Guidance for Industry

Pharmaceutical Components at Risk for Melamine Contamination

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
August 2009

Current Good Manufacturing Practice (CGMP)

Contains Nonbinding Recommendations

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GUIDANCE FOR INDUSTRY[1]

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to alert pharmaceutical manufacturers of finished products, pharmacy compounders, repackers, and suppliers to the potential risk of melamine[2] contamination in pharmaceutical components. In September 2008, FDA received reports from China about food articles contaminated with melamine, which have resulted in thousands of hospitalizations for kidney problems and at least three deaths. As of the date of this guidance, FDA is not aware of any pharmaceuticals that have been contaminated with melamine. However, because of the potential risk of drug contamination, it is important that manufacturers take steps to ensure that susceptible components are not contaminated with melamine.

This guidance provides recommendations that will help pharmaceutical manufacturers of finished products, repackers, other suppliers, and pharmacists who engage in drug compounding better control their use of at-risk components[3] that might be contaminated with melamine. FDA

[1] This guidance was developed by the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Veterinary Medicine (CVM) at the Food and Drug Administration.

[2] Melamine is a nitrogen-based compound that is characterized by its high nitrogen content. It is also known by other chemical names, such as triaminotriazine, cyanuramide, and cyanuric acid amide. Melamine is an industrial chemical used in the manufacturing of resins for surface laminates and adhesives in the production of wood-based panels. Melamine or its resins are also used in making melamine dinnerware, additives for textiles, and as flame-retardant additives for foam mattresses. For the purpose of this guidance, we use the term *melamine* in the following sections to mean melamine and related analogs (e.g., melamine and cyanuric acid).

[3] For the purpose of this guidance, we use the term *at-risk component* to mean those ingredients or raw materials that rely on a test for nitrogen content for their identity or purity or strength, and that contain nitrogen in amounts greater than 2.5 percent. Such a component can be derived from source material that might be contaminated with

considers the presence of melamine in any drug (unless specifically approved as an impurity) to render that drug adulterated under sections 501(a)(2)(B) and 501(d) of the Act (21 U.S.C. 351(a)(2)(B) and 351(d)).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances 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 Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In 2007, FDA learned that certain pet foods were sickening and killing cats and dogs. FDA found that vegetable proteins imported into the United States from China and used as ingredients in pet and livestock food products were contaminated with melamine.

In September 2008, FDA received reports of melamine-contaminated infant formula in China. In response, FDA issued a Health Information Advisory to make the public aware of FDA's ongoing effort to monitor the safety of the American food supply by testing certain imported food ingredients derived from milk. Pharmaceutical components that are similarly derived from milk are also at risk for being contaminated with melamine.

These two incidents share the following similarities:

- Melamine, a nitrogen-based compound, was apparently added to bolster the apparent protein content in foods or in ingredients used in processed food products intended to contain protein.

- Recipients using a test for nitrogen content would not have been able to distinguish between melamine and the desired protein.

- Melamine contamination became public only after numerous adverse health events, including deaths, were reported and associated with the use of contaminated products.

These incidents illustrate the potential for drug components to be contaminated with melamine; therefore, it is important for drug manufacturers to be diligent in assuring that no component used in the manufacture of any drug is contaminated with melamine.[4]

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melamine, or the component itself can be directly contaminated by melamine in an attempt to reduce its quality or strength or to substitute for it. Examples of each type appear in section IV.

[4] The risk assessment for melamine in foods does not fully address the risks applicable to drugs. At this time, the FDA has not established an appropriate level of melamine in drug products. Contamination of any type in drugs can result in the loss of active ingredient strength and potency and can disrupt the processing of the finished product. Contaminants can also affect product or component stability. Any of these results from contamination can lead to reduced therapeutic effectiveness. Decreased drug effectiveness and possible long-term exposure risks raise serious concern over the safety of drugs contaminated with melamine and its analogs.

III. REQUIREMENTS AND RECOMMENDATIONS

The current good manufacturing practice (CGMP) regulations require that all components (i.e., ingredients or raw materials) be tested before they are released for use in the manufacture or preparation of drug products (21 CFR 211.84). It is critical that all manufacturers determine whether they are using an *at-risk component* for melamine contamination to manufacture or prepare a drug product. Section IV of this guidance lists examples of at-risk components for melamine contamination and explains how such components were identified.

