U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Drugs

Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Returned and Salvaged Drug Products

1. What should a firm do if its drug products or components have been subjected to improper storage conditions such as those caused by a natural disaster?

Drug products that have been subjected to improper storage conditions (including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation) due, for example, to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Such exposure can pose a serious risk to a drug's identity, strength, quality, purity or safety (see 21 CFR Part 211.208, Drug Product Salvaging). This fundamental CGMP principle applies to any component, in-process material, or finished drug product subjected to such conditions.

In some cases, there may be substantial and reasonable uncertainty whether a drug was subjected to these conditions. In such a circumstance, it is essential that a firm nonetheless err on the side of caution in its risk assessment to assure an appropriate lot disposition decision and conduct a rigorous evaluation in accord with the standards described under 21 CFR Part 211.208.

When there is reasonable uncertainty whether a drug was subjected to such conditions, salvaging operations may be conducted only if there is evidence from laboratory testing that the drugs meet all applicable standards of identity, strength, quality, and purity, and from inspection that the drugs and their associated packaging were not subject to improper storage conditions as a result of the disaster or accident.

When determining whether drugs have been subjected to such improper conditions, a firm's actions should include but not be limited to:

- Obtaining supply chain information, including knowing the names and addresses of all suppliers and distributors of a drug (including components and packaging) to determine if there is a reasonable possibility that such materials were stored under improper conditions.
- Determining details such as the timeframe, duration, nature, scope, and location of exposure as well as identity of all lots potentially subjected to the improper conditions (e.g., ramifications of a natural disaster such as power disruptions should be considered to assure a complete risk assessment).
- Obtaining certification (either on the certificate of analysis or as a separate statement) declaring that drug lots, including components and packaging, were not subjected to improper storage conditions.

For more information, see references below.

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2. What if the improper storage conditions include exposure to toxic fumes or radiation?

Exposure to potentially harmful levels of toxic fumes or radiation is considered to be an improper storage condition (see above). It is essential that firms exercise due diligence to ensure that their drugs were manufactured, processed, packaged, and held under conditions consistent with current good manufacturing practice. This includes assuring acceptability of both raw materials and drug products.

FDA routinely monitors the quality of marketed drug products, including those imported into the U.S. In response to natural disasters, FDA may increase its monitoring and detection capabilities and apply appropriate regulatory action to help ensure the quality and safety of the drug supply.

References:

1. 21 CFR Part 211.208, Drug Product Salvaging
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.208
2. FDA Import Alert 99-33 - *Detention Without Physical Examination of Products from Japan Due to Radionuclide Contamination*
http://www.accessdata.fda.gov/cms_ia/importalert_621.html
3. FDA Public Health Focus - Radiation Safety http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm247403.htm
4. Food Safety: The EU Reinforces Controls on Imports from Japan http://europa.eu/rapid/pressReleasesAction.do?reference=IP/11/362

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http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm

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3.What should be considered in performing an assessment of whether a firm's drug product, or its components or packaging materials may have been contaminated with radioactive material?

Radioactive materials (radionuclides) release radiation, also called "ionizing radiation," as high-energy particles or electromagnetic energy (e.g., gamma rays) as their unstable atoms transition to a more stable state. Low levels of radiation occur naturally in the environment (as "background radiation"), but elevated levels may occur, for example, during or following a nuclear reactor accident. Radioactive materials released into the environment by such an accident may contaminate drug products, components, or packaging materials. In these circumstances, firms should determine if any of these articles has become contaminated with radionuclides. If a drug product has been subjected to improper storage, including contamination with radioactive material, the product must not be salvaged and returned to the marketplace (21 CFR 211.208). Similarly, contaminated drug components and packaging materials should not be used or salvaged to manufacture drug products. It is important for manufacturers to know the origin and complete supply chain of a drug product, component, or packaging to better enable an assessment for possible contamination arising from, e.g., the accidental release of radioactivity

Some general concerns about radionuclide contamination from nuclear accidents include, but are not limited to, the following:

- Drug products and/or components may become contaminated with radionuclides from various sources, including contaminated atmospheric fallout, ground water, soil, or naturally-derived raw materials.
- A contaminated water supply used in drug manufacture may result in poor-quality products that fail to meet specifications.
- Certain dosage forms, such as injectable and inhalable drugs, may present greater risk to patients if contaminated with radionuclides, because these drugs more directly enter into the bloodstream.
- Drug products and/or drug components contaminated with radionuclides may result in poor-quality products that fail to meet stability specifications (e.g., reduced efficacy).

Manufacturers of finished drugs must assure that their products comply with FDA regulations, which includes assurance that the components are of appropriate quality (see, e.g., 21 CFR 211). In addition, manufacturers of drug components and primary containers must also assure the quality of their material. FDA expects drug manufacturers and distributors to be extra vigilant and to take enhanced measures to assure the quality and safety of their drugs that may have been exposed to radioactive contaminants. It may be appropriate for a firm to undertake measures to prevent purchase of at-risk materials as well as to increase testing of incoming components and finished products before final release. See Title 21 Code of Federal Regulations (CFR), Part 211, including:

- CFR Part 211.65, *Testing and Release for Distribution*
- CFR Part 211.84, *Testing and Approval or Rejection of Components, Drug Product Containers, and Closures*
- CFR Part 211.94, *Drug Product Containers and Closures*
- CFR Part 211.208, *Drug Product Salvaging*

References:

1. 21 CFR Part 211
2. FDA Import Alert 99-33 - *Detention Without Physical Examination of Products from Japan Due to Radionuclide Contamination*
3. FDA Public Health Focus - Radiation Safety

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