta-lactam materials used in manufacturing include starting materials, intermediates, derivatives, and other compounds with potential to cause hypersensitivity. For example, 6-APA, the core molecule of penicillin drugs, has the potential to induce allergic reactions, and 7-ACA, the core molecule of cephalosporin drugs, has similar sensitizing properties. Starting materials, intermediates, derivatives, and associated compounds must also be considered for separation along with penicillin and non-penicillin beta-lactam drugs.

DRUG CLINICAL USE

Penicillin and non-penicillin lactam drugs interfere with development of the bacterial cell wall (3.) The targets of beta-lactam antibiotics are known as Penicillin Binding Proteins (PBPs) found within the cell wall. PBPs create a mesh-like network. Penicillins and other beta-lactams kill susceptible bacteria by specifically inhibiting the transpeptidase that catalyzes the final cross-linking step in cell wall biosynthesis. This inhibition causes the cell to burst.

Drug Allergic Reactions

Drug cross-contamination is the contamination of one drug with one or more different drugs (4). When penicillin or other beta-lactam drugs contaminate a non-beta lactam drug, serious hypersensitivity reactions may occur in patients who are allergic to beta-lactams. Immunoglobulin E (IgE) antibodies mediate the immediate hypersensitivity reactions that are responsible for 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 carbapenems.

Penicillin sensitivity is defined as a specific immunologic reaction to a penicillin drug (7.) Sensitivity may develop at any stage of life. Although approximately 10% of the population is reported as being sensitive to penicillin; most of those reported lose their sensitivity over time and can therefore eventually tolerate penicillin antibiotics. Sensitivity may arise from the beta-lactam core or from the various side-chain substitutions. While beta-lactam antibiotics are similar to one another in many ways, they may differ in their potential to cause serious allergic reactions. Penicillin sensitivity is differentiated by immediate reactions versus delayed reactions. An immediate reaction mediated by IgE arises quickly (within minutes or hours) after the last administered dose. Symptoms include sudden anaphylaxis with hypotension, abdominal distress, angioedema and urticaria. Delayed reactions are caused via non-IgE mediated mechanisms. These reactions may present within hours to days with symptoms such as fever, arthralgias, or uticaria. Mild allergic reactions (itching and skin rash) may be treated with an antihistamine. Oral glucocorticoids may be a viable option in patients who do not respond to or are unable to tolerate antihistamines. Serious anaphylactic reactions require more urgent treatment with an immediate epinephrine injection as well as hospital care to maintain blood pressure and support breathing.

Sensitivity Testing

Penicillin skin sensitivity testing of patients can help to confirm the safety of a drug and alleviate the fears of a drug allergic reaction (8-10.) The skin is pricked (intradermal injection) with weak solutions of the various penicillin preparations. A positive skin reaction is an itchy, red bump that lasts about one-half hour and then resolves. A positive test indicates the presence of IgE antibodies to penicillin which concludes to a patient's inability to use penicillin and related beta-lactam antibiotics. It should be noted, however, that a positive result does not allude to the type of reaction a patient would develop (Stevens-Johnson syndrome [SJS] or toxic epidermal necrolysis [TEN], erythroderma or erythema multiforme.) Also, the extent of skin sensitivity test accuracy is unknown for non-penicillin beta-lactams. Diagnostic testing is of limited value for agents such as cephalosporins or carbapenems.

In special populations of patients who have a history of penicillin allergy and tested negative for penicillin skin sensitivity, the resulting risk of rashes associated with penicillin antibiotics is no greater than any risk associated with any other class of antibiotics (9,10). If skin sensitivity testing in unavailable, challenge testing may be a viable option. A penicillin challenge (small dose of antibiotic) is given in an office setting. Should a patient lack any adverse reactions, sequential doses are given every 30-60 minutes. The goal would be to assess how large of a dose will illicit sensitivity, with the hopes of reaching the

therapeutic dose to allow infection resolution. If the patient tolerates the therapeutic dose, they are considered no longer allergic to penicillin drugs.

Desensitization

Penicillin desensitization is a technique that can allow a patient to tolerate a penicillin drug therapy for a specific infection (10). Doctors administer small but gradually increasing doses of penicillin orally or intravenously. If no allergic reaction occurs, penicillin treatment is initiated. Desensitization is serious -- desensitization can trigger a life-threatening reaction. Penicillin desensitization is typically attempted in a controlled hospital setting and only when penicillin therapy is absolutely necessary. Once a patient has discontinued therapy for at least 24 hours, they are considered to have penicillin sensitivity once again.