The CGMP regulations at 21 CFR 211.84(b) and (d) require that a component testing program consider such issues as the need for confidence levels and degree of precision required, as well as the past reliability of a supplier. Accordingly, once you have determined you are using an at-risk component, the Agency recommends that:

1. Manufacturers of finished drug products test for melamine in at-risk components before they are released for use in the manufacture or preparation of the drug products. FDA has posted assay methods for measuring melamine contamination in foods using liquid chromatography triple quadrupole tandem mass spectrometry (LC-MS/MS) and gas chromatography/mass spectrometry (GC-MS) (see Analytical Methods for Melamine and Triazine Analogs, available at http://www.fda.gov/AnimalVeterinary/ScienceResearch/ToolsResources/ucm135002.htm). These methods have been evaluated using dry protein materials.[5]

2. Manufacturers of finished pharmaceuticals know and monitor their supply chain for any at-risk components, which means knowing the identity and role of the actual manufacturer of such components and any repackers and distributors who handle the components before receipt by the manufacturer. Manufacturers should obtain certification from the manufacturer of at-risk components that these components are tested for the absence of melamine contamination. Manufacturers should also audit their component suppliers to ensure CGMP compliance.

3. Distributors of finished pharmaceutical products under their own brand or label obtain certification by the manufacturer that the products are tested for the absence of melamine contamination if their product contains an at-risk component.

FDA also recommends that compounders who use at-risk components in compounding drugs either test the components for melamine or ensure that such testing was properly done by a reliable supplier.

IV. EXAMPLES OF AT-RISK PHARMACEUTICAL COMPONENTS

The following listed components are considered to be at-risk for melamine contamination. These components were identified from a search of the United States Pharmacopeia/National

[5] An alternative method or methods can also be qualified for use in screening components for the presence of melamine. The test method used should be suitable for detecting melamine contamination in at-risk components down to at least 2.5 parts per million (ppm) to give a high degree of assurance that they are not contaminated.

Formulary (USP/NF) monographs and the FDA Inactive Ingredient Database (IID).[6] This list is not considered to be exhaustive, and it is essential that manufacturers evaluate their drug components to determine whether they are vulnerable to melamine contamination. For each compendial component listed, a test for total nitrogen content is specified in the USP monograph.[7] We have also listed certain noncompendial components that can be derived from animal-based materials and that could be tested by methods that are not specific to confirm the identity or structure of the material.

- Adenine (USP)
- Albumin (IID)[8]
- Amino acids derived from casein protein hydrolysates[8]
- Ammonium salts[9]
- Calcium pantothenate (USP)
- Caseinate or sodium caseinate (IID)[8,10]
- Chlorophyllin copper complex sodium (USP)
- Colloidal oatmeal (USP)
- Copovidone (USP/NF)
- Crospovidone (USP/NF)
- Dihydroxyaluminum aminoacetate (USP)
- Gelatin (IID)[8]
- Glucagon (USP)
- Guar gum (USP/NF)
- Hyaluronidase (USP)[8]
- Imidurea (USP/NF)
- Lactose (USP/NF, IID)[10]
- Melphalan (USP)
- Povidone (USP/NF)
- Povidone-Iodine (USP)
- Protamine sulfate (USP)
- Protein hydrolysate (powder) for injection (USP)
- Taurine (USP)

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[6] The FDA Inactive Ingredient Database (IID) is available on the Internet at http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

[7] The nitrogen assay (see USP General Test Monograph for Nitrogen Determination, USP <461>) converts all nitrogen in the sample to ammonia, and then the ammonia liberated by distillation is trapped as ammonium and measured using a pH titration.

[8] The sourced starting material can be derived from animal materials and tested for total nitrogen content to estimate protein content.

[9] This component includes any ammonium salt that is assayed using a pH titration to measure ammonia. Ammonium salts are being included here, in part, because of an October 2008 reported incident of melamine contamination in ammonium bicarbonate intended for food use. The ammonium bicarbonate contamination was not found in the United States.

[10] The sourced starting material can be derived from milk.

- Thioguanine (USP)
- Urea (USP)
- Wheat bran (USP)
- Zein (USP/NF)