Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Buildings and Facilities

1. What is Penicillin?

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

2. What are the Penicillin drugs?

The Manual of Clinical Microbiology, 9th edition, identifies penicillin drugs as follows:
Natural Penicillins:
• Benzylpenicillin* (commonly known as penicillin G)
• Benzylpenicilloyl-polylysine (BPP)
• Phenoxymethyl penicillin* (commonly known as penicillin V)
Semi-synthetic Penicillins:
• Methicillin
• Nafcillin
• Cloxacillin*
• Dicloxacillin*
• Ampicillin*
• Amoxicillin*
• Bacampicillin
• Pivampicillin
• Carbenicillin
• Ticarcillin*
• Azlocillin
• Mezlocillin
• Piperacillin
• Hetacillin*
*Penicillins approved for veterinary use

Please be aware that penicillin trade names may vary by region and country. Manufacturers, including repackers, are responsible for knowing whether their drug is penicillin. FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) or Drugs@FDA, both of which are located at FDA's website, enable searching by trade name (i.e., proprietary name) and by active ingredient name (i.e., generic or non-proprietary name).

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 chemically substituted 6-aminopenicillanic acid side chain can generate allergic reactions ranging from skin rashes to life-threatening anaphylaxis.

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 exits.

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 International Conference on Harmonization (ICH) Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. Chapter 4, section 4.4 of this guidance describes actions API manufacturers, including those who manufacture or package APIs or penicillin intermediates, are to follow to ensure such material is contained and does not contaminate other drugs.

References-See below

Contact for further information:

Division of Manufacturing and Product Quality (HFD-320): CGMP Subject Contacts
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm
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5. Why is FDA concerned about drug contamination with halogenated anisole compounds, such as 2,4,6-tribromoanisole (TBA)?

Reports, including some dating back several decades, describe a moldy or musty odor in food (and wine) products due to contamination with trace amounts of halogenated anisole compounds such as 2,4,6-tribromoanisole (TBA). An odor attributable to the presence of a halogenated anisole compound can be detected by consumers even when the offending compound is present at parts per billion or lesser levels. Recently, an upward trend in consumer complaints about musty or moldy odor led a drug firm to identify TBA as the odor-causing compound. The firm's investigation of this incident led to the detection of TBA in several oral products. The firm traced all of the contamination back to the use of certain wooden pallets used to transport drug packaging materials. TBA is prone to volatilize and adsorb onto articles stored near the TBA source. Because of their volatility, it appears that even minute levels of halogenated anisole compounds can adversely affect a large quantity of product in a single contamination incident.

6. Are there any health effects associated with ingestion of halogenated anisole compounds?

Although there is no meaningful toxicological data on TBA at these levels, the health risks appear to be minimal. Currently available data indicate that serious adverse health effects have not resulted from ingestion of drugs or foods contaminated with halogenated anisole compounds at the levels of contamination that have been reported. However, there are some reports of gastrointestinal events by consumers who also report sensing a foul odor, or taste, in drug products contaminated with the typical trace levels of TBA. Even if the health effects are minimal, FDA is concerned that patients sensing an unusual odor that is not intrinsic to the product will stop taking their medication.

7. Has FDA identified the source of the halogenated anisole compounds that have recently contaminated drug products?

The source of TBA-contaminated drug products appears to have been 2,4,6-tribromophenol (TBP), a chemical used as a wood preservative. Certain fungi are able to survive in TBP-treated wood by converting TBP to its anisole analog, TBA[1]. In the recent contamination incident, an investigation found that TBP-treated wood was used to manufacture pallets that were then used to ship and store drug packaging material. Currently, the use of halogenated phenolic compounds to preserve wood appears to be very rare as this practice is either discouraged or prohibited in many regions of the world, including the US. However, TBP treatment of wood continues in some regions that supply wood to the US and other countries.

8. What is FDA's expectation for preventing contamination of drug products with halogenated anisole compounds?

FDA recommends that manufacturers and distributors take precautions to prevent the use of wood products treated with or exposed to a halogenated phenolic preservative anywhere in supply chain. This includes all facilities that manufacture, hold, or distribute drug products, components, or packaging materials. We recommend that manufacturers not store drug products, components, or packaging materials near wood or wood-derived storage materials unless there is assurance that the wood material has not been treated with a halogenated phenolic preservative.

FDA further recommends that manufacturers establish agreements and request certification from suppliers to provide assurance that halogenated phenolic preservatives are not present. Manufacturers should also be vigilant to the characteristic odor of the offending compounds so they can intervene before product is contaminated or further distributed.

9. Are there any standards applicable to preventing contamination of drug products with halogenated anisole compounds?

U.S. (ASTM) and international standards (International Standard for Phytosanitary Measures (ISPM)) recommend heat treatment, or fumigation with methyl bromide, for the preservation of wood-derived packaging storage materials, including wood pallets. For more information, including certification to these standards, refer to Standard Practice for Treatment and/or Marking of Wood Packaging Materials (ASTM D 6253-05a) and Guidelines for Regulating Wood Packaging Material in International Trade (ISPM 15).

10. Can contamination of drug products with halogenated anisole compounds be detected?

Although methods for detection exist and might be practical for periodic screening, FDA expects that manufacturers prevent such contamination through adherence to Current Good Manufacturing Practices (CGMPs). A CGMP-compliant quality system will ensure that assurances are obtained from suppliers and that measures are taken to prevent exposure to problematic compounds. Manufacturers of finished pharmaceuticals are reminded that the CGMP regulations at 21 CFR 211.56(c) require written procedures for sanitation designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, and drug products. Analogous recommendations for manufacturers of active pharmaceutical ingredients are included in internationally harmonized (European Union, Japan, United States) guidance for industry ICH Q7, Good Manufacturing Practice for Active Pharmaceutical Ingredients (section 4.72).

[1] Trichlorophenol (TCP) is another example of a compound that can be converted to a halogenated anisole compound

References:

1. Yao, Joseph D. C., and Robert C. Moellering, Jr. "Antibacterial Agents." Manual of Clinical Microbiology. 9th ed. Washington D.C., ASM, 2007
2. FDA CGMP regulations (21 C.F.R. Parts 210-211)
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm095412.htm
3. The Federal Food, Drug, & Cosmetic Act 501(a)(2)(B)
http://www.fda.gov/RegulatoryInformation/Legislation/ FederalFoodDrugandCosmeticActFDCAct/default.htm
4. Code of Federal Regulations – 21 CFR Part 211.56 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.56
5. ICH Q7, Good Manufacturing Practice for Active Pharmaceutical Ingredients (section 4.72)
6. Standard Practice for Treatment and/or Marking of Wood Packaging Materials (ASTM D 6253-05a) - ASTM International (http://www.astm.org/)
7. Guidelines for Regulating Wood Packaging Material in International Trade (ISPM 15) - Secretariat of the International Plant Protection Convention of the Food and Agriculture Organization of the United Nations (https://www.ippc.int/)

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