Manufacturing Penicillins And Non-Penicillin Beta-Lactam Drugs

All penicillin pharmaceutical manufacturers and re-packers are required by CGMP to establish a comprehensive control strategy designed to prevent beta-lactam cross-contamination of non-beta-lactam drugs in their facilities. Relevant CGMP requirements are stated in the following:

- 21 CFR 211.42(d): Separation of facility and equipment
- 21 CFR 211.46(d): Separate air handling systems (HVAC)
- 21 CFR 211.176: Test for traces of penicillin where possible exposure exists.

Each of the above sections specifically mention penicillin in their respective texts. The above must be considered along with ICH Q7A (11) and other global general requirements for API and drug product manufacturing.

The 2013 FDA guidance provides useful and comprehensive information applicable to manufacturing both penicillin and non-penicillin beta-lactam drugs. Pharmaceutical manufacturing and quality personnel must consider all penicillin and non-penicillin beta-lactam drugs in their facilities when designing and developing control systems for these drugs. Topics addressed in the FDA guidance included importance of preventing cross-contamination, relative health risks and potential for cross sensitivity, and FDA expectation for facility separation in manufacturing. Recommendations are applicable to penicillin and non-penicillin beta-lactam drugs since these drugs may cause hypersensitivity reactions. Aside from theoretical plausibility, noted documentation exists confirming that patients who have hypersensitivity to penicillin drugs also experience similar IgE-mediated reactions to other beta-lactam drugs.

FDA Guidance Recommendations

FDA clearly states its expectations for beta-lactam manufacturing in the 2013 guidance (2):

“Because of the potential health risks associated with cross-reactivity (cross-sensitivity) of the beta-lactams, manufacturers should assess and establish stringent controls (including appropriate facilitate 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.*
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. Manufacturing that is restricted to a specific class of beta-lactam compound (i.e., 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.”

The Agency should likely be contacted if a unique new category of beta-lactam drug is developed to determine appropriate separation practices in the facility.

Finally, the guidance comments that recommendations for separation also applies to starting material, intermediates,

derivatives, and related compounds that may induce allergic reactions. 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.

FDA Warning Letter Examples

Two FDA Warning Letters demonstrate FDA"s expectation for a comprehensive approach to preventing cross contamination consistent with the above recommendations.

An FDA Warning Letter to a Canadian company (12) demonstrates the breadth of FDA expectations regarding potential lactam drug cross-contamination:

1. *"Failure to package beta-lactam drug products (including penicillin and non-penicillin beta-lactams) and other drug products under appropriate conditions to avoid potential cross contamination*

a. Your firm failed to use separate facilities to manufacture penicillins, non-penicillin beta-lactams, and non-beta-lactam APIs.

i. you packaged a number of beta-lactams…in a facility that is not dedicated to packaging beta-lactam drugs.

ii. You did not use dedicated equipment (for example, hoods) or air handling systems to prevent cross-contamination.

b. Your firm increased the risk of cross-contamination by allowing personnel and materials to move freely between beta-lactam and non-beta-lactam manufacturing areas.

The Warning Letter continues to comment on non-penicillin beta-lactam drugs having the potential for hypersensitivity reactions, using shared equipment, cleaning beta-lactam residues, beta-lactam molecule inactivation, no known no safe levels of cross-contamination, and the inability to sample and analytically determine low levels of contamination. A retrospective review of previous product potential contamination was recommended.

Another FDA Warning Letter to a UK company (13) identified numerous instances of penicillin products in non-penicillin areas during a four-year monitoring period. The Warning Letter bluntly stated that the firm facility and controls were "wholly inadequate." The letter also addressed problems with analytical method validation for penicillin determination and inadequate penicillin cleaning validation. The letter further recommended two options to the firm:

- Dedication of the facility to beta-lactam manufacturing
- Full decontamination of beta-lactam residues (FDA comment: "profoundly difficult") and subsequent dedication to manufacturing non-beta-lactam drugs.

SUMMARY AND FINAL THOUGHTS

While the original intent of this GXP Talk Q&A focused on penicillin manufacturing, its scope expanded to include many additional and related discussion topics relevant to manufacturing and compliance. These may be generally summarized as drug considerations and facility considerations. Compliance professionals with responsibility for beta-lactam drug processing must thoroughly address drug considerations – the compositions and properties of all drugs, starting materials, intermediates, and related materials must be evaluated and understood. More complex are facility-related separation issues – manufacturing processes, facility, equipment, utilities, personnel, and other non-manufacturing facility and logistic considerations – that are controlled by procedure and depend on personnel compliance. Quality and compliance professionals must take a comprehensive approach to drug considerations and facility considerations regarding beta-lactam drugs.

Drug Considerations

Penicillins are well known to cause hypersensitivity reactions. However, penicillins are not the only problem drugs. Quality managers must consider all lactam drugs and not just penicillins -- considerations must include all drugs containing the lactam chemical structure that might be expected to induce allergic reactions. Penicillins, cephalosporins, and other categories of drug molecules have been identified as needing additional controls to prevent cross-contamination. Further, in addition to drug products, these controls apply to bulk drugs, starting materials, intermediates, and related process molecules. A plant whose business includes investigational drugs, contract manufacturing, contract packaging, and similar activities must investigate the potential for drug hypersensitivity before initiating processing with any beta-lactam drug in their facility.

Separation – Facilities, Equipment, People

There should be no confusion regarding FDA expectations for facilities for manufacturing penicillin and associated drugs: "…manufacturers should assess and establish stringent controls (including appropriate facilitate design provisions assuring separation) to prevent cross-contamination. (2)." Separate HVAC systems are specifically mentioned in the CGMP 21CFR 211.46. Regarding facilities, FDA has clarified their position in1977 as follows: "…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 (14). Note FDA wording: "Completely and comprehensively separated."

Drug manufacturers who process penicillins, non-penicillin beta-lactam drugs, and non-beta-lactam drugs must develop thorough, complete, and comprehensive plans to prevent cross-contamination. A thorough and complete risk assessment should be initiated to develop a sound separation and monitoring program.

Facilities, equipment, and HVAC separation are straightforward determinations. Non-specific facilities are a more difficult challenge, especially in a retrofitted facility. Separation in facilities must consider storage areas, drug dispensing, warehousing, and similar non-manufacturing areas with common area traffic and use. Routine non-manufacturing activities such as material distribution, waste disposal, environmental monitoring, and similar activities with multiple personnel contact must be controlled to prevent beta-lactam contamination. Personnel movement within common areas such as administrative offices, corridors, cafeterias, rest rooms, employee lounges, and similar areas must be restricted. An ongoing monitoring program for non-beta-lactam manufacturing areas and non-manufacturing areas using validated testing systems to demonstrate an established state of control must be implemented. Cross-contamination due to non-compliant personnel restrictions or inadvertent transfer of potential contamination by non-manufacturing personnel are easily overlooked problems leading to site cross-contamination.

Final Thoughts

While FDA has theoretically allowed manufacturing sites to manufacture beta-lactam drugs and non-beta-lactam drugs in the same facility, designing, developing, executing, and monitoring successfully may be a literally impossible task. FDA auditors may have different interpretations of "separation." International auditors may require absolute facility separation as required or interpreted in their country requirements. Reliance on procedural (non-engineering) controls that depend on personnel for execution is not 100% reliable. Separation in manufacturing and equipment is probably among the easiest of beta-lactam separation challenges to accomplish. The numerous other challenges -- separation in supportive functional areas (e,g., drug dispensing, warehousing,) restricting routine non-manufacturing activities (e.g., material transportation, waste disposal, environmental monitoring,) controlling personnel movement within common areas (e.g., administrative offices, cafeterias, rest rooms,) – are all formidable challenges. Analytical methods are sensitive – penicillins are detectable at a low level. Facility cross-contamination due to non-compliant personnel or inadvertent transfer of potential contamination by non-manufacturing personnel are easily overlooked problems leading to site cross-contamination -- and every negative result would require an investigation and CAPA.

To summarize original question #80. Must penicillin be manufactured in a separate CGMP manufacturing facility?

Answer: Penicillin and related lactam drugs may be manufactured in a common facility with non-penicillin drugs, but to do so successfully – completely, comprehensively, and reliably -- may in reality be an impossible task.

ACKNOWLEDGMENTS

Comments by Alan M. Mancini, Richard Poska, and Paul L. Pluta are gratefully appreciated.

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